



**A PHASE 3, RANDOMIZED, DOUBLE-BLIND TRIAL TO EVALUATE THE  
SAFETY OF A 20-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN  
HEALTHY INFANTS**

**Investigational Product Number:** PF-06482077  
**Investigational Product Name:** 20-valent pneumococcal conjugate vaccine  
(20vPnC)  
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**Phase:** 3  
**Short Title:** 20-valent Pneumococcal Conjugate Vaccine Safety Study in Healthy  
Infants

## Protocol Amendment Summary of Changes Table

Document History		
Document	Version Date	Summary of Changes and Rationale
Amendment 1	31 Mar 2022	<p><a href="#">Section 1.3</a>, <a href="#">Section 8.10.5</a>, <a href="#">Section 8.10.6</a>, <a href="#">Section 8.10.7</a>, <a href="#">Section 10.9</a>: Amended relevant sections of the protocol to detail the United States and Puerto Rico country-specific amendment. Modifications impacted Visit 5 and Visit 7 timing, and added flexibility in the format of Visit 6.</p> <p><a href="#">Section 2.1</a>, <a href="#">Section 4.1</a>: Updated wording to reflect details related to the United States and Puerto Rico country-specific amendment.</p> <p><a href="#">Section 7.2</a>: Clarified guidance for participants who are discontinued prior to completing all 4 doses of study intervention.</p>
Original protocol	19 Feb 2020	Not applicable (N/A)

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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<sup>®</sup>/Prevenar 13<sup>®</sup>), but contains an additional 7 polysaccharide conjugates targeting serotypes responsible for a substantial burden of remaining pneumococcal disease. 20vPnC uses the same platform and contains the same excipients as 7-valent pneumococcal conjugate vaccine (7vPnC; Prevnar<sup>®</sup>) and 13vPnC. Phase 2 safety and immunogenicity data in infants support further development of 20vPnC in the pediatric population.

This Phase 3, multicenter, randomized, double-blind study with a 2-arm parallel design will be conducted at investigator sites in the United States and potentially other countries to be determined. CCI [REDACTED]

[REDACTED] The purpose of this study is to describe the safety of 20vPnC.

Approximately 1500 infants  $\geq 42$  to  $\leq 98$  days of age will be randomized (2:1) to receive either 20vPnC or 13vPnC at 2, 4, and 6 months of age (Doses 1 through 3) and 12 to 15 months of age (Dose 4).

Other routine pediatric vaccines are permitted according to official local recommendations/regulations at any time throughout study participation. The targeted age of the population for this study, infants  $\geq 42$  to  $\leq 98$  days of age, has been selected as this is the routinely recommended age for initial vaccination with pneumococcal conjugate vaccines and other vaccines in infants.

Local reactions (redness, swelling, and pain at the injection site) and systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) will be prompted for and collected by an electronic diary (e-diary) device or application, for 7 days following vaccination (Days 1 to 7, where Day 1 is the day of vaccination).

Adverse events (AEs) will be collected from the time the participant's parent(s)/legal guardian(s) provides informed consent through 1 month after Dose 3 (Visit 4) and from Dose 4 (Visit 5) through 1 month after Dose 4 (Visit 6). Serious adverse events (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) will be collected from informed consent through 6 months after Dose 4 (Visit 7).



## Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Safety:	Primary Safety:	Primary Safety:
<ul style="list-style-type: none"><li>To describe the safety profile of 20vPnC.</li></ul>	<p>In participants receiving at least 1 dose of investigational product and who have safety data reported after any vaccination:</p> <ul style="list-style-type: none"><li>The percentage of participants reporting prompted local reactions within 7 days after each dose in each group.</li><li>The percentage of participants reporting prompted systemic events within 7 days after each dose in each group.</li><li>The percentage of participants reporting AEs from Dose 1 through 1 month after Dose 3 in each group.</li><li>The percentage of participants reporting AEs from Dose 4 through 1 month after Dose 4 in each group.</li><li>The percentage of participants reporting SAEs up to 6 months after Dose 4 in each group.</li><li>The percentage of participants reporting NDCMCs up to 6 months after Dose 4 in each group.</li></ul>	<ul style="list-style-type: none"><li>Prompted local reactions (redness, swelling, and pain at the injection site).</li><li>Prompted systemic events (fever, decreased appetite, irritability, and drowsiness/increased sleep).</li><li>AEs.</li><li>SAEs.</li><li>NDCMCs.</li></ul>

## Number of Participants

Approximately 1500 participants will be randomized (approximately 1000 in the 20vPnC group and approximately 500 in the 13vPnC group).

## Duration of Participation for Each Participant

Each participant will participate in the study for approximately 16 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 vaccine group. A 3-tier approach will be used to summarize AEs.

### **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	4	5 <sup>a</sup>	6 <sup>a</sup>	7 <sup>a</sup>
Visit Description	Dose 1 Visit	Dose 2 Visit	Dose 3 Visit	Dose 3 Follow-up Visit	Dose 4 Visit	Dose 4 Follow-up Visit	Dose 4 6-Month Telephone Contact
Visit Window (Days)	Day 1	42 to 63 Days After Visit 1	42 to 63 Days After Visit 2	28 to 42 Days After Visit 3	365 to 455 Days of Age	28 to 42 Days After Visit 5	168 to 196 Days After Visit 5
Obtain informed consent	X						
Assign participant number via IRT	X						
Record demography	X						
Perform clinical assessment including medical history	X						
Record vaccine history	X						
Record concomitant medications <sup>b</sup>	X	X	X	X	X	X	X
Obtain prevaccination temperature (measured as appropriate for age)	X	X	X		X		
Review inclusion and exclusion criteria	X						
Review temporary delay criteria	X	X	X		X		
Review continued eligibility		X	X	X	X	X	
Assign randomization number	X						
Administer investigational product (20vPnC or 13vPnC) into the left thigh	X <sup>c</sup>	X <sup>c</sup>	X <sup>c</sup>		X <sup>c</sup>		

Visit Number	1	2	3	4	5 <sup>a</sup>	6 <sup>a</sup>	7 <sup>a</sup>
Visit Description	Dose 1 Visit	Dose 2 Visit	Dose 3 Visit	Dose 3 Follow-up Visit	Dose 4 Visit	Dose 4 Follow-up Visit	Dose 4 6-Month Telephone Contact
Visit Window (Days)	Day 1	42 to 63 Days After Visit 1	42 to 63 Days After Visit 2	28 to 42 Days After Visit 3	365 to 455 Days of Age	28 to 42 Days After Visit 5	168 to 196 Days After Visit 5
If applicable, administer and record routine pediatric vaccinations <sup>d</sup>	X	X	X		X		
Observe and record acute (immediate) reactions for 30 minutes after investigational product administration	X	X	X		X		
Provide a participant contact card	X						
Provide parent(s)/legal guardian(s) with an e-diary (device or application, as appropriate), digital thermometer, and measuring device and instruct how to collect prompted local reactions, systemic events, and use of antipyretic/pain medications <sup>e</sup>	X				X		
Review e-diary <sup>f</sup>		X	X	X		X	
Collect e-diary (if applicable)				X		X	

Visit Number	1	2	3	4	5 <sup>a</sup>	6 <sup>a</sup>	7 <sup>a</sup>
Visit Description	Dose 1 Visit	Dose 2 Visit	Dose 3 Visit	Dose 3 Follow-up Visit	Dose 4 Visit	Dose 4 Follow-up Visit	Dose 4 6-Month Telephone Contact
Visit Window (Days)	Day 1	42 to 63 Days After Visit 1	42 to 63 Days After Visit 2	28 to 42 Days After Visit 3	365 to 455 Days of Age	28 to 42 Days After Visit 5	168 to 196 Days After Visit 5
Record and report adverse events	X-----X				X-----X		
Record and report SAEs and NDCMC <sub>S</sub> <sup>g,h</sup>	X-----X						

Abbreviations: e-diary = electronic diary; IRT = interactive response technology; NDCMC = newly diagnosed chronic medical condition.

- Per Protocol Amendment 1: For the United States and Puerto Rico country-specific amendment details, pertaining to Visits 5, 6, and 7, please refer to [Section 10.9](#) (Appendix 9: Amendment 1 Country-Specific Requirements – Applicable to United States and Puerto Rico Only).
- Collect and record only concomitant medications used to treat SAEs and NDCMCs.
- 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).
- If applicable, administer routine pediatric vaccinations after the investigational product into a limb other than the site of 20vPnC or 13vPnC injection. The name, date of administration, and site of administration for all vaccinations given on the same day as investigational product administration at Visits 1, 2, 3, and 5 will be recorded.
- The participant's parent(s)/legal guardian(s) will record in an e-diary prompted local reactions and systemic events occurring within 7 days following each dose of 20vPnC or 13vPnC. Use of antipyretic/pain medications will also be prompted for and collected daily in an e-diary for 7 days after vaccination. The participant's parent(s)/legal guardian(s) will be instructed to contact the study staff if the participant experiences redness or swelling measuring >14 device units, severe pain at the 20vPnC or 13vPnC injection site, or a fever >40.0°C (>104.0°F), or has an emergency room visit or hospitalization.
- Designated site staff will review e-diary data online at frequent intervals (daily is optimal) for the 7 days following each dose of 20vPnC or 13vPnC to evaluate participant compliance and reported events as part of the ongoing safety review.
- 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.
- If the parent(s)/legal guardian(s) consents, participants withdrawn from the study will receive a 6-month telephone safety follow-up after their last dose of study vaccination for collection of any SAEs and NDCMCs.

## 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.<sup>1,2,3</sup> Serious pneumococcal disease may occur at any age; however, children <5 years and adults ≥65 years of age are at particularly increased risk.<sup>4</sup> 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.<sup>2</sup> 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.<sup>5</sup>

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.<sup>6</sup> 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.<sup>7</sup> 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.<sup>8</sup> 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.<sup>9,10</sup> 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.<sup>11</sup> 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.<sup>12,13</sup> 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.<sup>12,14</sup> 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 equally (1-4 year olds) and meningitis (<1 year olds).<sup>8</sup> 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.<sup>15</sup> *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.<sup>3</sup> 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.<sup>16,17</sup> Anticapsular antibodies directed against the specific serotype bind to the capsule and promote complement-mediated opsonophagocytic killing and clearance of the organism.<sup>18</sup> 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.<sup>19</sup>

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.<sup>20,21</sup> 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.<sup>4,21,22,23</sup> Moreover, their ability to prevent nonbacteremic pneumonia, CAP, and AOM is limited or lacking.<sup>19,23,24,25,26</sup> In addition, polysaccharide vaccines do not reduce vaccine-type (VT) nasopharyngeal carriage, which is important for herd immunity.<sup>26</sup> 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.<sup>19</sup>

### **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.<sup>22,27</sup> 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<sub>197</sub>), 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).<sup>28,29,30,31,32</sup> These serotypes also accounted for a high proportion of antibiotic-resistant strains.<sup>33</sup> 7vPnC demonstrated efficacy against VT IPD, pneumonia, and AOM in large randomized, controlled efficacy studies in infants.<sup>34,35</sup> The 7vPnC components contained in a related pneumococcal conjugate vaccine also were demonstrated to be efficacious against clinically/radiographically defined pneumonia.<sup>36,37,38,39</sup> 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.<sup>40</sup>

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.<sup>27,31,41</sup> The vaccine was licensed for use in infants and young children based on comparisons of serotype-specific serum immunoglobulin G (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.<sup>42</sup>



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.<sup>43,44,45,46</sup> It has also been prequalified by the World Health Organization (WHO) for use in national infant immunization programs in lower- and middle-income countries.<sup>47,48</sup> 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.<sup>49,50,51</sup>

## 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<sub>197</sub>. 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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The purpose of the study is to assess the safety of 20vPnC in infants, and to provide key safety data to support licensure in this population. The targeted age of the population for this study, infants ≥42 to ≤98 days of age, has been selected as this is the routinely recommended age for initial vaccination with pneumococcal conjugate vaccines and other vaccines in infants. The participants will be administered either 20vPnC or 13vPnC at 2, 4, 6, and 12 to 15 months of age.

Amendment 1 is a United States and Puerto Rico country-specific amendment, which is being implemented to complete the vaccination schedule in a timely manner, as all participants are age-eligible for their final dose (Dose 4) as of the amendment date. There is no benefit to the participant to delay completion of the series. Delaying vaccination and in-person study visits in the trial also carries a risk of even further delays in vaccination and exposure risks that may occur with a potential resurgence of coronavirus disease in the near future. Finally, the 20vPnC pediatric program has been granted Breakthrough Therapy designation by the Food and Drug Administration (FDA), indicating that it has the potential to meet an unmet medical need to prevent serious disease in the pediatric population. Therefore, avoiding further delays in study completion will support our shared goal of generating the key data with 20vPnC in this vulnerable population and, if successful, allow this vaccine to be licensed and available to help protect young children as soon as possible. The modifications in this amendment impact only a very small overall proportion of participants who have not yet received Dose 4 and those who received Dose 4 after a certain date, and do not adversely affect the safety, scientific integrity, or management of the study.

## 2.2. Background

20vPnC is being developed to further expand protection against the global burden of vaccine-preventable pneumococcal disease in children and adults over that of 13vPnC. 20vPnC contains the serotypes present in 13vPnC, and 7 new serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) individually conjugated to CRM<sub>197</sub>. 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).<sup>52,53,54,55,56,57,58,59,60,61,62,63</sup> 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.<sup>64,65,66,67,68,69,70</sup> These 7 serotypes contribute to the burden of IPD in the United States and elsewhere. It is estimated that between 2015 and 2016, these 7 serotypes accounted for 34% to 39% of IPD in children in the United States.<sup>71</sup> 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.<sup>8</sup>

A meta-analysis of serotypes causing IPD in children <5 years of age in regions of the world that have introduced higher-valent pneumococcal conjugate vaccines (such as 13vPnC) showed that, overall, these 7 serotypes accounted for approximately 70% of disease not due to the 13vPnC vaccine types.<sup>66</sup>

### 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 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.

A Phase 2 study (B7471003) of 20vPnC in healthy infants  $\geq 42$  to  $\leq 98$  days of age was also 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 consistent with other pneumococcal conjugate vaccines. Immune responses (either IgG geometric mean concentrations or percentages of participants meeting a predefined IgG concentration) after 3 doses of 20vPnC were similar to those in the 13vPnC group. These data support continued development of 20vPnC in a pediatric population.

### 2.3. Benefit/Risk Assessment

13vPnC is a licensed vaccine and the most common AEs noted in children <5 years of age after vaccination are primarily related to local reactions (injection site pain or tenderness, redness, and swelling) and systemic events (fever, irritability, decreased appetite, and increased sleep).

The 20vPnC investigational product contains the same components and excipients as 13vPnC, but also contains the polysaccharide conjugates for the 7 additional pneumococcal serotypes. Thus, the AE profile of 20vPnC is expected to be similar to that of 13vPnC, but AEs may be different with the investigational 20vPnC.

In a randomized, active-controlled, double-blind study with a 2-arm parallel design (B7471003), 20vPnC was administered to 460 infants  $\geq 42$  to  $\leq 98$  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.

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.

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13vPnC is approved for the prevention of pneumococcal disease due to the serotypes in the vaccine, and may provide a clinical benefit to those receiving it.

In the B7471003 study, 20vPnC induced immune responses to the pneumococcal serotypes in the vaccine. This suggests that protection against pneumococcal disease will be similar to that with 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 (invasive and noninvasive) due to vaccine serotypes.

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

More detailed information about the known and expected benefits and risks and reasonably expected AEs of 20vPnC may be found in the IB, which is the single reference safety document (SRSD) for this study. The SRSD for the 13vPnC control vaccine is the US package insert (USPI).

### 3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
<b>Primary Safety:</b>	<b>Primary Safety:</b>	<b>Primary Safety:</b>
<ul style="list-style-type: none"> <li>To describe the safety profile of 20vPnC.</li> </ul>	<p>In participants receiving at least 1 dose of investigational product and who have safety data reported after any vaccination:</p> <ul style="list-style-type: none"> <li>The percentage of participants reporting prompted local reactions within 7 days after each dose in each group.</li> <li>The percentage of participants reporting prompted systemic events within 7 days after each dose in each group.</li> <li>The percentage of participants reporting AEs from Dose 1 through 1 month after Dose 3 in each group.</li> <li>The percentage of participants reporting AEs from Dose 4 through 1 month after Dose 4 in each group.</li> <li>The percentage of participants reporting SAEs up to 6 months after Dose 4 in each group.</li> <li>The percentage of participants reporting NDCMCs up to 6 months after Dose 4 in each group.</li> </ul>	<ul style="list-style-type: none"> <li>Prompted local reactions (redness, swelling, and pain at the injection site).</li> <li>Prompted systemic events (fever, decreased appetite, irritability, and drowsiness/increased sleep).</li> <li>AEs.</li> <li>SAEs.</li> <li>NDCMCs.</li> </ul>

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## 4. STUDY DESIGN

### 4.1. Overall Design

This Phase 3, multicenter, randomized, double-blind study with a 2-arm parallel design will be conducted at investigator sites in the United States and potentially other countries to be determined. CCI

The purpose of this study is to describe the safety of 20vPnC.

Approximately 1500 infants  $\geq 42$  to  $\leq 98$  days of age will be randomized (2:1) to receive either 20vPnC or 13vPnC at 2, 4, and 6 months of age (Doses 1 through 3) and 12 to 15 months of age (Dose 4). Other routine pediatric vaccines are permitted according to official local recommendations/regulations at any time throughout study participation.

On Day 1 (Visit 1, Dose 1 vaccination) of the study, participants will be assessed for eligibility and information will be collected, including medical history and vaccine history. Participants will receive 20vPnC or 13vPnC Dose 1. Participants will be observed for 30 minutes after vaccination, and any reactions occurring during that time will be recorded as AEs. The participant's parent(s)/legal guardian(s) will be provided with an e-diary (or e-diary application), thermometer, and measuring device and instructed to collect prompted local reactions (redness, swelling, and pain at the injection site) and systemic events (fever, decreased appetite, drowsiness/increased sleep, and irritability) occurring within 7 days after each vaccination. Use of antipyretic/pain medications will also be prompted for and collected daily in the e-diary for 7 days after vaccination. The participant's parent(s)/legal guardian(s) will be instructed to contact the study staff if the participant experiences redness or swelling  $>14$  caliper units, severe pain at the injection site, or fever  $>40.0^{\circ}\text{C}$  ( $>104.0^{\circ}\text{F}$ ), or has an emergency room visit or hospitalization.

Participants will return for Visit 2 (42 to 63 days after Visit 1, study Day 43 to 64) and Visit 3 (42 to 63 days after Visit 2). 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 will be recorded. Dose 2 will be given at Visit 2 and Dose 3 will be given at Visit 3. 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 instructed to collect prompted local reactions and systemic events occurring within 7 days after 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 redness or swelling  $>14$  caliper units, severe pain at the injection site, or fever  $>40.0^{\circ}\text{C}$  ( $>104.0^{\circ}\text{F}$ ), or has an emergency room visit or hospitalization.

Participants will return for Visit 4, approximately 1 month (28 to 42 days) after Visit 3. Information will be collected from the participant's parent(s)/legal guardian(s) on AEs, SAEs, NDCMCs, and e-diary follow-up (as needed). Concomitant medications used to treat SAEs or NDCMCs will be recorded.

Participants will return for Visit 5 (365 to 455 days of age). Information will be collected from the participant's parent(s)/legal guardian(s) on SAEs, NDCMCs, and e-diary follow-up (as needed). Concomitant medications used to treat SAEs or NDCMCs will be recorded. Dose 4 will be administered at this visit. 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 instructed to collect prompted local reactions and systemic events occurring within 7 days after 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 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.

All participants will return for Visit 6, approximately 1 month (28 to 42 days) after Visit 5. Information will be collected from the participant's parent(s)/legal guardian(s) on AEs, SAEs, NDCMCs, and e-diary follow-up (as needed). Concomitant medications used to treat SAEs or NDCMCs will be recorded.

All participants will have Visit 7, approximately 6 months (168 to 196 Days) after Visit 5. 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 and NDCMCs.

Amendment 1 applies to the small number of participants in this study who have not received Dose 4 of study intervention (these participants are solely from investigator sites in the United States and Puerto Rico and all are age-eligible for Dose 4), and for participants who received Dose 4 after 16 Feb 2022. The following modifications are being introduced as part of a United States and Puerto Rico country-specific amendment: 1) the window for Visit 5 (time-based rather than age-based, as all participants are now age-eligible), 2) an option of conducting Visit 6 by telephone, and 3) Visit 7 windows for a small number of participants will be modified slightly (see [Section 10.9](#) – Appendix 9). The modified follow-up windows are consistent with the original protocol, as they will still allow for approximately 6 months of follow-up after the final vaccination in the series.

#### **4.1.1. Approximate Duration of Participation for Each Participant**

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

#### **4.1.2. Approximate Number of Participants**

Approximately 1500 participants will be randomized (approximately 1000 in the 20vPnC group and approximately 500 in the 13vPnC group).



## 4.2. Scientific Rationale for Study Design

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The Phase 3 study described in this protocol will provide key safety data of 20vPnC in infants to support licensure in this population. Infants born at  $\geq 34$  weeks of gestation and 2 months of age ( $\geq 42$  to  $\leq 98$  days of age) at the time of consent will be eligible if they are naïve to pneumococcal vaccination. This study population has been selected as this is the historical population studied for licensure of 7vPnC and 13vPnC in infants. The participants will be administered either 20vPnC or 13vPnC at 2, 4, 6, and 12 to 15 months of age. This is consistent with the current pneumococcal vaccine recommendations for infants in the United States. 13vPnC will serve as the comparator to 20vPnC for assessment of safety.<sup>31</sup>

## 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<sub>197</sub>. The vaccine is formulated to contain 2.2  $\mu\text{g}$  of each saccharide, except for 4.4  $\mu\text{g}$  of 6B, per 0.5-mL dose. In infants, 3 doses of pneumococcal conjugate vaccine given in infancy at 2, 4, and 6 months of age and 1 dose given at 12 to 15 months of age induces protective immune responses.

## 4.4. End of Study Definition

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

## 5. STUDY POPULATION

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

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

### 5.1. Inclusion Criteria

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

#### Age and Sex:

1. Male or female infants born at  $\geq 34$  weeks of gestation and who are 2 months of age ( $\geq 42$  to  $\leq 98$  days) at the time of consent (the day of birth is considered day of life 1).

### **Type of Participant and Disease Characteristics:**

2. Participants whose parent(s)/legal guardian(s) is willing and able to comply with scheduled visits, treatment plan, and other study procedures.
3. Healthy infants determined by clinical assessment, including medical history and clinical judgment, to be eligible for the study.
4. Expected to be available for the duration of the study and whose parent(s)/legal guardian(s) can be contacted by telephone during study participation.

### **Informed Consent:**

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

### **5.2. Exclusion Criteria**

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

#### **Medical Conditions:**

1. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of 13vPnC, 20vPnC, or any other diphtheria toxoid-containing vaccine.
2. Significant neurological disorder or history of seizure including febrile seizure, or significant stable or evolving disorders such as cerebral palsy, encephalopathy, hydrocephalus, or other significant disorders. Does not include resolving syndromes due to birth trauma, such as Erb's palsy and/or hypotonic-hyporesponsive episodes.
3. Major known congenital malformation or serious chronic disorder.
4. 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.
5. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
6. Other acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.



**Prior/Concomitant Therapy:**

7. Previous vaccination with any licensed or investigational pneumococcal vaccine, or planned receipt through study participation.
8. Currently receives treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, or planned receipt through the visit occurring 1 month after Dose 4 (Visit 6). If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before investigational product administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, or ears) corticosteroids are permitted.

**Prior/Concurrent Clinical Study Experience:**

9. 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:**

10. 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**

No restrictions are required.

**5.4. Screen Failures**

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

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

## 5.5. Temporary Delay Criteria

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

### 5.5.1. Criteria for Temporarily Delaying Vaccine Administration

- Current febrile illness (eg, body temperature  $\geq 38.0^{\circ}\text{C}$  [ $\geq 100.4^{\circ}\text{F}$ ]) or other acute illness within 48 hours before investigational product administration.

## 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<sub>197</sub>. CCI [REDACTED]

13vPnC is a sterile liquid suspension formulation containing saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to CRM<sub>197</sub>. The vaccine is formulated to contain 2.2 µg of each saccharide, except for 4.4 µg of 6B, per 0.5-mL dose. The vaccine contains 295 µg succinate buffer, 0.85% sodium chloride, 100 µg polysorbate 80, and 125 µg aluminum as aluminum phosphate, per 0.5-mL dose.

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20vPnC and 13vPnC are both white suspensions and are identical in appearance. 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

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

20vPnC and 13vPnC should be administered intramuscularly by injecting 0.5 mL into the anterolateral thigh muscle of the left leg at the vaccination visits.

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

Administration of 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 and 13vPnC prefilled syringes.

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

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the study personnel throughout the study. Please refer to [Section 8.3.6](#) 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.

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### **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**

### **6.3.1. Allocation to Investigational Product**

Allocation (randomization) of participants to vaccine groups will proceed through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the participant number.

The site personnel will then be provided with a vaccine assignment, randomization number, and 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, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

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

### **6.3.2. Breaking the Blind**

The study will be participant and investigator blinded.

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

### **6.3.3. Blinding of the Sponsor**

Sponsor personnel directly involved in evaluating participant data will be blinded to vaccine assignment until the analysis of available data through 1 month after Dose 4, following the principles outlined in the International Council for Harmonisation E9 guideline on Statistical Principles for Clinical Trials.<sup>72</sup> A data blinding plan will be created to describe the blinding requirements and unblinding events.

#### **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 participant participation in the study.
- Receipt of any nonstudy pneumococcal vaccine is prohibited during participant participation in the study.

##### **6.5.2. Permitted Concomitant Vaccines and Treatments**

- Other routine pediatric vaccines, including influenza vaccine, are permitted at any time throughout study participation, given according to official local recommendations/regulations.
- 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 participant participation in the study.

##### **6.5.3. Recording Prior and Concomitant Vaccines and Treatments**

The name, date of administration, and site of administration for all vaccinations given on the same day as investigational product administration (Visits 1, 2, 3 and 5) will be recorded in the CRF. At Visit 1, information on prior vaccinations received by the participant will be recorded in the CRF.

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

#### **6.6. 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**

Participant eligibility must be confirmed prior to each vaccination in order to continue in the study.

If a participant no longer meets the eligibility criteria during the vaccination period of the study, further vaccinations should be discontinued, but the participant may remain in the study. If a participant is discontinued from vaccination and the participant's parent(s)/legal guardian(s) consents, safety follow-up will be conducted as per [Section 7.2](#).

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

### **7.2. Participant Discontinuation/Withdrawal From the Study**

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

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 study reference manual (SRM) 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 participant will be permanently discontinued both from the study intervention and from the study at that time. 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.

For participants who are discontinued prior to completing all 4 doses of study intervention, the parent(s)/legal guardian(s) should be encouraged to follow up with their primary care physician to have the participant complete the pneumococcal conjugate vaccine series as part of their recommended standard of care.

A final telephone contact 6 months after the last vaccination (similar to [Section 8.10.7](#)) for the collection of safety information should be completed for all participants 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 only from further receipt of investigational product or also 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 (see below) 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 VaccineCT 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 be considered to have been withdrawn from the study.



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

### **8.1. Efficacy Assessments**

Not applicable.

## 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 observed during physical examination (if performed) will be recorded in the medical history CRF. Temperature measurement prior to vaccination will be documented and recorded in the CRF.

The participant will be observed for 30 minutes after each 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 (fever, decreased appetite, drowsiness/increased sleep, and irritability) 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, and antipyretic/pain medications taken for 7 days, each evening following each vaccination using an e-diary (in a provisioned device or application on a personal device), which allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience. Data on local reactions, specific systemic events, and antipyretic/pain medications 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 and 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 FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for adults and adolescent volunteers enrolled in preventive vaccine clinical trials, but have been adapted for applicability to healthy infants.<sup>73</sup>

#### **8.2.2.1. Local Reactions**

For the first 7 days following each vaccination from Day 1 through Day 7, the participant's parent(s)/legal guardian(s) will be asked to assess redness, swelling, and pain at the 20vPnC or 13vPnC injection site and to record the symptoms in the e-diary in the evening. Redness and swelling will be measured and recorded in measuring device (caliper) units (range: 1 to >14; an entry in the e-diary of 15 will denote >14), and then categorized during analysis as mild, moderate, or severe based on the grading scale in [Table 1](#) 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 scale 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 investigator site file (ISF) or equivalent.

**Table 1. Grading Scales for Local Reactions**

	<b>GRADE 1 Mild</b>	<b>GRADE 2 Moderate</b>	<b>GRADE 3<sup>a</sup> Severe</b>	<b>GRADE 4<sup>b</sup></b>
Redness	1 to 4 caliper units (or measuring device units) = >0 to 2.0 cm	5 to 14 caliper units (or measuring device units) = >2.0 to 7.0 cm	>14 caliper units (or measuring device units) = >7 cm	Necrosis or exfoliative dermatitis
Swelling	1 to 4 caliper units (or measuring device units) = >0 to 2.0 cm	5 to 14 caliper units (or measuring device units) = >2.0 to 7.0 cm	>14 caliper units (or measuring device units) = >7 cm	Necrosis
Pain at injection site (tenderness)	Hurts if gently touched (eg, whimpers, winces, protests, or withdraws)	Hurts if gently touched, with crying	Causes limitation of limb movement	Emergency room visit or hospitalization for severe pain (tenderness) at injection site

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.

- Parents/legal guardians of the participants experiencing local reactions >14 caliper units (>7.0 cm) are to be contacted by the study site. An unscheduled visit may be required.
- 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 severity grading scale provided in the protocol.

## 8.2.2.2. Systemic Events – Symptoms and Fever

### 8.2.2.2.1. Symptoms

For the first 7 days following each vaccination from Day 1 through Day 7, the participant's parent(s)/legal guardian(s) will be asked to assess decreased appetite, drowsiness/increased sleep, and irritability and to record the symptoms in the e-diary (in a provisioned device or application on a personal device) in the evening. The symptoms will be assessed by the participant's parent(s)/legal guardian(s) as mild, moderate, or severe according to the grading scale in [Table 2](#) 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) within 7 days after vaccination. Study staff may also contact the participant's parent(s)/legal guardian(s) to obtain additional information on Grade 3 events entered into the e-diary.

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

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

**Table 2. Grading Scales for Systemic Events**

Systemic Event	GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 <sup>a</sup>
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 the protocol.

#### 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 (as appropriate for the age of the child) at home. Temperature will be collected in the evening, daily, for 7 days following vaccination (Days 1 to 7, where Day 1 is the day of vaccination) and at any time during the 7 days that fever is suspected. Fever is defined as a temperature of  $\geq 38.0^{\circ}\text{C}$  ( $\geq 100.4^{\circ}\text{F}$ ). 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  $38.0^{\circ}\text{C}$  [ $100.4^{\circ}\text{F}$ ]) 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 temperature  $>40.0^{\circ}\text{C}$  ( $>104.0^{\circ}\text{F}$ ) to assess the fever and perform an unscheduled assessment, as applicable (see unscheduled assessments in [Section 8.10.8](#)). Study staff may also contact the participant's parent(s)/legal guardian(s) to obtain additional information if a temperature of  $>38.9^{\circ}\text{C}$  ( $>102.0^{\circ}\text{F}$ ) is entered into an e-diary. Temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis; see [Table 3](#) below.

**Table 3. Ranges for Fever**

≥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 after each dose of investigational product, where Day 1 is the day of vaccination.

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

#### **8.2.3. Clinical Safety Laboratory Assessments**

Clinical safety laboratory assessments 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. Biological Samples**

Collection of biological samples are not required by this protocol.

### **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 AEs. Examples may include, but are not limited to, teething, contact diaper rash, spitting up, colic, or typical fussiness/crying in infants and children.

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

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

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

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each participant begins from the time the participant’s parent(s)/legal guardian(s) provides informed consent, which is obtained before the participant’s participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including Visit 4, and from Visit 5 to Visit 6. Between Visit 4 and Visit 5, only SAEs and NDCMCs will be reported. At Visit 7 (final telephone contact), the participant’s parent(s)/legal guardian(s) will be contacted by telephone to inquire about SAEs, including hospitalizations and NDCMCs, since Visit 6.

AEs that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section.

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.

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**

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF.

### **8.3.2. Method of Detecting AEs and SAEs**

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

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

### **8.3.3. Follow-up of AEs and SAEs**

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

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

Further information on follow-up procedures is given in [Appendix 3](#).

### **8.3.4. Regulatory Reporting Requirements for SAEs**

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/ethics committees (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 is reportable to Pfizer Safety within 24 hours of investigator awareness.

#### **8.3.5.1. Exposure During Pregnancy**

Details of all pregnancies in females (via occupational exposure) will be collected after the start of study intervention and until at least 6 months after exposure.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in CCI

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

#### **8.3.5.2. Exposure During Breastfeeding**

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

#### **8.3.5.3. 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. Medical Device Incidents (Including Malfunctions)**

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 incident or malfunction that occur during the study with such devices.

The definition of a medical device incident can be found in [Appendix 8](#).

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in [Section 8.3.3](#) and [Appendix 3](#) of the protocol.

#### **8.3.6.1. Time Period for Detecting Medical Device Incidents**

Medical device incidents 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 incident 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 incidents is provided in [Appendix 8](#).

#### **8.3.6.2. Follow-up of Medical Device Incidents**

All medical device incidents 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 incident.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

#### **8.3.6.3. Prompt Reporting of Medical Device Incidents to Sponsor**

Medical device incidents will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident.

Refer to the IP manual for instructions on reporting medical device incidents.

The same individual will be the contact for the receipt of medical device reports and SAEs.

#### **8.3.6.4. Regulatory Reporting Requirements for Medical Device Incidents**

The investigator will promptly report all incidents 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 incidents to the IRB/EC.

### 8.3.7. 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:

- a. Medication errors involving participant exposure to the investigational product;
- b. 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 0.5 mL 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 immediately.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE**.

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

#### **8.5. Pharmacokinetics**

Pharmacokinetic parameters are not evaluated in this study.

#### **8.6. Pharmacodynamics**

Pharmacodynamic parameters are not evaluated in this study.

#### **8.7. Genetics**

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

#### **8.8. Biomarkers**

Biomarkers are not evaluated in this study.

#### **8.9. 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](#). The day of Dose 1 is considered to be Day 1.

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

### 8.10.1. Visit 1 (Dose 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 to critically evaluate the safety profile by age.
- Perform a clinical assessment including medical history (including significant birth history); record any findings on the medical history CRF.
- Record vaccine history.
- Measure and record the participant's prevaccination temperature using a method appropriate for the age of the child, according to routine local practice (°F/°C).
- Ensure that all inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met.
- Assign a randomization number and investigational product container number via the IRT. This must be the last step before proceeding. A blinded site staff member will prepare the investigational product according to the IP manual.

After randomization:

- Administer a single 0.5-mL injection of 20vPnC or 13vPnC into the left anterolateral thigh.
- If applicable, administer routine pediatric vaccinations into a limb other than the site of 20vPnC or 13vPnC injection and capture all details of the concomitant vaccine given on the same day as investigational product administration, including the name, date of administration, and site of administration, on the CRF.
- Site staff will observe the participant for 30 minutes after vaccination for any reactions. Record any AEs on the CRF and on an SAE form as applicable. Record concomitant medications used to treat SAEs and NDCMCs.
- Issue the participant's parent(s)/legal guardian(s) a measuring device to measure injection site reactions and a digital thermometer and provide instructions on their use.

- Issue the participant's parent(s)/legal guardian(s) an e-diary (device or application). Provide instructions on use and completion of the e-diary. Ask the participant's parent(s)/legal guardian(s) to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant's parent(s)/legal guardian(s) to contact the investigator site staff or investigator as soon as possible during the 7-day postvaccination period if the participant has a fever  $>40.0^{\circ}\text{C}$  ( $>104.0^{\circ}\text{F}$ ), redness and/or swelling at the injection site measuring  $>14$  measuring device units ( $>7$  cm), or severe injection site pain (causes limitation of limb movement) to determine if the event requires further assessment by the investigator.
- Ask the 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 a participant contact card with the study and investigator information (see [Section 10.1.10](#)).
- Remind the participant's parent(s)/legal guardian(s) that use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).
- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.
- 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 ongoing safety review.

#### **8.10.2. Visit 2 (Dose 2: 42 to 63 Days After Dose 1, ie, Study Day 43 to 64)**

- Ensure and document that the participant continues to be eligible for the study (see [Section 7.2](#) for participant withdrawal information) and none of the temporary delay criteria are met ([Section 5.5](#)).
- Confirm whether the parent(s)/legal guardian(s) still possesses the participant contact card.
- Review the participant's e-diary data with the participant's parent(s)/legal guardian(s); collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.
- Determine whether any AEs (includes nonserious AEs, SAEs, and NDCMCs) have occurred since the previous visit and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in [Section 10.3](#), and record concomitant medications used to treat NDCMCs and SAEs.

- Measure and record the participant's prevaccination temperature using a method appropriate for the age of the child, according to routine local practice (°F/°C).
- Administer a single 0.5-mL injection of 20vPnC or 13vPnC into the left anterolateral thigh.
- If applicable, administer routine pediatric vaccinations into a limb other than the site of 20vPnC or 13vPnC injection and capture all details of the concomitant vaccine given on the same day as investigational product administration, including the name, date of administration, and site of administration, on the CRF.

After vaccination:

- Site staff will observe the participant for 30 minutes after vaccination for any reactions. Record any AEs on the CRF and on an SAE form as applicable. Record concomitant medication used to treat NDCMCs and SAEs.
- Confirm that the e-diary is working and review instructions if necessary. Remind the participant's parent(s)/legal guardian(s) to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination. Provide a thermometer or measuring device if needed.
- Ask the participant's parent(s)/legal guardian(s) to contact the investigator site staff or investigator as soon as possible during the 7-day postvaccination period if the participant experiences fever  $>40.0^{\circ}\text{C}$  ( $>104.0^{\circ}\text{F}$ ), redness or swelling at the injection site measuring  $>14$  measuring device units ( $>7$  cm), or severe injection site pain (causes limitation of limb movement) to determine if the event requires further assessment by the investigator.
- Remind the participant's parent(s)/legal guardian(s) to contact the investigator or investigator site staff as soon as possible if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs during the study period.
- Remind the participant's parent(s)/legal guardian(s) that use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).
- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.
- 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 ongoing safety review.

### 8.10.3. Visit 3 (Dose 3: 42 to 63 Days After Dose 2)

- Ensure and document that the participant continues to be eligible for the study (see [Section 7.2](#) for participant withdrawal information) and none of the temporary delay criteria are met ([Section 5.5](#)).
- Confirm whether the parent(s)/legal guardian(s) still possesses the participant contact card.
- Review the participant's e-diary data with the participant's parent(s)/legal guardian(s); collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.
- Determine whether any AEs (includes nonserious AEs, SAEs, and NDCMCs) have occurred since the previous visit and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in [Section 10.3](#), and record concomitant medications used to treat NDCMCs and SAEs.
- Measure and record the participant's prevaccination temperature using a method appropriate for the age of the child, according to routine local practice (°F/°C).
- Administer a single 0.5-mL injection of 20vPnC or 13vPnC into the left anterolateral thigh.
- If applicable, administer routine pediatric vaccinations into a limb other than the site of 20vPnC or 13vPnC injection and capture all details of the concomitant vaccine given on the same day as investigational product administration, including the name, date of administration, and site of administration, on the CRF.

#### After vaccination:

- Site staff will observe the participant for 30 minutes after vaccination for any reactions. Record any AEs on the CRF and on an SAE form as applicable. Record concomitant medications used to treat SAEs and NDCMCs.
- Confirm that the e-diary is working appropriately and review instructions if needed. Remind the participant's parent(s)/legal guardian(s) to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination. Provide a thermometer and/or measuring device if needed.
- Ask the participant's parent(s)/legal guardian(s) to contact the investigator site staff or investigator as soon as possible during the 7-day postvaccination period if the participant experiences fever  $>40.0^{\circ}\text{C}$  ( $>104.0^{\circ}\text{F}$ ), redness or swelling at the injection site measuring  $>14$  measuring device units ( $>7$  cm), or severe injection site pain (causes limitation of limb movement) to determine if the event requires further assessment by the investigator.



- Remind the participant's parent(s)/legal guardian(s) to contact the investigator or investigator site staff immediately if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs during the study period.
- Remind the participant's parent(s)/legal guardian(s) that use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).
- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.
- 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 ongoing safety review.

#### **8.10.4. Visit 4 (Follow-up: 28 to 42 to Days After Dose 3)**

- Ensure and document that the participant continues to be eligible for the study (see [Section 7.2](#) for participant withdrawal information).
- Confirm whether the parent(s)/legal guardian(s) still possesses the participant contact card.
- 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.
- Remind the participant's parent(s)/legal guardian(s) that use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).
- Remind the participant's parent(s)/legal guardian(s) to contact the investigator or investigator site staff as soon as possible if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs during the study period.
- The investigator or an authorized designee completes the CRF.

#### 8.10.5. Visit 5 (Dose 4: 365 to 455 Days of Age)

NOTE: For the United States and Puerto Rico country-specific amendment related to Visit 5, please refer to Section 10.9.

- Ensure and document that the participant continues to be eligible for the study (see [Section 7.2](#) for participant withdrawal information) and none of the temporary delay criteria are met ([Section 5.5](#)).
- Confirm whether the parent(s)/legal guardian(s) still possesses the participant contact card.
- 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. Measure and record the participant's prevaccination temperature using a method appropriate for the age of the child, according to routine local practice (°F/°C).
- Administer a single 0.5-mL injection of investigational product (20vPnC or 13vPnC) into the anterolateral left thigh.
- If applicable, administer routine pediatric vaccinations into a limb other than the site of 20vPnC or 13vPnC injection and capture all details of the concomitant vaccine given on the same day as investigational product administration, including the name, date of administration, and site of administration, on the CRF.

After vaccination:

- Site staff will observe the participant for 30 minutes after vaccination for any reactions. Record any AEs on the CRF and on an SAE form as applicable. Record concomitant medications used to treat SAEs and NDCMCs.
- Issue the participant's parent(s)/legal guardian(s) an e-diary (device or application). Review and 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 investigational product vaccination. Provide the participant's parent(s)/legal guardian(s) with a thermometer or measuring device if needed.
- Ask the participant's parent(s)/legal guardian(s) to contact the investigator site staff or investigator immediately during the 7-day postvaccination period if the participant experiences fever >40.0°C (>104.0°F), redness or swelling at the injection site measuring >14 measuring device units (>7 cm), or severe injection site pain (causes limitation of limb movement) to determine if the event requires further assessment by the investigator.

- Remind the 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.
- Remind the participant's parent(s)/legal guardian(s) that use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).
- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.
- 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 ongoing safety review.

#### **8.10.6. Visit 6 (Follow-up: 28 to 42 to Days After Dose 4)**

NOTE: For the United States and Puerto Rico country-specific amendment related to Visit 6, please refer to [Section 10.9](#).

- Ensure and document that the participant continues to be eligible for the study (see [Section 7.2](#) for participant withdrawal information).
- Confirm whether the parent(s)/legal guardian(s) still possesses the participant contact card.
- 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.
- Remind the participant's parent(s)/legal guardian(s) to contact the investigator or investigator site staff immediately if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs.
- The investigator or an authorized designee completes the CRF.

#### **8.10.7. Visit 7 (Follow-up: 168 to 196 Days After Dose 4)**

NOTE: For the United States and Puerto Rico country-specific amendment related to Visit 7, please refer to [Section 10.9](#).

- Contact the participant's parent(s)/legal guardian(s) by telephone approximately 6 months after the last study vaccination; this contact should be attempted for all participants who have received at least 1 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 SAEs and NDCMCs.
- The investigator or an authorized designee completes the CRF and the source documents.

#### **8.10.8. Unscheduled Visits**

If the participant's parent(s)/legal guardian(s) reports redness or swelling at the injection site measuring >14 measuring device units (>7 cm) 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. A visit should be scheduled as soon as possible to assess the extent of the injection site reaction, unless any of the following is true:

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

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

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

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

- Measure 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, irritability, or local reaction within 7 days of vaccination.

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

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

## 9. STATISTICAL CONSIDERATIONS

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

## 9.1. Estimands and Statistical Hypotheses

### 9.1.1. Estimands

The primary objective of the study is to describe the safety profile of 20vPnC in healthy infants. Estimands to address the primary objective are provided in [Section 3](#). In the safety evaluation, missing e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

There is no formal hypothesis test for any safety results.

## 9.2. Sample Size Determination

The study size in each vaccine group is not based on any formal hypothesis test for any safety endpoints. All statistical analyses will be descriptive.

The primary safety objectives include the endpoints for AEs reported between Dose 1 and 1 month after Dose 3 and also between Dose 4 and 1 month after Dose 4. The number of participants receiving 20vPnC is 1000, which provides a greater than 95% chance of observing at least 1 AE in this group, assuming a true rate of at least 0.3% (Table 4).

**Table 4. Probability of Detecting at Least 1 AE in the 20vPnC and 13vPnC Groups**

Group	Sample Size	True Rate of AEs	Probability of Observing at Least 1 AE
20vPnC	1000	0.1%	63.2%
		0.2%	86.5%
		0.3%	95.0%
		0.4%	98.2%
		0.5%	99.3%
13vPnC	500	0.1%	39.4%
		0.2%	63.2%
		0.3%	77.7%
		0.4%	86.5%
		0.5%	91.8%

## 9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Safety	All randomized participants who receive at least 1 dose of the investigational product and have safety data after any dose.

## 9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analysis in [Section 9.5.1](#) 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 CCI endpoints, as applicable.

### 9.4.1. Safety Analyses

All safety analyses will be performed on the safety population.

Endpoint	Statistical Analysis Methods
Primary	<ul style="list-style-type: none"><li>Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each dose will be presented by severity cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% confidence intervals (CIs). Between-group differences (20vPnC – 13vPnC) in percentage and 2-sided 95% CIs will be provided. The Miettinen and Nurminen method will be used to derive the 95% CI for the difference in percentages between vaccine groups.</li><li>AEs will be categorized according to Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered “relatively common”; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, the 95% CIs for the difference in percentage of participants reporting the events between the 20vPnC and 13vPnC groups will be calculated using the Miettinen and Nurminen method. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference in percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. There is no Tier 1 event identified for 20vPnC at this stage. Descriptive summary statistics (counts and percentages and the associated Clopper-Pearson 95% CIs) will be provided for Tier 3 events for each vaccine group.</li><li>SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs and NDCMCs from Dose 1 to 6 months after Dose 4 will be provided for each vaccine group.</li></ul> <p>The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.</p>
Secondary	<ul style="list-style-type: none"><li>There are no secondary endpoints in the study.</li></ul>

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## 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 Dose 4 from all participants may be analyzed (Primary Analysis 1) by the study team when available (at which time the study team will be unblinded). Safety data from 1 month after Dose 4 through 6 months after Dose 4 will be analyzed (Primary Analysis 2) and reported after the final visit.

The investigator site staff will remain blinded to participant vaccine group until the last participant completes the final visit telephone call.

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## **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 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).

#### **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](http://www.clinicaltrials.gov) (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or [www.pfizer.com](http://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](http://www.clinicaltrials.gov)

Pfizer posts clinical trial US Basic Results on [www.clinicaltrials.gov](http://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. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

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

#### EudraCT

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

[www.pfizer.com](http://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](http://www.pfizer.com) for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to [www.clinicaltrials.gov](http://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 a participant's parent(s)/legal guardian(s) calls that number, he or she will be directed back to the investigator site.

## 10.2. Appendix 2: Clinical Laboratory Tests

Not applicable.

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

### 10.3.1. Definition of AE

<b>AE Definition</b>
<ul style="list-style-type: none"><li>• 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.</li><li>• 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.</li></ul>

<b>Events Meeting the AE Definition</b>
<ul style="list-style-type: none"><li>• 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).</li><li>• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.</li><li>• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.</li><li>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.</li><li>• 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.</li><li>• 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.</li></ul>



<b>Events NOT Meeting the AE Definition</b>
<ul style="list-style-type: none"> <li>• Events that, in the clinical judgment of the investigator, are 1) consistent with normal growth and development and 2) do not differ significantly in frequency or severity from expected, are not generally to be considered AEs. Examples may include, but are not limited to, teething, contact diaper rash, spitting up, colic, or typical fussiness/crying in infants and children.</li> <li>• 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.</li> <li>• 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.</li> <li>• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.</li> <li>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).</li> <li>• 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.</li> </ul>

### 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).

<b>An SAE is defined as any untoward medical occurrence that, at any dose:</b>
<b>a. Results in death</b>
<b>b. Is life-threatening</b> 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.

**An SAE is defined as any untoward medical occurrence that, at any dose:**

**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.

#### 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 serious adverse events on the Vaccine SAE Reporting Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious 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.

<b>Safety Event</b>	<b>Recorded on the CRF</b>	<b>Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness</b>
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	None	All (and exposure during pregnancy [EDP] supplemental form for EDP)

- 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.

### Assessment of Causality

- 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

<b>SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool</b>
<ul style="list-style-type: none"><li>• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.</li><li>• 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.</li><li>• The site will enter the SAE data into the electronic system as soon as the data become available.</li><li>• 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.</li><li>• 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.</li></ul>



<b>SAE Reporting to Pfizer Safety via Vaccine SAE Reporting Form</b>
<ul style="list-style-type: none"><li>• Facsimile transmission of the Vaccine SAE Reporting Form is the preferred method to transmit this information to Pfizer Safety.</li><li>• 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.</li><li>• 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.</li></ul>

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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 ( $\times$  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 ( $>2 \times$  ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above  $3 \times$  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  $>3 \times \text{ULN}$  AND a TBili value  $>2 \times \text{ULN}$  with no evidence of hemolysis and an alkaline phosphatase value  $<2 \times \text{ULN}$  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  $>3 \times \text{ULN}$ ; or  $>8 \times \text{ULN}$  (whichever is smaller).
  - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least  $1 \times \text{ULN}$  **or** if the value reaches  $>3 \times \text{ULN}$  (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 Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

##### Definitions of a Medical Device Incident

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).

Medical Device Incident Definition
<ul style="list-style-type: none"><li>• A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.</li><li>• Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of healthcare personnel.</li></ul>

##### It is sufficient that:

- An **incident** associated with a device happened.

AND

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness;
- Permanent impairment of body function or permanent damage to body structure;
- Condition necessitating medical or surgical intervention to prevent one of the above;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

#### **Examples of Incidents**

- A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A participant's study intervention is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A participant's health deteriorates due to medical device failure.

### **Documenting Medical Device Incidents**

#### **Medical Device Incident Documentation**

- Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form.
- For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in [Appendix 3](#).
- The CRF will be completed as thoroughly as possible and signed by the investigator before transmittal to the sponsor or designee.
- It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by the sponsor) at the time of the initial AE or SAE report and 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 an incident. This includes any amendment to the device design to prevent recurrence.

## **10.9. Appendix 9: Amendment 1 Country-Specific Requirements – Applicable to United States and Puerto Rico Only**

Per Protocol Amendment 1, the following list summarizes the modifications of the protocol that are specific to sites in the United States and Puerto Rico only. The modifications impact Visit 5 and Visit 7 timing, and add flexibility in the format of Visit 6 as follows:

- Per Protocol Amendment 1: The last day to be eligible for Dose 4 (Visit 5) is 20 Apr 2022. Participants who have not received Dose 4 by this date are ineligible and will be discontinued per Section 7 of the protocol.
- Per Protocol Amendment 1: Visit 6 may be conducted by telephone.
- Per Protocol Amendment 1: The window for Visit 7 is modified for participants who have Visit 5 (receive Dose 4) after 16 Feb 2022:
  - Visit 5 performed on 17 Feb 2022 through 14 Mar 2022: the target Visit 7 window remains 168 to 196 days after Visit 5, but Visit 7 is to be completed by 31 Aug 2022, whichever is earlier.
  - Visit 5 performed on 15 Mar 2022 through 01 Apr 2022: the window is 145 to 168 days after Visit 5, or until 31 Aug 2022, whichever is earlier.
  - Visit 5 performed on 02 Apr 2022 through 20 Apr 2022: the window is 126 to 145 days after Visit 5, or until 31 Aug 2022, whichever is earlier.

## 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
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	creatinine kinase
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRM <sub>197</sub>	cross-reactive material 197
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
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	
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
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation

Abbreviation	Term
ID	identification
IgG	immunoglobulin G
IND	investigational new drug application
INR	international normalized ratio
IPD	invasive pneumococcal disease
IP manual	investigational product manual
IRB	institutional review board
IRT	interactive response technology
ISF	investigator site file
IWR	interactive Web-based response
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
PCD	primary completion date
PI	principal investigator
PPSV23	23-valent pneumococcal polysaccharide vaccine
PT	prothrombin time
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
TBili	total bilirubin
ULN	upper limit of normal
US	United States
USPI	United States package insert
VT	vaccine-type
WHO	World Health Organization

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## Document Approval Record

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A PHASE 3, RANDOMIZED, DOUBLE-BLIND TRIAL TO EVALUATE  
THE SAFETY OF A 20-VALENT PNEUMOCOCCAL CONJUGATE VA  
CCINE IN HEALTHY INFANTS

**Signed By:**

**Date(GMT)**

**Signing Capacity**

PPD

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Final Approval

PPD

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