



**A PHASE 3, RANDOMIZED, DOUBLE-BLIND TRIAL TO EVALUATE THE  
SAFETY AND IMMUNOGENICITY OF A 20-VALENT PNEUMOCOCCAL  
CONJUGATE VACCINE IN PNEUMOCOCCAL VACCINE-NAÏVE ADULTS 18  
YEARS OF AGE AND OLDER**

<b>Investigational Product Number:</b>	PF-06482077
<b>Investigational Product Name:</b>	20-valent Pneumococcal Conjugate Vaccine (20vPnC)
<b>United States (US) Investigational New Drug (IND) Number:</b>	CCI
<b>European Clinical Trials Database (EudraCT) Number:</b>	2018-004279-11
<b>Protocol Number:</b>	B7471007
<b>Phase:</b>	3

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**Document History**

Document	Version Date	Summary of Changes
Amendment 2	11 February 2019	<p><b>Section 1.3:</b> Added benefit-risk assessment (country specific-amendment, required for Sweden by the Swedish Medical Products Agency [MPA]).</p> <p>European Clinical Trials Database (EudraCT) Number: Updated to 2018-004279-11.</p>
Amendment 1	25 September 2018	<p>Added editorial changes throughout the document to improve clarity and to correct typographic errors.</p> <p>Protocol Summary: Revised to reflect the modifications made in the body of the protocol.</p> <p>Schedule of Activities: Expanded the age range for Cohort 1 to include subjects 65 years of age and older; added flexibility to the clinical assessment wording.</p> <p><b>CCI</b> [REDACTED]</p> <p>Sections 2.1, 2.2, 2.5, and 2.6: Revised the age range in applicable objectives and applicable endpoints to include adults 65 years of age and older.</p> <p>Section 3: Added the potential for investigator sites in Europe, increased the number of study subjects, updated the age range in Cohort 1, added information regarding approximate target enrollment numbers for certain age groups, and added information regarding age stratification.</p> <p>Section 4.1: Revised the Cohort 1 age range to include subjects 65 years of age and older. Revised the</p>

		<p>inclusion criteria to reflect flexibility in the clinical assessment.</p> <p>Sections 6.1 and 6.2: Revised the scope of clinical assessment, allowing for physical examination based on medical history.</p> <p>Section 7.2: Revised the section to reflect clinical assessment wording. Removed Fahrenheit and adjusted the temperature ranges in Table 7 to close any gaps between the ranges.</p> <p>CCI [REDACTED]</p> <p>Section 8. Added instruction for the investigator to contact the sponsor or designee for SAEs occurring within 30 days after vaccination.</p> <p>Section 9: Revised the Data Analysis/Statistical Methods summary to reflect the modifications made in the body of the protocol.</p> <p>Section 9.1.1: Updated the study size and power information for Cohort 1 with the updated study size. CCI [REDACTED].</p> <p>Section 9.1.2: Clarified that the immunogenicity bridging analysis will be performed between each of Cohort 2 and Cohort 3 and the subset of subjects 60 through 64 years of age in Cohort 1.</p> <p>CCI [REDACTED]</p> <p>CCI [REDACTED]</p> <p>CCI [REDACTED]</p>
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Original Protocol	13 July 2018	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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## PROTOCOL SUMMARY

### **Background and Rationale**

*Streptococcus pneumoniae* are gram-positive encapsulated cocci that have been a leading cause of bacteremia, bacterial meningitis, pneumonia, and acute otitis media (AOM) and continue to be a major global public health concern. Serious pneumococcal disease may occur at any age; however, children <5 years and adults ≥65 years of age are at particularly increased risk. Individuals with certain comorbidities and immunocompromising conditions are also at risk. *S pneumoniae* remains an important cause of serious disease in the United States and worldwide. Globally, pneumococcal pneumonia was estimated to cause approximately 1,517,000 deaths in 2015 and, across all ages, accounted for approximately 55% of deaths due to lower respiratory tract infections.

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, only a subset of serotypes are more commonly associated with severe disease. Pneumococcal disease can be prevented with polysaccharide-based vaccines that induce antibody responses with functional (opsonophagocytic) activity and target the capsular serotypes responsible for disease. Pneumococcal vaccines that contain free polysaccharides, such as the licensed 23-valent pneumococcal polysaccharide vaccine (PPSV23) formulated with capsular polysaccharides for 23 pneumococcal serotypes, elicit a T-cell-independent immune response. These vaccines are poorly immunogenic for many of the serotypes contained in the vaccine in children less than 2 years of age, immunocompromised populations, and older adults. They do not induce memory responses in any population, and have limited or no protection against nonbacteremic disease, including community-acquired pneumonia (CAP). Pneumococcal conjugate vaccines, which contain capsular polysaccharides covalently linked to a protein carrier, elicit a T-cell-dependent immune response inducing protective responses in young children, older adults, and populations with high-risk conditions, as well as memory responses and protection against nonbacteremic disease.

Prevnar<sup>®</sup> (7-valent pneumococcal conjugate vaccine), which was licensed in the United States in 2000, and Prevnar 13<sup>®</sup> (13-valent pneumococcal conjugate vaccine [13vPnC]), which was licensed in the United States in 2010, are pneumococcal conjugate vaccines containing 7 and 13 capsular polysaccharides, respectively. The pneumococcal capsular polysaccharides in those vaccines are individually conjugated to cross-reactive material 197 (CRM<sub>197</sub>), a nontoxic variant of diphtheria toxin. These vaccines target serotypes that caused the majority of pneumococcal disease in infants and older adults at the time of their introduction. They have demonstrated efficacy/effectiveness against vaccine-type (VT) invasive pneumococcal disease (IPD), AOM, and pneumonia and the ability to reduce nasopharyngeal carriage and transmission, resulting in indirect beneficial effects.

Pfizer is developing a new 20-valent pneumococcal conjugate vaccine (20vPnC) candidate to further expand protection against the global burden of vaccine-preventable pneumococcal disease in children and adults over that of Prevnar 13. 20vPnC has the same composition as Prevnar 13, but contains an additional 7 pneumococcal conjugates to protect against serotypes responsible for a substantial burden of remaining pneumococcal disease. 20vPnC uses the same platform as Prevnar and Prevnar 13 and contains components that have undergone extensive clinical research. Safety and immunogenicity data from a 20vPnC Phase 1 study conducted in healthy adults 18 through 49 years of age and from a Phase 2 study in adults 60 through 64 years of age demonstrate 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 adult and pediatric populations. See the 20vPnC investigator's brochure for additional details.

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The Phase 3 study described in this protocol will provide safety data in adults  $\geq 18$  years of age and provide key immunogenicity data in each of 3 specific age groups (18 through 49, 50 through 59, and  $\geq 60$  years of age).

### **Study Design**

This Phase 3, multicenter, randomized, double-blind study will be conducted at investigator sites in the United States and Europe. Approximately 3880 adults 18 years of age and older with no history of pneumococcal vaccination will be enrolled into 1 of 3 cohorts based on their age at enrollment, and randomized to 1 of 2 vaccine groups (20vPnC or control).

Cohort 1: Approximately 3000 subjects 60 years of age and older at enrollment will be assigned to Cohort 1 and will be randomized (1:1) into 1 of 2 vaccine groups. Each subject will receive either 20vPnC or 13vPnC (control vaccine) at Vaccination 1. Subjects in Cohort 1 who received 20vPnC at Vaccination 1 will receive saline at Vaccination 2. Subjects in Cohort 1 who received 13vPnC at Vaccination 1 will receive PPSV23 at Vaccination 2. Approximately 2000 subjects 60 through 64 years of age and 1000 subjects 65 years of age and older will be enrolled and stratified by age.

Cohort 2: Approximately 440 subjects 50 through 59 years of age at enrollment will be assigned to Cohort 2 and randomized (3:1) into 1 of 2 vaccine groups to receive 20vPnC or 13vPnC at Visit 1.

Cohort 3: Approximately 440 subjects 18 through 49 years of age at enrollment will be assigned to Cohort 3 and randomized (3:1) into 1 of 2 vaccine groups to receive either 20vPnC or 13vPnC at Visit 1.

On Day 1 (Visit 1), subjects will be assessed for eligibility, have blood drawn for immunogenicity assessments, and receive 20vPnC or 13vPnC. Subjects will be observed for at least 30 minutes after vaccination by blinded site staff, who will record adverse events (AEs) occurring during that time. Subjects will also receive safety follow-up and electronic diary (e-diary) instructions at the visit. Prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) occurring within 7 days after vaccination and prompted local

reactions (redness, swelling, and pain at the injection site) occurring at the 20vPnC or 13vPnC injection site within 10 days after vaccination will be collected daily in the e-diary. Use of antipyretic/pain medications will be collected daily in an e-diary for 7 days after vaccination.

**Subjects in Cohort 1** will return for Visit 2 (28 to 42 days after Visit 1), and information will be collected from the subjects on AEs, serious adverse events (SAEs), newly diagnosed chronic medical conditions (NDCMCs), and e-diary follow-up (as needed). Blood will be drawn for immunogenicity assessments. Saline will be administered to subjects who previously received 20vPnC, and PPSV23 will be administered to subjects who previously received 13vPnC, by a third-party unblinded site staff member. Subjects will be observed for at least 30 minutes after vaccination by blinded site staff, who will record AEs occurring during that time. Subjects will also be reminded about safety follow-up.

The subjects in Cohort 1 will return for Visit 3 (28 to 42 days after Visit 2) and information will be collected from the subjects on AEs, SAEs, and NDCMCs. Blood will be drawn for immunogenicity assessments.

**Subjects in Cohorts 2 and 3** will return for Visit 2 (28 to 42 days after Visit 1), and information will be collected from the subjects on AEs, SAEs, NDCMCs and e-diary follow-up (as needed). Blood will be drawn for immunogenicity assessments.

**Cohorts 1, 2, and 3** will have a final visit, approximately 6 months [168 to 196 days] after Visit 1; for this visit, the sites will contact the subject in all cohorts via telephone to inquire about SAEs, NDCMCs, and nonstudy vaccinations, as well as concomitant medications used to treat SAEs or NDCMCs.

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## **Objectives and Endpoints**

### **Primary Safety Objective (All Cohorts)**

- To describe the safety profile of 20vPnC in adults 18 years of age and older.

### **Primary Safety Endpoints (All Cohorts)**

- Reported prompted local reactions (redness, swelling, and pain at the injection site) within 10 days after vaccination.
- Reported prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) within 7 days after vaccination.

- Reported AEs within 1 month after vaccination.
- Reported SAEs and NDCMCs within 6 months after vaccination.

#### **Primary Immunogenicity Objectives – Cohort 1 (60 Years of Age and Older)**

- To demonstrate that the immune responses to the 13 serotypes in 13vPnC (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) induced by 20vPnC in adults 60 years of age and older are noninferior to the immune response induced by 13vPnC.
- To demonstrate that the immune responses to the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) induced by 20vPnC in adults 60 years of age and older are noninferior to the immune response induced by PPSV23.

#### **Primary Immunogenicity Endpoint – Cohort 1 (60 Years of Age and Older)**

- Serotype-specific opsonophagocytic activity (OPA) titers 1 month after vaccination.

#### **Secondary Objective – Cohort 2 (50 Through 59 Years of Age)**

- To demonstrate that the immune responses to the 20 serotypes in 20vPnC induced in adults 50 through 59 years of age are noninferior to the immune responses induced by 20vPnC in adults 60 through 64 years of age.

#### **Secondary Endpoint – Cohort 2 (50 Through 59 Years of Age)**

- Serotype-specific OPA titers 1 month after vaccination.

#### **Secondary Objective – Cohort 3 (18 Through 49 Years of Age)**

- To demonstrate that the immune responses to the 20 serotypes in 20vPnC induced in adults 18 through 49 years of age are noninferior to the immune responses induced by 20vPnC in adults 60 through 64 years of age.

#### **Secondary Endpoint – Cohort 3 (18 Through 49 Years of Age)**

- Serotype-specific OPA titers 1 month after vaccination.

#### **Secondary Objective – All Cohorts**

- To describe the immune responses to 20vPnC in adults 60 years of age and older, 50 through 59 years of age, and 18 through 49 years of age.

#### **Secondary Endpoints – All Cohorts**

- Fold rise in serotype-specific OPA titers from before to 1 month after vaccination.

- $\geq 4$ -Fold rise in serotype-specific OPA titers from before to 1 month after vaccination.
- Serotype-specific OPA titers greater than or equal to the lower limit of quantitation ( $\geq$  LLOQ) 1 month after vaccination.

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**Statistical Methods**

Primary immunogenicity objectives will be evaluated by formal hypothesis tests for noninferiority between the 20vPnC/saline and 13vPnC/PPSV23 vaccine groups in Cohort 1. Noninferiority for a serotype will be declared if the lower bound of the 2-sided confidence interval for the serotype-specific OPA geometric mean ratio (GMR) of 20vPnC relative to control is greater than 0.5 (2-fold criterion). CCI [REDACTED]

[REDACTED] Serotype-specific OPA geometric means, serotype-specific OPA geometric mean fold rises, percentages of subject with OPA titers  $\geq$  LLOQ, and  $\geq 4$ -fold rises in OPA titers, CCI [REDACTED] will also be provided for each vaccine group and each cohort.

The safety objectives will be evaluated by summary statistics for local reactions, systemic events, and AEs, including SAEs and NDCMCs for each vaccine group and each cohort.

## SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to the Study Procedures and Assessments sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

**Table 1. Cohort 1 (60 Years of Age and Older): Schedule of Activities**

Visit Number	1	2	3	4
Visit Description	Vaccination 1	Vaccination 2	Follow-up After Vaccination 2	6-Month Safety Collection
Visit Type	Clinic Visit	Clinic Visit	Clinic Visit	Telephone Contact
Visit Window (Days)	Day 1	28 to 42 Days After Vaccination 1	28 to 42 Days After Vaccination 2	168 to 196 Days After Vaccination 1
Obtain informed consent	X			
Assign subject number	X			
Record demography	X			
Conduct clinical assessment, including collecting medical history data and smoking history	X			
Record medications currently being taken for medical conditions	X			
Record nonstudy vaccinations and concomitant medications <sup>a</sup>	X	X	X	X
Measure height and weight	X			
Measure prevaccination oral temperature	X	X		
Contraception check, if applicable <sup>b</sup>	X	X	X	
Review inclusion and exclusion criteria	X			
Review temporary delay criteria	X	X	X	
Review continued eligibility		X	X	
Assign randomization number	X			
Obtain blood sample for immunogenicity (~50 mL) <sup>c</sup>	X	X	X	
Administer investigational product	X	X		
Assess and record acute (immediate) reactions for at least 30 minutes after investigational product administration	X	X		

**Table 1. Cohort 1 (60 Years of Age and Older): Schedule of Activities**

Visit Number	1	2	3	4
Visit Description	Vaccination 1	Vaccination 2	Follow-up After Vaccination 2	6-Month Safety Collection
Visit Type	Clinic Visit	Clinic Visit	Clinic Visit	Telephone Contact
Visit Window (Days)	Day 1	28 to 42 Days After Vaccination 1	28 to 42 Days After Vaccination 2	168 to 196 Days After Vaccination 1
Provide subject with an e-diary, thermometer, and measuring device and instruct how to collect prompted local reactions, systemic events, and use of pain/antipyretic medications <sup>d</sup>	X			
Review e-diary <sup>e</sup>		X		
Collect e-diary		X		
Record and report adverse events	X-----X			
Record and report serious adverse events and newly diagnosed chronic medical conditions <sup>f</sup>	X-----X			

Abbreviation: e-diary = electronic diary,

- a. Record nonstudy vaccinations as well as concomitant medications used to treat SAEs or newly diagnosed chronic medical conditions.
- b. The investigator or designee will inform male subjects who are able to father children of the need to use highly effective contraception consistently and correctly until 28 days after the last dose of investigational product and document the conversation and the subject's affirmation in the subject's chart.
- c. Blood sample will be collected prior to vaccination.
- d. Subjects will record in an e-diary prompted local reactions and systemic events occurring within 10 and 7 days, respectively, after Vaccination 1. Use of antipyretic/pain medications will also be prompted for and collected daily in an e-diary for 7 days after Vaccination 1. Subjects will be instructed to contact the study staff if they experience redness or swelling measuring >20 measuring device units or severe pain at the injection site or any Grade 4 prompted systemic event.
- e. Designated site staff will review e-diary data online at frequent intervals for the 10 days following Vaccination 1 to evaluate subject compliance and reported events as part of the ongoing safety review and will collect the e-diary at Visit 2.
- f. A newly diagnosed chronic medical condition is defined as a disease or medical condition, not previously identified, that is expected to be persistent or otherwise long-lasting in its effects.

**Table 2. Cohort 2 (50 Through 59 Years of Age) and Cohort 3 (18 Through 49 Years of Age): Schedule of Activities**

Visit Number	1	2	3
Visit Description	Vaccination 1	Follow-up After Vaccination 1	6-Month Safety Collection
Visit Type	Clinic Visit	Clinic Visit	Telephone Contact
Visit Window (Days)	Day 1	28 to 42 Days After Vaccination 1	168 to 196 Days After Vaccination 1
Obtain informed consent	X		
Assign subject number	X		
Record demography	X		
Conduct clinical assessment, including collecting medical history data and smoking history	X		
Record medications currently being taken for medical conditions	X		
Record nonstudy vaccinations and concomitant medications <sup>a</sup>	X	X	X
Measure height and weight	X		
Measure prevaccination oral temperature	X		
Contraception check, if applicable <sup>b</sup>	X	X	
Perform urine pregnancy test for female subjects of childbearing potential	X		
Review inclusion and exclusion criteria	X		
Review temporary delay criteria	X	X	
Review continued eligibility		X	
Assign randomization number	X		
Obtain blood sample for immunogenicity (~50 mL) <sup>c</sup>	X	X	
Administer investigational product	X		
Assess and record acute (immediate) reactions for at least 30 minutes after investigational product administration	X		
Provide subject with an e-diary, thermometer, and measuring device and instruct how to collect prompted local reactions, systemic events, and use of pain/antipyretic medications <sup>d</sup>	X		
Review e-diary <sup>e</sup>		X	
Collect e-diary		X	

**Table 2. Cohort 2 (50 Through 59 Years of Age) and Cohort 3 (18 Through 49 Years of Age): Schedule of Activities**

Visit Number	1	2	3
Visit Description	Vaccination 1	Follow-up After Vaccination 1	6-Month Safety Collection
Visit Type	Clinic Visit	Clinic Visit	Telephone Contact
Visit Window (Days)	Day 1	28 to 42 Days After Vaccination 1	168 to 196 Days After Vaccination 1
Record and report adverse events	X-----X		
Record and report serious adverse events and newly diagnosed chronic medical conditions <sup>f</sup>	X-----X		

Abbreviation: e-diary = electronic diary.

- a. Record nonstudy vaccinations as well as concomitant medications used to treat SAEs or newly diagnosed chronic medical conditions.
- b. The investigator or designee will inform female subjects of childbearing potential and male subjects who are able to father children of the need to use highly effective contraception consistently and correctly until 28 days after the last dose of investigational product and document the conversation and the subject's affirmation in the subject's chart.
- c. Blood sample will be collected prior to vaccination.
- d. Subjects will record in an e-diary prompted local reactions and systemic events occurring within 10 and 7 days, respectively, after Vaccination 1. Use of antipyretic/pain medications will also be prompted for and collected daily in an e-diary for 7 days after Vaccination 1. Subjects will be instructed to contact the study staff if they experience redness or swelling measuring >20 measuring device units or severe pain at the injection site or any Grade 4 prompted systemic event.
- e. Designated site staff will review e-diary data online at frequent intervals for the 10 days following Vaccination 1 to evaluate subject compliance and reported events as part of the ongoing safety review and will collect the e-diary at Visit 2.
- f. A newly diagnosed chronic medical condition is defined as a disease or medical condition, not previously identified, that is expected to be persistent or otherwise long-lasting in its effects.

## 1. INTRODUCTION

### 1.1. Indication

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

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

### 1.2. Background and Rationale

#### 1.2.1. Pneumococcal Disease

*S pneumoniae* are gram-positive encapsulated cocci that have been 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 increased risk. Surveillance studies conducted in 2010-2012 by the Centers for Disease Control and Prevention (CDC) found that *S pneumoniae* remains among the most common bacterial pathogens identified in community-acquired pneumonia (CAP) requiring hospitalization in the United States in both children and adults.<sup>5,6</sup> Bacteremic pneumococcal pneumonia (accounting for the majority of invasive pneumococcal disease [IPD] in adults) is less common than nonbacteremic pneumococcal pneumonia (an estimated 3 or more cases of nonbacteremic pneumococcal pneumonia occur for every 1 case of bacteremic pneumonia). Both bacteremic and nonbacteremic pneumococcal pneumonia are associated with significant morbidity and mortality in all age groups.<sup>1</sup> Pneumococcal disease in older adults represents a high clinical and economic healthcare burden. In Australia the incidence of hospitalization for all-cause pneumonia in adults ≥65 years of age, from 2011 through 2012, corresponded to an incidence rate of 1347/100,000 population. Incidence rates were higher in adults ≥85 years of age (3507/100,000). Pneumococcal pneumonia accounted for 20.6% of pneumonia hospitalizations, with an incidence of 274/100,000 population.<sup>7</sup> In a study of the global burden of disease using data from 195 countries, it was estimated that in 2015 lower respiratory tract infections (LRIs) were the leading infectious cause of death and the fifth leading cause of death overall, causing 2.74 million deaths globally. Pneumococcal pneumonia caused 55.4% of LRI deaths in all ages, totaling 1,517,388 deaths; of those, approximately 400,000 deaths were in children younger than 5 years and approximately 700,000 deaths were in adults ≥70 years of age.<sup>8</sup> The CDC estimated that in 2016 there were 30,400 cases and 3690 deaths due to IPD in the United States.<sup>9</sup> As these numbers suggest, *S pneumoniae* remains an important cause of serious disease in the United States and worldwide.

The polysaccharide capsule has been identified as an important virulence factor for this pathogen. While more than 95 pneumococcal serotypes differentiated by their capsular polysaccharide composition have been identified, only a subset of serotypes are more commonly associated with severe disease.<sup>10,11</sup> Anticapsular antibodies directed against the specific serotype bind to the capsule and promote complement-mediated opsonophagocytic killing and clearance of the organism.<sup>12</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>13</sup>

## **1.2.2. Vaccines to Prevent Pneumococcal Disease**

### **1.2.2.1. Pneumococcal Polysaccharide Vaccines**

Vaccines containing free polysaccharides have been licensed since the 1970s. One such vaccine, the 23-valent pneumococcal polysaccharide vaccine (PPSV23), has been licensed in the United States since 1983.<sup>14,15</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). PPSV23 elicits a T-cell-independent immune response. Unconjugated polysaccharide vaccines do not induce robust responses in certain populations (eg, immunocompromised persons, children <2 years of age, and adults ≥65 years of age), nor do they generate immunologic memory, so their protective effect wanes over 2 to 5 years.<sup>4,15,16,17</sup> Moreover, their ability to prevent nonbacteremic pneumonia and AOM is limited or lacking.<sup>13,17,18,19</sup> They also do not have an impact on nasopharyngeal carriage, and therefore do not afford herd protection.<sup>20</sup> Another limitation is that in several studies, individuals vaccinated with pneumococcal polysaccharide vaccine had lower functional antibody responses following subsequent vaccination with either another dose of pneumococcal polysaccharide vaccine or a dose of pneumococcal conjugate vaccine, compared to the first dose of polysaccharide vaccine.<sup>21,22,23</sup> Such “hyporesponsiveness” has been observed with other polysaccharide vaccines as well, and raises concern regarding the quality of response after revaccination or natural exposure to an invading vaccine-type (VT) pneumococcus.<sup>24</sup> Despite waning immunity, these concerns of hyporesponsiveness, as well as other factors, have led most recommending bodies to restrict PPSV23 to a single lifetime dose in adults ≥65 years of age and 1 to 2 doses in most other high-risk populations.<sup>24,25,26</sup>

### **1.2.2.2. Pneumococcal Polysaccharide Conjugate Vaccines**

Pneumococcal conjugate vaccines contain polysaccharides that are covalently linked (conjugated) to an immunogenic protein. This modification results in T-cell-dependent immune responses, which have been shown to be protective in young children, older adults, and populations with high-risk conditions and also induce memory responses.<sup>16,27</sup> Prevnar<sup>®</sup> (7-valent pneumococcal conjugate vaccine [7vPnC]) was the first pneumococcal conjugate vaccine to be licensed (in the United States in 2000) and was indicated for prevention of pneumococcal disease in infants and young children. 7vPnC contained 7 pneumococcal capsular polysaccharides each conjugated to cross-reactive material 197 (CRM<sub>197</sub>), a nontoxic variant of diphtheria toxin. The pneumococcal capsular polysaccharide conjugates represented the serogroups/serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) responsible for most of the IPD and AOM in young children in the United States (80%-90% of IPD) and much of the world at the time (1998 to 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</sup>

Following introduction of 7vPnC, reduction of nasopharyngeal carriage and transmission has resulted in indirect herd effects, with a 92% reduction of VT IPD in older adults  $\geq 65$  years of age.<sup>38,39</sup>

Prevnar 13<sup>®</sup> (13-valent pneumococcal conjugate vaccine [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>27,31,40</sup> The vaccine was licensed for use in infants and young children based on comparisons of serotype-specific immunoglobulin G (IgG) to 7vPnC, with supportive data to demonstrate the functional activity of the immune responses. 13vPnC was subsequently licensed in adults based on an accelerated approval pathway demonstrating comparable serotype-specific opsonophagocytic activity (OPA) responses to PPSV23, followed by traditional approval based on demonstration of efficacy against VT CAP in CApiTA (Community-Acquired Pneumonia Immunization Trial in Adults), a randomized controlled study of adults 65 years of age and older.<sup>41</sup> Prevention of nonbacteremic VT CAP in this older adult population was also demonstrated and protection was observed through 4 years of follow-up. This is notable given the lack of definitive data showing that PPSV23 prevents nonbacteremic disease in older adults, and evidence that protection against IPD wanes significantly over time.<sup>15</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>42,43,44,45</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>46,47</sup> Surveillance data from several countries following introduction of 13vPnC into the routine infant immunization program have demonstrated vaccine effectiveness against VT IPD in the vaccinated population.<sup>48,49,50</sup>

Prevnar 13 was licensed for adults  $\geq 50$  years of age in 2011, and recommended by the Advisory Committee on Immunization Practices (ACIP) for use in adults with immunocompromising conditions in 2012. In July 2016, it was also licensed for use in adults 18 through 49 years of age. The potential burden of VT CAP in adults in the United States was demonstrated by a study conducted well after the introduction of Prevnar into the routine infant immunization schedule, suggesting potential value in direct immunization of adults rather than reliance solely on the herd effect.<sup>51</sup> The data on disease burden, combined with the results of CApiTA, led to the August 2014 ACIP recommendation for all adults  $\geq 65$  years of age to receive Prevnar 13, followed by PPSV23.<sup>26,52</sup> The recommendation for Prevnar 13 was made based on the potential added benefit in protecting against disease, particularly nonbacteremic pneumonia caused by the vaccine serotypes. The continued recommendation for PPSV23 was intended to provide expanded protection against IPD for serotypes not in Prevnar 13. However, the prevalence of IPD due to most of the serotypes contained only in PPSV23 has remained stable or slightly increased in the United States and other countries despite continued recommendation and use of PPSV23 in adults  $\geq 65$  years of age and high-risk adults.<sup>53,54,55</sup> These serotypes account for a significant amount of

pneumococcal disease, and their continued presence highlights the need for a better vaccine than PPSV23 to expand protection.

### 1.2.2.3. Rationale for 20vPnC and Study B7471007

20vPnC is being developed to further expand protection against the global burden of vaccine-preventable pneumococcal disease in children and adults over that of 13vPnC. 20vPnC contains the serotypes present in 13vPnC plus 7 new serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F). The 7 additional serotypes were selected based on their relative prevalence as a cause of IPD, their generalized geographic distribution, and other factors that would support inclusion, such as the presence of antibiotic resistance and greater disease severity (eg, meningitis, mortality).<sup>56,57,58,59,60,61,62,63,64,65,66,67,68,69</sup> These 7 serotypes are also present in PPSV23.<sup>70</sup> Adding these 7 additional serotypes to the 13 serotypes in 13vPnC is anticipated to further reduce the global burden of pneumococcal disease and provide protection comparable to, or greater than, that of PPSV23.

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>. CCI



Safety and immunogenicity data from a Phase 1 study (B7471001) conducted in healthy adults 18 through 49 years of age and from a Phase 2 study (B7471002) in adults 60 through 64 years of age demonstrate 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 adult and pediatric populations. See the 20vPnC IB for additional details.

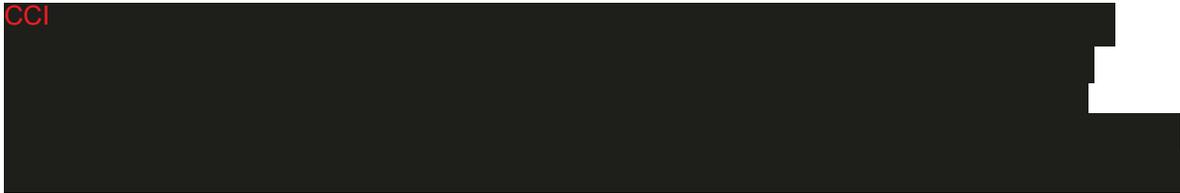
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This study is part of the clinical development program and the purpose of this study is to assess the safety and generate key immunogenicity data with 20vPnC in adults.

The pivotal immunogenicity comparison will be performed in the cohort of subjects 60 years of age and older. These subjects will receive 20vPnC and saline or 13vPnC and PPSV23 separated by a 1-month interval. This follows the Phase 2 study design (B7471002) in subjects 60 through 64 years of age and facilitates comparison of responses to all serotypes in 20vPnC to responses in licensed vaccines (13vPnC for the matched 13 serotypes, and PPSV23 for the 7 additional serotypes). Additionally, immune responses to 20vPnC in the younger age cohorts (18 through 49 years and 50 through 59 years) will be compared to 20vPnC responses in the subset of subjects 60 through 64 years of age in the older cohort.

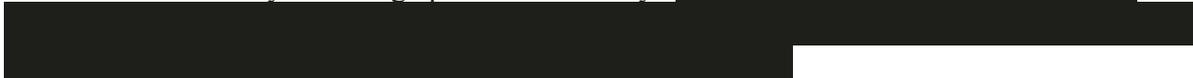
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Additional information for this compound may be found in the summary of product characteristics (for 13vPnC and PPSV23) and the single reference safety document (SRSD). The SRSD for 20vPnC is the IB. The SRSD for 13vPnC is the US package insert (USPI). The SRSD for PPSV23 is the USPI.

### 1.3. Benefit-Risk Assessment

20vPnC has been administered to 33 adults 18 through 49 years of age in the Phase 1 Study B7471001 and to 221 adults 60 through 64 years of age in the Phase 2 Study B7471002. The vaccine was well tolerated and the adverse event (AE) profile reflected events that may be observed in subjects in these age groups. The most common AEs after 20vPnC administration were primarily related to local reactions (pain, redness, swelling) and systemic events (fever, fatigue, headache, muscle pain, joint pain). 20vPnC has not been evaluated in adults older than 65 years of age prior to this study. CCI



Both 13vPnC and PPSV23 are licensed vaccines, and the most common AEs noted after vaccination are primarily related to local reactions and systemic events. Injection with saline (placebo) may produce pain and redness at the injection site.

As with any vaccine, an allergic reaction can occur. The allergic reaction can vary from skin rash to swelling of the face or lips and/or shortness of breath. A severe allergic reaction (anaphylactic shock) may also occur. There may also be additional risks related to the vaccines administered in the study that are unknown at this time.

Risks that may be associated with study procedures include risk from blood sampling, such as feeling faint, fainting, pain, swelling, bruising, and infection where blood is taken.

Safety assessments described in the protocol and reviews of safety data by the investigator, sponsor study team CCI CCI to monitor and mitigate these risks.

In the B7471001 and B7471002 studies, 20vPnC induced antibodies with functional (opsonophagocytic) activity to the pneumococcal serotypes in the vaccine; these antibodies may provide clinical benefit. 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.

13vPnC and PPSV23 are vaccines approved for the prevention of pneumococcal disease due to the serotypes in the vaccines, and may provide a clinical benefit to those receiving them.

Pfizer considers that the available information from Studies B7471001 and B7471002 with 20vPnC, the available safety profile of similar pneumococcal conjugate vaccines (ie, 13vPnC), and the limited risks from study procedures support a favorable benefit-risk profile for 20vPnC and this study.

The current IB provides additional details on the B7471001 and B7471002 studies and the potential risks and benefits of 20vPnC. Please refer to the respective summary of product characteristics/USPI for potential risks of licensed vaccines 13vPnC and PPSV23.

## **2. STUDY OBJECTIVES AND ENDPOINTS**

### **2.1. Primary Safety Objective (All Cohorts)**

- To describe the safety profile of 20vPnC in adults 18 years of age and older.

#### **2.1.1. Primary Safety Endpoints (All Cohorts)**

- Reported prompted local reactions (redness, swelling, and pain at the injection site) within 10 days after vaccination.
- Reported prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) within 7 days after vaccination.
- Reported adverse events (AEs) within 1 month after vaccination.
- Reported serious adverse events (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) within 6 months after vaccination.

### **2.2. Primary Immunogenicity Objectives – Cohort 1 (60 Years of Age and Older)**

- To demonstrate that the immune responses to the 13 serotypes in 13vPnC (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) induced by 20vPnC in adults 60 years of age and older are noninferior to the immune response induced by 13vPnC.
- To demonstrate that the immune responses to the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) induced by 20vPnC in adults 60 years of age and older are noninferior to the immune response induced by PPSV23.

#### **2.2.1. Primary Immunogenicity Endpoint – Cohort 1 (60 Years of Age and Older)**

- Serotype-specific OPA titers 1 month after vaccination.

### **2.3. Secondary Objective – Cohort 2 (50 Through 59 Years of Age)**

- To demonstrate that the immune responses to the 20 serotypes in 20vPnC induced in adults 50 through 59 years of age are noninferior to the immune responses induced by 20vPnC in adults 60 through 64 years of age.

**2.3.1. Secondary Endpoint – Cohort 2 (50 Through 59 Years of Age)**

- Serotype-specific OPA titers 1 month after vaccination.

**2.4. Secondary Objective – Cohort 3 (18 Through 49 Years of Age)**

- To demonstrate that the immune responses to the 20 serotypes in 20vPnC induced in adults 18 through 49 years of age are noninferior to the immune responses induced by 20vPnC in adults 60 through 64 years of age.

**2.4.1. Secondary Endpoint – Cohort 3 (18 Through 49 Years of Age)**

- Serotype-specific OPA titers 1 month after vaccination.

**2.5. Secondary Objective – All Cohorts**

- To describe the immune responses to 20vPnC in adults 60 years of age and older, 50 through 59 years of age, and 18 through 49 years of age.

**2.5.1. Secondary Endpoints – All Cohorts**

- Fold rise in serotype-specific OPA titers from before to 1 month after vaccination.
- $\geq 4$ -Fold rise in serotype-specific OPA titers from before to 1 month after vaccination.
- Serotype-specific OPA titers greater than or equal to the lower limit of quantitation ( $\geq$  LLOQ) 1 month after vaccination.

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### 3. STUDY DESIGN

This will be a Phase 3, multicenter, randomized, double-blind study that will be conducted at investigator sites in the United States and Europe. Approximately 3880 adults 18 years of age and older with no history of pneumococcal vaccination will be enrolled into 1 of 3 cohorts based on their age at enrollment, and randomized to 1 of 2 vaccine groups (20vPnC or control) (Table 3).

Cohort 1: Approximately 3000 subjects will be enrolled into Cohort 1, 2000 subjects will be 60 through 64 years of age and 1000 subjects will be 65 years of age and older and stratified by age. CCI

Each subject will receive either 20vPnC or 13vPnC (control vaccine) at Vaccination 1. Subjects in Cohort 1 who received 20vPnC at Vaccination 1 will receive saline at Vaccination 2. Subjects in Cohort 1 who received 13vPnC at Vaccination 1 will receive PPSV23 at Vaccination 2.

Approximately 440 subjects 50 through 59 years of age at enrollment will be assigned to Cohort 2, and randomized (3:1) to receive 20vPnC or 13vPnC at Visit 1.

Approximately 440 subjects 18 through 49 years of age at enrollment will be assigned to Cohort 3, and randomized (3:1) into 1 of 2 vaccine groups, to receive 20vPnC or 13vPnC at Visit 1.

**Table 3. Vaccinations Given to Each Cohort**

Cohort	Age	Vaccination 1 (Visit 1)	Vaccination 2 (Visit 2)	N
Cohort 1	60 years of age and older	20vPnC	Saline	1500
		13vPnC	PPSV23	1500
Cohort 2	50 through 59 years of age	20vPnC <sup>a</sup>	-	330
		13vPnC <sup>a</sup>	-	110
Cohort 3	18 through 49 years of age	20vPnC <sup>a</sup>	-	330
		13vPnC <sup>a</sup>	-	110

a. Single dose on Day 1.

On Day 1 (Visit 1), subjects will be assessed for eligibility, have blood drawn for immunogenicity assessments, and receive 20vPnC or 13vPnC. Subjects will be observed for at least 30 minutes after vaccination by blinded site staff, who will record AEs occurring during that time. Subjects will also receive safety follow-up and electronic diary (e-diary) instructions at the visit. Prompted systemic events (fever, headache, fatigue, muscle pain,

and joint pain) occurring within 7 days after vaccination and prompted local reactions (redness, swelling, and pain at the injection site) occurring at the 20vPnC or 13vPnC injection site within 10 days after vaccination will be collected daily in the e-diary. Use of antipyretic/pain medications will be collected daily in an e-diary for 7 days after vaccination.

**Subjects in Cohort 1** will return for Visit 2 (28 to 42 days after Visit 1), and information will be collected from the subjects on AEs, SAEs, NDCMCs, and e-diary follow-up (as needed). Blood will be drawn for immunogenicity assessments. Saline will be administered to subjects who previously received 20vPnC, and PPSV23 will be administered to subjects who previously received 13vPnC, by a third-party unblinded site staff member. Subjects will be observed for at least 30 minutes after vaccination by blinded site staff, who will record AEs occurring during that time. Subjects will also be reminded about safety follow-up.

The subjects in Cohort 1 will then return for Visit 3 (28 to 42 days after Visit 2), and information will be collected from the subjects on AEs, SAEs, and NDCMCs. Blood will be drawn for immunogenicity assessments.

**Subjects in Cohorts 2 and 3** will return for Visit 2 (28 to 42 days after Visit 1), and information will be collected from the subjects on AEs, SAEs, NDCMCs, and e-diary follow-up (as needed). Blood will be drawn for immunogenicity assessments.

**Cohorts 1, 2, and 3** will have a final visit, approximately 6 months (168 to 196 days) after Visit 1; for this visit, the sites will contact the subject in all cohorts via telephone to inquire about SAEs, NDCMCs, and nonstudy vaccinations, as well as concomitant medications used to treat SAEs or NDCMCs.

The applicable control groups for the assessments of the 20vPnC group for each cohort are summarized in [Table 4](#).

**Table 4. Applicable Control Groups for Safety and Immunogenicity Assessments – Cohorts 1, 2, and 3**

<b>Cohort 1</b>			
	<b>Investigational</b>	<b>Control</b>	
	<b>20vPnC</b>	<b>13vPnC<sup>a</sup></b>	<b>PPSV23<sup>b</sup></b>
Prompted local reactions	X (10 days after Visit 1)	X (10 days after Visit 1)	-
Prompted systemic events	X (7 days after Visit 1)	X (7 days after Visit 1)	-
Adverse events <sup>c</sup>	X (1 month after Visits 1 and 2)	X (1 month after Visit 1)	X (1 month after Visit 2)
Immune responses to the 13vPnC serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F	X (1 month after Visit 1)	X (1 month after Visit 1)	-
Immune responses to the additional 7 serotypes: 8, 10A, 11A, 12F, 15B, 22F, 33F	X (1 month after Visit 1)	--	X (1 month after Visit 2)

**Cohort 2 and Cohort 3**

	<b>Investigational</b>	<b>Control</b>
	<b>20vPnC</b>	<b>13vPnC</b>
Prompted local reactions	X (10 days after Visit 1)	X (10 days after Visit 1)
Prompted systemic events	X (7 days after Visit 1)	X (7 days after Visit 1)
Adverse events <sup>c</sup>	X (1 month after Visit 1)	X (1 month after Visit 1)
Immune responses to the 13vPnC serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F	X (1 month after Visit 1 - comparison is to subjects 60 through 64 years of age in Cohort 1 20vPnC group 1 month after vaccination)	--
Immune responses to the additional 7 serotypes: 8, 10A, 11A, 12F, 15B, 22F, 33F	X (1 month after Visit 1 - comparison is to subjects 60 through 64 years of age in Cohort 1 20vPnC group 1 month after vaccination)	--

- a. Control group from enrollment and vaccination with 13vPnC at Visit 1 until vaccination with PPSV23 at Visit 2.
- b. Control group after vaccination with PPSV23 at Visit 2.
- c. SAEs and newly diagnosed chronic medical conditions (NDCMCs) will be collected through 6 months after Visit 1.

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### **3.1. Duration of Subject Participation**

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

### **3.2. Duration of the Study**

Based on a 6-month enrollment period, the study duration will be approximately 12 months.

### **3.3. Number of Subjects**

Approximately 3880 subjects will be enrolled to achieve a target of 3492 evaluable subjects (assuming a 10% dropout rate). Of these, 3000 will be 60 years of age and older (Cohort 1), 440 will be 50 through 59 years of age (Cohort 2), and 440 will be 18 through 49 years of age (Cohort 3).

Subjects who withdraw or are withdrawn from the study after randomization will not be replaced, regardless of the reason for withdrawal.

## **4. SUBJECT ELIGIBILITY CRITERIA**

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

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

### **4.1. Inclusion Criteria**

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document (ICD) indicating that the subject has been informed of all pertinent aspects of the study.
2. Willing and able to comply with scheduled visits, treatment plan, and other study procedures.
3. Expected to be available for the duration of the study and can be contacted by telephone during study participation.
4. Cohort 1: Male or female adults 60 years of age and older.  
Cohort 2: Male or female adults 50 through 59 years of age.  
Cohort 3: Male or female adults 18 through 49 years of age.
5. Adults determined by clinical assessment, including medical history and clinical judgment, to be eligible for the study, including adults with preexisting stable disease,

defined as disease not requiring significant change in therapy in the previous 6 weeks or hospitalization for worsening disease within 12 weeks before receipt of investigational product.

6. **Cohort 1 only:** Female subject of nonchildbearing potential or male subject not able to father children; male subject who is able to father children and willing to use a highly effective method of contraception as outlined in this protocol until at least 28 days after the last dose of investigational product.

**Cohorts 2 and 3 only:** Female subject of childbearing potential or male subject who is able to father children, and willing to use a highly effective method of contraception as outlined in this protocol for at least 28 days after the last dose of investigational product; or female subject not of childbearing potential or male subject not able to father children.

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#### 4.2. Exclusion Criteria

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

1. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.
2. 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.
3. Previous vaccination with any licensed or investigational pneumococcal vaccine, or planned receipt through study participation.
4. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of 20vPnC, 13vPnC, or any other diphtheria toxoid-containing vaccine or PPSV23.
5. Serious chronic disorder including metastatic malignancy, severe chronic obstructive pulmonary disease (COPD) requiring supplemental oxygen, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, or any other disorder that, in the investigator's opinion, excludes the subject from participating in the study.
6. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or

may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

7. History of microbiologically proven invasive disease caused by *S pneumoniae*.
8. Subjects who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, or planned receipt through the last blood draw. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, subjects should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before investigational product administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.
9. Subjects with known or suspected immunodeficiency or other conditions associated with immunosuppression, including, but not limited to, immunoglobulin class/subclass deficiencies, generalized malignancy, human immunodeficiency virus (HIV) infection, leukemia, lymphoma, or organ or bone marrow transplant.
10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
11. Receipt of blood/plasma products or immunoglobulin, from 60 days before investigational product administration, or planned receipt through study participation.
12. Pregnant female subjects or breastfeeding female subjects (known or suspected).

#### **4.3. Temporary Delay Criteria**

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

The blood draws prior to Vaccination 1 (all cohorts) and Vaccination 2 (Cohort 1 only) should take place on the same day as the vaccination.

##### **4.3.1. Criteria for Temporarily Delaying Vaccine Administration**

- Current febrile illness (body temperature  $\geq 100.4^{\circ}\text{F}$  [ $\geq 38^{\circ}\text{C}$ ]) or other acute illness within 48 hours before investigational product administration.
- Receipt of any inactivated or otherwise nonlive vaccine within 14 days or any live vaccine within 28 days before investigational product administration.
- Receipt of short-term (<14 days) systemic corticosteroids. Investigational product administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

#### **4.3.2. Criteria for Temporarily Delaying Immunogenicity Blood Draw**

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

#### **4.4. Lifestyle Requirements**

##### **4.4.1. Contraception**

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

##### **4.5. Sponsor's Qualified Medical Personnel**

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study 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 subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

#### **5. INVESTIGATIONAL PRODUCTS**

For the purposes of this study, and per International Council for Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational products are 20vPnC, 13vPnC, PPSV23, and saline.

### 5.1. Allocation to Investigational Product

Allocation of subjects to vaccine groups will proceed through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]). The site personnel will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the subject number. The site personnel will then be provided with a randomization number and 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 subject 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 will provide the contact information and further details on the use of the IRT system.

### 5.2. Blinding of Site Personnel

Site personnel taking part in any subject randomization, assessments, interviews, data collection, or case report form (CRF) data entry, including the principal investigator (PI), will be blinded to investigational product assignments during the study.

Vaccination 1 will be administered in a double-blind fashion, as the appearance and prefilled syringes of 20vPnC and 13vPnC are identical (prefilled syringes packaged in blinded cartons).

At Vaccination 2 (Cohort 1 only), saline and PPSV23 will be prepared and administered by a third-party unblinded site staff member. All other study personnel including the PI, and the subject, will be blinded. The unblinded site staff member(s) will not participate in subject assessments.

The PI will assign the responsibility of administering saline and PPSV23 to third-party unblinded site staff who will not participate in the evaluation of any study subject. More than 1 unblinded site staff member will be assigned. A member of the study site staff or clinic pharmacy should fulfill this role. Contact between the unblinded staff member who will administer saline and PPSV23 and study subjects should be kept to a minimum.

### 5.3. Blinding of the Sponsor

Sponsor personnel directly involved in evaluating subject data will be blinded CCI [REDACTED]  
[REDACTED]  
following the principles outlined in ICH E9 guideline on Statistical Principles for Clinical Trials.<sup>71</sup> A data blinding plan will be created to describe the blinding requirements and unblinding events. CCI [REDACTED]  
[REDACTED]

Laboratory personnel performing the immunologic assays will be blinded until the database has been locked and unblinded.

#### **5.4. Breaking the Blind**

The study will be subject and investigator blinded.

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

#### **5.5. Subject Compliance**

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

#### **5.6. Investigational Product Supplies**

20vPnC, 13vPnC, PPSV23, and saline will be provided by the sponsor to the study sites.

Study vaccines will be packed and labeled as investigational product in accordance with current guidelines and applicable local and legal regulatory requirements. The formulation of the investigational products is described below.

##### **5.6.1. Dosage Form(s) and Packaging**

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

13vPnC contains saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to CRM<sub>197</sub>. CCI

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

PPSV23 is a licensed commercial product and is a clear, sterile solution consisting of a mixture of purified capsular polysaccharides from 23 serotypes of *S pneumoniae*: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F. The vaccine is formulated to contain 25 µg of each of the 23 purified polysaccharide serotypes per 0.5-mL dose of vaccine in an isotonic saline solution containing 0.25% phenol as a preservative. PPSV23 will be supplied by the sponsor to the site as packaged vials and labeled according to local regulatory requirements.

The placebo will consist of a sterile normal saline solution for injection (0.9% sodium chloride injection) and will be supplied to the site as packaged vials and labeled according to local regulatory requirements.

### **5.6.2. Preparation and Dispensing**

See the Investigational Product Manual (IP manual) or package insert 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.

Investigational product will be prepared by qualified site personnel according to the IP manual. The investigational product will be administered to blinded subjects.

### **5.7. Administration**

At Vaccination 1, a 0.5-mL dose of 20vPnC or 13vPnC will be administered intramuscularly in the deltoid muscle of the nondominant arm by a blinded site staff member (20vPnC and 13vPnC have the same appearance).

At Vaccination 2 (Cohort 1 only), a 0.5-mL dose of saline or PPSV23 will be prepared and administered by third-party unblinded site staff member(s) and will be administered intramuscularly in the deltoid muscle of the nondominant arm to blinded subjects. All other study personnel including the principal investigator, and the subject, will be blinded. The unblinded site staff members will not participate in subject assessments.

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 CRF.

### **5.8. Investigational Product Storage**

The investigator or an approved representative, eg, pharmacist, unblinded dispenser/administrator, will ensure that all investigational products, including any comparator and/or marketed products, are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

20vPnC, 13vPnC, PPSV23, and saline will be shipped to the study site after required regulatory and legal documents have been received by the sponsor.

CCI



Any storage conditions stated in the SRSD (20vPnC IB, 13vPnC USPI, and PPSV23 USPI) will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all nonworking days upon return to normal operations. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

### **5.9. Investigational Product Accountability**

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

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

#### **5.9.1. Destruction of Investigational Product Supplies**

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

### **5.10. Concomitant Treatment(s)**

#### **5.11. Prohibited Concomitant Treatments**

- Receipt of any investigational vaccines, drugs, or medical devices is prohibited during subject participation in the study.
- Receipt of nonstudy pneumococcal vaccine is prohibited during subject participation in the study.
- Receipt of blood/plasma products, immunoglobulins, and/or immunosuppressive therapy (including a  $\geq 14$ -day course of systemic corticosteroids) is prohibited during study participation.

#### **5.12. Permitted Concomitant Treatments**

- Prescription and nonprescription medications, vitamins, minerals, and herbal remedies are permitted during subject participation in the study.
- Licensed inactivated influenza vaccine may be given  $>14$  days prior to or  $>14$  days after investigational product administration (Visit 1 or Visit 2 for Cohort 1, or Visit 1 for Cohorts 2 and 3). If medically necessary (eg, pandemic), influenza vaccine may be given at any time.

- Receipt of other licensed nonstudy vaccine (except pneumococcal [prohibited] or influenza vaccine [permitted] as described above) is permitted after Visit 3 (Cohort 1 only) or after Visit 2 (Cohorts 2 and 3).
- The use of prophylactic antipyretic medication, while permitted, is not recommended on the day prior to vaccination or the day of investigational product administration.
- Inhaled/nebulized, topical (skin, eyes, or ears), or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted during subject participation in the study.

### **5.13. Recording Concomitant Treatments**

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

Details of any medications that the subject is currently taking for medical conditions at enrollment will be recorded in the CRF.

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

## **6. STUDY PROCEDURES**

The study procedures are summarized in the Schedule of Activities ([Table 1](#) and [Table 2](#)). The day of vaccination is considered to be Day 1.

### **6.1. Cohort 1**

#### **6.1.1. Cohort 1: Visit 1 (Vaccination 1 – Day 1)**

Prior to vaccination:

- Obtain written informed consent before performing any study-specific procedures.
- Assign a subject number via the IRT.
- Obtain and record the subject demography (sex, date of birth, ethnicity, and race). The complete date of birth (ie, DD-*MMM*-*YYYY*) will be collected to critically evaluate the immune response and safety profile by age.
- Obtain and record the medical history including the presence of chronic conditions (eg, diabetes, asthma, cardiac disease, COPD) and/or medical history of significance such as relevant surgical procedures.
- Assess and record smoking history.
- Record details of any medications currently being taken for any medical conditions.

- Record nonstudy vaccinations and medications as described in [Section 5.13](#).
- Measure and record the subject's height, weight, and oral temperature (°F/°C).
- Conduct a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the subject, perform a physical examination and record any findings in the source documents and, if significant, record on the medical history CRF.
- Instruct the subject to use appropriate contraceptives until 28 days after Vaccination 2, if applicable, and document the conversation and the subject's affirmation in the subject's chart.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met and that none of the temporary delay criteria are met.
- Assign a randomization number and an investigational product container number via the IRT. This must be the last step before proceeding. A site staff member will prepare the investigational product according to the IP manual.

After randomization:

- Collect a blood sample of approximately 50 mL for immunogenicity assessments prior to vaccination.
- Administer a single 0.5-mL injection of investigational product into the deltoid muscle of the nondominant arm.

After vaccination:

- Blinded site staff will observe the subject for at least 30 minutes after investigational product administration for any acute (immediate) reactions. Record any acute (immediate) reactions on the AE CRF and on an SAE form as applicable.
- Issue the subject a measuring device to measure injection site reactions and a digital thermometer and provide instructions on their use.
- Issue the subject an e-diary and provide instructions on its use and completion. Ask the subject to complete the e-diary from Day 1 to Day 10, with Day 1 being the day of vaccination.
- Ask the subject to contact the site staff or investigator immediately during the 10 days after vaccination if he or she experiences redness or swelling at the injection site measuring >20 measuring device units (>10.0 cm) or severe injection site pain (prevents daily activity) to determine if the event requires further assessment by the investigator.

- Subjects will also be instructed to contact site staff or the investigator if they experience any possible Grade 4 prompted local reaction or systemic event (refer to [Section 6.3](#)).
- Inform the subject that use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).
- Ask the subject to contact the site staff or investigator immediately if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs during the study period.
- Remind the subject to use appropriate contraceptives until 28 days after Vaccination 2, if applicable.
- Record AEs, SAEs, and NDCMCs as described in [Section 8.1.4](#).
- 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 10 days following vaccination to evaluate subject compliance and as part of the ongoing safety review.

#### **6.1.2. Cohort 1: Visit 2 (Vaccination 2 – 28 to 42 Days After Visit 1)**

Prior to vaccination:

- Record nonstudy vaccinations and medications as described in [Section 5.13](#).
- Measure and record the subject's oral temperature (°F/°C).
- Perform a contraception check (see [Section 4.4.1](#)), if applicable.
- Ensure and document that the subject continues to be eligible for the study and that none of the temporary delay criteria are met.
- Review the subject's e-diary data and collect e-diary. 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 if any AEs, SAEs, or NDCMCs have occurred since Visit 1 and follow up on any previously reported ongoing AEs, SAEs, or NDCMCs to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in [Section 8.1.4](#).
- Collect a blood sample of approximately 50 mL for immunogenicity assessments prior to vaccination.

- An unblinded site staff member will administer a single 0.5-mL injection of PPSV23 or saline into the deltoid muscle of the nondominant arm.

After vaccination:

- Blinded site staff will observe the subject for at least 30 minutes after investigational product administration for any acute (immediate) reactions. Record any acute (immediate) reactions on the AE CRF and on an SAE form as applicable.
- Ask the subject to contact the site staff or investigator immediately if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs during the study period.
- Remind the subject to use appropriate contraceptives until 28 days after vaccination, if applicable.
- The investigator or an authorized designee completes the CRF and updates the investigational product accountability records.

#### **6.1.3. Cohort 1: Visit 3 (Follow-up – 28 to 42 Days After Vaccination 2)**

- Record nonstudy vaccinations and concomitant medications as described in [Section 5.13](#).
- Perform a contraception check (see [Section 4.4.1](#)), if applicable .
- Ensure and document that the subject continues to be eligible for the study and that none of the temporary blood draw delay criteria are met.
- Determine if any AEs, SAEs, or NDCMCs have occurred since Visit 2 and follow up on any previously reported ongoing AEs, SAEs, or NDCMCs to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in [Section 8.1.4](#).
- Collect a blood sample of approximately 50 mL for immunogenicity assessments.
- Remind the subject to contact the site staff or investigator immediately if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs during the study period.
- The investigator or an authorized designee completes the CRF.

#### **6.1.4. Cohort 1: Visit 4 (6-Month Safety Collection [Telephone Contact] – 168 to 196 Days After Vaccination 1)**

- Record nonstudy vaccinations and medications as described in [Section 5.13](#).
- Determine whether any NDCMCs or SAEs have occurred since Visit 3 and follow up on any previously reported ongoing AEs, SAEs, or NDCMCs to determine the outcome

(ie, record stop dates or confirm if they are still continuing) and record as described in [Section 8.1.4](#).

- The investigator or an authorized designee completes the CRF.

## **6.2. Cohorts 2 and 3**

### **6.2.1. Cohorts 2 and 3: Visit 1 (Vaccination – Day 1)**

Prior to vaccination:

- Obtain written informed consent before performing any study-specific procedures.
- Assign a subject number via the IRT.
- Obtain and record the subject demography (sex, date of birth, ethnicity, and race). The complete date of birth (ie, DD-~~MM~~-YYYY) will be collected to critically evaluate the immune response and safety profile by age.
- Obtain and record the medical history including the presence of chronic conditions (eg, diabetes, asthma, cardiac disease, COPD) and/or medical history of significance such as relevant surgical procedures.
- Assess and record smoking history.
- Record details of any medications currently being taken for any medical conditions
- Record nonstudy vaccinations and medications as described in [Section 5.13](#).
- Measure and record the subject's height, weight, and oral temperature (°F/°C).
- Conduct a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the subject, perform a physical examination and record any findings in the source documents and, if significant, record on the medical history CRF.
- Instruct the subject to use appropriate contraceptives until 28 days after vaccination, if applicable, and document the conversation and the subject's affirmation in the subject's chart.
- Perform urine pregnancy test for female subjects of childbearing potential (see [Section 7.1](#)).
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met and that none of the temporary delay criteria are met.

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

After randomization:

- Collect a blood sample of approximately 50 mL for immunogenicity assessments prior to vaccination.
- Administer a single 0.5-mL injection of investigational product into the deltoid muscle of the nondominant arm.

After vaccination:

- Blinded site staff will observe the subject for at least 30 minutes after investigational product administration for any acute (immediate) reactions. Record any acute (immediate) reactions on the AE CRF and on an SAE form as applicable.
- Issue the subject a measuring device to measure injection site reactions and a digital thermometer and provide instructions on their use.
- Issue the subject an e-diary and provide instructions on its use and completion. Ask the subject to complete the e-diary from Day 1 through Day 10, with Day 1 being the day of vaccination.
- Ask the subject to contact the site staff or investigator immediately during the 10 days after vaccination if he or she experiences redness or swelling at the injection site measuring  $>20$  measuring device units ( $>10.0$  cm) or severe injection site pain (prevents daily activity) to determine if the event requires further assessment by the investigator.
- Subjects will also be instructed to contact site staff or the investigator if they experience any possible Grade 4 prompted local reaction or systemic event (refer to [Section 6.3](#)).
- Inform the subject that use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).
- Ask the subject to contact the site staff or investigator immediately if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs during the study period.
- Remind the subject to use appropriate contraceptives until 28 days after vaccination, if applicable.
- Record AEs, SAEs, and NDCMCs as described in [Section 8.1.4](#).

- 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 10 days following vaccination to evaluate subject compliance and as part of the ongoing safety review.

#### **6.2.2. Cohorts 2 and 3: Visit 2 (Follow-up – 28 to 42 Days After Visit 1)**

- Record nonstudy vaccinations and concomitant medications as described in [Section 5.13](#).
- Perform a contraception check (see [Section 4.4.1](#)), if applicable.
- Ensure and document that the subject continues to be eligible for the study and that none of the temporary blood draw delay criteria are met.
- Review the subject's e-diary data and collect the e-diary. 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 if any AEs, SAEs, or NDCMCs have occurred since Visit 1 and follow up on any previously reported ongoing AEs, SAEs, or NDCMCs to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in [Section 8.1.4](#).
- Collect a blood sample of approximately 50 mL for immunogenicity assessments.
- Remind the subject to contact the site staff or investigator immediately if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs during the study period.
- The investigator or an authorized designee completes the CRF.

#### **6.2.3. Cohorts 2 and 3: Visit 3 (6-Month Safety Collection [Telephone Contact] – 168 to 196 Days After Vaccination 1)**

- Record nonstudy vaccinations and medications as described in [Section 5.13](#).
- Determine whether any NDCMCs or SAEs have occurred since Visit 2 and follow up on any previously reported ongoing AEs, SAEs, or NDCMCs to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in [Section 8.1.4](#).
- The investigator or an authorized designee completes the CRF.

### 6.3. Unscheduled Visits (All Cohorts)

Following vaccination (Vaccination 1 in Cohort 1), if the subject reports redness or swelling at the injection site measuring >20 measuring device units (>10.0 cm) or severe injection site pain during the 10 days following vaccination, a telephone contact must occur as soon as possible between the investigator or medically qualified designee and the subject to assess if an unscheduled site visit is required. A site visit must be scheduled as soon as possible to assess the extent of the reaction unless any of the following is true:

- The subject is unable to attend the unscheduled visit.
- The reaction is no longer present at the time of the telephone contact.
- The subject recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error).
- The PI or authorized designee determined it was not needed.

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

If the subject is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing reactions must be assessed at the next study visit.

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

- Measure oral temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in [Section 7.2.2.1](#).
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

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

Subjects will also be instructed to contact site staff or the investigator if they experience any possible Grade 4 prompted systemic event (ie, emergency room visit or hospitalization for headache, fatigue, muscle pain, or joint pain) or local reaction (ie, necrosis, exfoliative dermatitis, or emergency room visit/hospitalization for injection site pain) within 7 or 10 days, respectively, after vaccination. Lastly, subjects will be instructed to contact site

staff or the investigator to report any significant illness, medical event, or hospitalization that occurs during the study period. The site should determine if an unscheduled visit to further evaluate the event is warranted in all such cases.

#### **6.4. Subject Withdrawal**

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

Reasons why a subject may discontinue or be withdrawn from the study by the investigator or sponsor include, but are not limited to, failure to meet entrance criteria (screening failure), AE, death, pregnancy, protocol deviation, lost to follow-up, no longer willing to participate in the study, study terminated by the sponsor, or any other reason. Subjects who have received the investigational product will not be replaced, regardless of the reason for withdrawal.

The investigator should capture the reason for withdrawal in the database for all subjects, and a follow-up telephone contact 6 months after Vaccination 1 for the collection of safety information should be completed for all subjects who have been withdrawn after administration of investigational product unless consent for further contact has been withdrawn.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also [Section 8.1.3](#)) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

#### **Withdrawal of Consent**

Subjects who request to discontinue receipt of investigational product will remain in the study and must continue to be followed for protocol specified follow-up procedures through 6 months after the first vaccination. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized

by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

### **Lost to Follow-up**

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

## **7. ASSESSMENTS**

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

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.

### **7.1. Pregnancy Testing**

For female subjects of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed immediately before administration of the investigational product. A negative pregnancy test result is required before the subject may receive the

investigational product. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy at Visit 1, the subject will be withdrawn from administration of investigational product and from the study.

## **7.2. Safety Parameters**

Safety parameters will be assessed as described in the Schedule of Activities ([Table 1](#) and [Table 2](#)), [Section 6](#), and below.

A clinical assessment, including medical history and measurement of oral temperature, will be performed on all subjects prior to vaccination to determine subject eligibility and to establish a clinical baseline. Significant medical history, significant findings from any physical examination, if performed, and temperature measurements will be documented and recorded in the source documents and/or the CRF.

Acute reactions (immediate events) within the first 30 minutes after investigational product administration will be assessed and documented as an AE or SAE, as appropriate, in the CRF.

Prompted e-diary events, including local reactions and systemic events that occur 10 and 7 days, respectively, after investigational product administration, are graded as described in [Section 7.2.2](#). Furthermore, AEs, SAEs, and NDCMCs will be collected as defined in [Section 8.1.4](#).

### **7.2.1. Subject Electronic Diary**

The subject will be asked to monitor and record local reactions for 10 days, and systemic events, fever, and antipyretic/pain medication usage for 7 days, each evening following vaccination (Vaccination 1 in Cohort 1) (Day 1 through Day 10 or Day 7, where Day 1 is the day of vaccination) using an e-diary. This allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the subject's experience at that time. Data on local reactions, specific systemic events, fever, and antipyretic/pain medication usage reported on the e-diary will be transferred electronically to the e-diary vendor, where they will be available for review by investigators, their appropriately qualified designees, and sponsor staff at all times via an internet-based portal. At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically to Pfizer for analysis and reporting.

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

The investigators (or appropriately qualified designees) are required to review the e-diary data online at frequent intervals to evaluate subject compliance and reported events as part of the ongoing safety review.

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

### **7.2.2. Grading Scale for Prompted Events**

The grading scales used in this study to assess AEs as described below are based on concepts outlined in the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.<sup>72</sup>

#### **7.2.2.1. Local Reactions**

From Day 1 through Day 10 after vaccination (Vaccination 1 in Cohort 1), where Day 1 is the day of vaccination, subjects will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the e-diary in the evening. Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21 and >21), and then categorized during analysis as mild, moderate, or severe based on the grading scale in [Table 5](#) below. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. Pain at the vaccine injection site will be assessed by the subject as mild, moderate, or severe according to the grading scale in [Table 5](#). A subject with a severe (Grade 3 or above) local reaction will be prompted to contact the investigator to assess the reaction and perform an unscheduled assessment or visit as appropriate.

Only an investigator is able to classify a subject's local reaction as Grade 4, after physical examination of the subject or documentation from another medically qualified source (eg, emergency room or hospital record) or, in the case of pain at the injection site only, telephone contact with the subject. If a subject experiences a Grade 4 local reaction, the investigator must immediately notify the sponsor. Site staff will educate the subject regarding signs and symptoms that would prompt site contact. Grade 4 reactions will be collected as an AE on the CRF. The event will be graded using the AE severity grading scale ([Section 8.3](#)).

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

**Table 5. Grading Scales for Local Reactions**

	<b>Mild Grade 1</b>	<b>Moderate Grade 2</b>	<b>Severe Grade 3<sup>a</sup></b>	<b>Grade 4<sup>b</sup></b>
Redness	5 to 10 measuring device units = >2.0 to 5.0 cm	11 to 20 measuring device units = >5.0 to 10.0 cm	>20 measuring device units = >10.0 cm	Necrosis or exfoliative dermatitis
Swelling	5 to 10 measuring device units = >2.0 to 5.0 cm	11 to 20 measuring device units = >5.0 to 10.0 cm	>20 measuring device units = >10.0 cm	Necrosis
Pain at injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity <sup>c</sup>	Emergency room visit or hospitalization for severe injection site pain

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.

- Subjects experiencing Grade 3 local reactions are required to contact the investigator site. In the event that the subject does not call, the investigator will call the subject.
- Grade 4 assessment should be made by the investigator; Grade 4 will not be collected in the e-diary but will be collected as an AE on the CRF. The severity of the local reaction should be graded using the AE severity grading scale.
- Prevents daily activity, eg, results in missed days of work or school or is otherwise incapacitating.

#### 7.2.2.2. Systemic Events

From Day 1 through Day 7 after vaccination (Vaccination 1 in Cohort 1), where Day 1 is the day of vaccination, subjects will be asked to assess headache, fatigue, muscle pain, and joint pain and to record the symptoms in the e-diary in the evening. The symptoms will be assessed by the subject as mild, moderate, or severe according to the grading scale in [Table 6](#) below. Subjects will also be instructed to contact site staff or the investigator if they experience any possible Grade 4 prompted systemic event (ie, emergency room visit or hospitalization for severe headache, severe fatigue, severe muscle pain, or severe joint pain) within 7 days after vaccination. Study staff may also contact the subject to obtain additional information on Grade 3 events entered into the e-diary.

Only an investigator is able to classify a subject's systemic event as Grade 4, after physical examination of the subject or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the subject. If a subject experiences a Grade 4 systemic event, the investigator must immediately notify the sponsor. Grade 4 events will be collected as an AE on the CRF. The event will be graded using the AE severity grading scale ([Section 8.3](#)).

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

**Table 6. Grading Scales for Systemic Events**

	<b>Mild Grade 1</b>	<b>Moderate Grade 2</b>	<b>Severe Grade 3<sup>a</sup></b>	<b>Grade 4<sup>b</sup></b>
Fatigue (tiredness)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe muscle pain
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe joint pain

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

- Prevents daily routine activity, eg, results in missed days of work or school or is otherwise incapacitating; includes use of narcotics for analgesia.
- Grade 4 assessment should be made by the investigator; Grade 4 will not be collected in the e-diary but will be collected as an AE on the CRF. The severity of the systemic event should be graded using the AE severity grading scale in [Section 8.3](#).

### 7.2.2.3. Fever

In order to record information on fever, a digital thermometer will be given to the subject with instructions on how to measure oral temperature at home. Temperature will be collected in the evening daily for 7 days following Vaccination 1 (Days 1 through 7, where Day 1 is the day of vaccination) and at any time during the 7 days that fever is suspected. Fever is defined as an oral temperature of  $\geq 100.4^{\circ}\text{F}$  ( $\geq 38.0^{\circ}\text{C}$ ). The highest temperature for each day will be recorded in the e-diary. In the event of a fever on Day 7, temperature will be collected daily until fever has resolved (1 day of temperature  $< 100.4^{\circ}\text{F}$  [ $< 38.0^{\circ}\text{C}$ ]) in order to collect a stop date in the CRF. Temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis according to Table 7 below. Temperatures reported in degrees Fahrenheit will be programmatically converted to degrees Celsius for reporting.

**Table 7. Ranges for Fever**


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$\geq 38.0^{\circ}\text{C}$  to  $38.4^{\circ}\text{C}$

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$> 38.4^{\circ}\text{C}$  to  $38.9^{\circ}\text{C}$

---

$> 38.9^{\circ}\text{C}$  to  $40.0^{\circ}\text{C}$

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$> 40.0^{\circ}\text{C}$

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Note: Fever is defined as temperature  $\geq 38.0^{\circ}\text{C}$ .

#### **7.2.2.4. Use of Antipyretic/Pain Medication**

The subject will be asked to record the use of antipyretic/pain medication (yes/no) in the e-diary in the evening daily for 7 days following Vaccination 1. The use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).

#### **7.3. Immunogenicity**

Blood samples (approximately 50 mL per sample) will be collected from all subjects at Visit 1 (prior to administration of 20vPnC or 13vPnC) and at Visit 2 (note this is before administration of saline or PPSV23 for subjects in Cohort 1). Subjects in Cohort 1 will also have blood collected at Visit 3.

The total volume of blood collected from each subject in Cohort 1 completing participation through Visit 3 will be approximately 150 mL. The total volume of blood collected from each subject in Cohort 2 or Cohort 3 completing participation through Visit 2 will be approximately 100 mL.

Sample collection, processing, storage, and shipping information can be found in the SRM or equivalent manual.

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

#### **Pneumococcal Antibody Response**

OPA titers for serotypes present in 20vPnC (1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F) will be determined on all sera collected prior to study vaccination and 1 month (28 to 42 days) after Vaccination 1 in Cohort 1, and 1 month (28 to 42 days) after vaccination in Cohorts 2 and 3. OPA titers for the 7 additional serotypes only (8, 10A, 11A, 12F, 15B, 22F, and 33F) will be determined on sera collected 1 month (28 to 42 days) after Vaccination 2 in Cohort 1.

CCI [REDACTED]

[REDACTED]

#### 7.4. Biological Samples

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

No testing of the subject's genetic material will be performed.

The subject may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the subject's genetic material is performed.

### 8. ADVERSE EVENT REPORTING

#### 8.1. Requirements

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

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), <b>except occupational exposure</b>	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of vaccine group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study.** In particular, if the SAE is fatal or life-threatening,

notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

In addition to the reporting requirements to Pfizer Safety (above), the investigator must contact the Pfizer study physician or sponsor designee directly as soon as possible after becoming aware of an SAE occurring within 30 days after vaccination. Additional information regarding such events and the reporting requirements can be found in the SRM or equivalent.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

#### **8.1.1. Additional Details on Recording Adverse Events on the CRF**

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

#### **8.1.2. Eliciting Adverse Event Information**

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a nonleading manner.

### **8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal section)**

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

### **8.1.4. Time Period for Collecting AE/SAE Information**

The time period for actively eliciting and collecting AEs and SAEs and NDCMCs (“active collection period”) for each subject begins from the time the subject provides informed consent, which is obtained before the subject’s participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product).

In Cohort 1, AEs will be recorded and reported from the signing of the ICD through Visit 3.

In Cohorts 2 and 3, AEs will be recorded and reported from the signing of the ICD through Visit 2.

For all subjects, SAEs and NDCMCs will be recorded and reported from the signing of the ICD until the final visit (approximately 6 months after Visit 1). An NDCMC is defined as a disease or medical condition, not previously identified, that is expected to be persistent or is otherwise long-lasting in its effects.

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

#### **8.1.4.1. Reporting SAEs to Pfizer Safety**

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

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

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

#### **8.1.4.2. Recording Nonserious AEs and SAEs on the CRF**

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

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

#### **8.1.5. Causality Assessment**

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

#### **8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities**

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

### **8.2. Definitions**

#### **8.2.1. Adverse Events**

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;

- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

### **8.2.2. Abnormal Test Findings**

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

### **8.2.3. Serious Adverse Events**

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);

- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Medical device complaints may meet the SAE reporting requirement criteria (see the Medical Device Complaint Reporting Requirements section). An incident is any malfunction (ie, the failure of a device to meet its performance specifications or to perform as intended; performance specifications include all claims made in the labeling for the device) that, directly or indirectly, might lead to or might have led to the death of a subject, or user, or of other persons, or to a serious deterioration in their state of health.

A serious injury that can cause a serious deterioration in state of health can include:

- A life-threatening illness, even if temporary in nature;
- A permanent impairment of a body function or permanent damage to a body structure;
- A condition necessitating medical or surgical intervention to prevent the above 2 bulleted items;

Examples: clinically relevant increase in the duration of a surgical procedure; a condition that requires hospitalization or significant prolongation of existing hospitalization;

- Any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

#### **8.2.4. Hospitalization**

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was

performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

### 8.3. Severity Assessment

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:

MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

### 8.4. Special Situations

#### 8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

#### 8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are “susceptible” to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal ( $\times$  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 subject presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations ( $>2 \times$  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 subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values  $>3 \times \text{ULN}$  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 subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
  - Preexisting AST or ALT baseline values above the normal range: AST or ALT values  $>2$  times the baseline values AND  $>3 \times \text{ULN}$ ; 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 subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase, and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history

of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

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

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

#### **8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure**

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

##### **8.4.3.1. Exposure During Pregnancy**

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until the end of the subject's participation.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy CCI.

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

##### **8.4.3.2. Exposure During Breastfeeding**

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

##### **8.4.3.3. Occupational Exposure**

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

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated

SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

#### **8.4.4. Medication Errors and Lack of Efficacy**

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors and lack of efficacy.

<b>Safety Event</b>	<b>Recorded on the CRF</b>	<b>Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness</b>
Medication errors and lack of efficacy	All (regardless of whether associated with an AE)	Only if associated with an SAE

##### **8.4.4.1. Medication Errors**

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

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject;
- The administration of expired investigational product;
- The administration of an incorrect investigational product;
- The administration of an incorrect dosage;
- The administration of investigational product that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the investigational product under question is acceptable for use.

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

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

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated 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 CT SAE Report Form **only when associated with an SAE**.

#### **8.4.4.2. Lack of Efficacy**

Lack of efficacy in an approved indication should be reported as an SAE to Pfizer Safety.

### **8.5. Medical Device Complaint Reporting Requirements**

All medical device complaints (prefilled syringes at Vaccination 1), regardless of whether the medical device complaint is associated with an AE, will be recorded on the applicable pages within the CRF. This includes potential incidents or malfunctions associated with the use of a medical device product. An incident or malfunction is an event that might have led to death or serious deterioration in health, or if it occurred again might lead to death or serious deterioration in health.

Pfizer is to be notified of all medical device complaints within 24 hours of the investigator's awareness of the event.

Medical device complaints should be forwarded to Pharmaceutical Sciences.

## **9. DATA ANALYSIS/STATISTICAL METHODS**

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

### **9.1. Sample Size Determination and Hypothesis Testing**

#### **9.1.1. Cohort 1 (Subjects 60 Years of Age and Older)**

Hypothesis testing will be used to assess noninferiority between the 20vPnC/saline and 13vPnC/PPSV23 vaccine groups in Cohort 1 (subjects 60 years of age and older) for the primary endpoint for each of the 20 serotypes. The null hypothesis for each serotype-specific OPA titer is

$$H_0: \ln(\mu_A) - \ln(\mu_B) \leq \ln(0.5)$$

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

- $\ln(\mu_A)$  is the natural log of the geometric mean OPA titer 1 month after 20vPnC administration for the 20vPnC/saline group;
- $\ln(\mu_B)$  is the natural log of the geometric mean OPA titer 1 month after 13vPnC administration for the 13vPnC/PPSV23 group when the endpoint is the geometric mean OPA titer from 1 of the shared 13 serotypes in 13vPnC or

- $\ln(\mu_B)$  is the natural log of the geometric mean OPA titer 1 month after PPSV23 administration for the 13vPnC/PPSV23 group when the endpoint is the geometric mean OPA titer from 1 of the 7 additional serotypes.

Noninferiority for serotype-specific OPA geometric mean titers (GMTs) will be formally evaluated by a CCI confidence interval (CI) for the ratio of serotype-specific OPA GMTs (20vPnC/saline group over 13vPnC/PPSV23 group) with results from 1 month after vaccination with 20vPnC (Visit 2) and 1 month after 13vPnC (Visit 2) for the 13 matched serotypes, and 1 month after PPSV23 (Visit 3) for the 7 additional serotypes from all subjects at the primary analysis. Noninferiority for a serotype will be declared if the lower bound of the CCI CI for the geometric mean ratio (GMR) of  $\text{GMT}_A/\text{GMT}_B$  is greater than 0.5 (2-fold criterion). CCI

Sample size and power for Cohort 1 are based on simulations with assumptions supported by the OPA results from an ongoing Phase 2 study of 20vPnC (B7471002) and an efficacy study of 13vPnC in subjects 65 years of age and older (CAlPiTA). Assuming the true GMRs and variance-covariance matrices for the 20 serotype-specific OPA titers from subjects 60 through 64 years of age (~ two-thirds of the evaluable population in Cohort 1) are the same as that obtained from B7471002, and with the same assumed OPA GMRs and adjustments for variance assumptions CCI from subjects  $\geq 65$  years of age (~ one-third of the evaluable population in Cohort 1), the estimated probabilities to demonstrate noninferiority for at least 18 out of 20, at least 19 out of 20, and for all 20 serotypes are approximately 99%, 96%, and 72%, respectively, assuming 1350 evaluable subjects in each group.



### 9.1.2. Cohort 2 (Subjects 50 Through 59 Years of Age) and Cohort 3 (Subjects 18 Through 49 Years of Age) Compared to Subjects 60 Through 64 Years of Age From Cohort 1

Hypothesis testing will be used to assess noninferiority between each of the 2 younger cohorts and the 60 through 64 years of age from Cohort 1 for each of the 20 serotype-specific OPA titers. Testing will be performed only for subjects receiving 20vPnC. The null hypothesis for each serotype-specific OPA titer is

$$H_0: \ln(\mu_C) - \ln(\mu_A) \leq \ln(0.5)$$

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

- $\ln(\mu_C)$  is the natural log of the geometric mean OPA titer 1 month after 20vPnC administration for the younger group, subjects 50 through 59 years of age (Cohort 2) or subjects 18 through 49 years of age (Cohort 3);
- $\ln(\mu_A)$  is the natural log of the geometric mean OPA titer 1 month after 20vPnC administration for subjects 60 through 64 years of age from Cohort 1.

Noninferiority for serotype-specific OPA GMTs will be evaluated by a 2-sided 95% CI for the ratio of serotype-specific OPA GMTs (younger/older) with results 1 month after vaccination (Visit 2) from all subjects receiving 20vPnC. Noninferiority will be declared for a serotype if the lower bound of the 2-sided 95% CI for the GMR of  $\text{GMT}_C/\text{GMT}_A$  is greater than 0.5 (2-fold criterion).

With the planned sample sizes in Cohorts 2 and 3 and assuming that approximately 900 evaluable subjects enrolled in Cohort 1 will be 60 through 64 years of age, the study has greater than 90% power to demonstrate noninferiority in serotype-specific OPA GMRs for all 20 serotypes. (CC)



## 9.2. Analysis Populations

Safety and immunogenicity results from each cohort will be analyzed separately within each cohort with the exception of the immunogenicity bridging analysis that compares the 20vPnC results from each of Cohort 2 and Cohort 3 to subjects 60 through 64 years of age from Cohort 1 as detailed in [Section 9.3.2](#).

### 9.2.1. Safety Population

The safety population will include all subjects who receive at least 1 dose of 20vPnC, 13vPnC, PPSV23, or saline and have reported safety data. Subjects will be included in the vaccine group corresponding to the vaccine actually received. The safety population will be the only analysis population for safety endpoints.

### **9.2.2. Immunogenicity Population for Cohort 1**

Two evaluable immunogenicity populations are defined for the analyses of the immunogenicity results: the evaluable 13-matched immunogenicity population and the evaluable 7-additional immunogenicity population. The evaluable 13-matched immunogenicity population will be the primary analysis population for immunogenicity results of the 13 matched serotypes in Cohort 1. This population will generally include any subject who:

1. receives the first vaccine as randomized,
2. is enrolled in the appropriate cohort based on age on the day of first vaccination (ie, 60 years of age and older in Cohort 1),
3. has Visit 2 blood collection within an appropriate window for Visit 2,
4. has at least 1 valid and determinate OPA titer for any of the 13 matched serotypes at Visit 2,
5. does not receive any prohibited vaccinations after Vaccination 1 and before Visit 2, and
6. has no other major protocol deviations as determined by the clinician.

The evaluable 7-additional immunogenicity population will be the primary analysis population for immunogenicity examination of the 7 additional serotypes in Cohort 1. This population will generally include any subject who:

1. receives the vaccine sequence (20vPnC/saline or 13vPnC/PPSV23) as randomized,
2. is enrolled in the appropriate cohort based on age on the day of first vaccination (ie, 60 years of age and older in Cohort 1),
3. has either Visit 2 blood collection for the 20vPnC/saline group or Visit 3 blood collection for the 13vPnC/PPSV23 group within appropriate windows for Visit 2 or 3, respectively,
4. has at least 1 valid and determinate OPA titer for any of the 7 additional serotypes at either Visit 2 for the 20vPnC/saline group or Visit 3 for the 13vPnC/PPSV23 group,
5. does not receive any prohibited vaccinations after Vaccination 1 and before Visit 2 from the 20vPnC/saline group, or after Vaccination 1 and before Visit 3 from the 13vPnC/PPSV23 group, and
6. has no other major protocol deviations as determined by the clinician.

Subjects will be included in the vaccine group as randomized in the analyses of evaluable subjects.

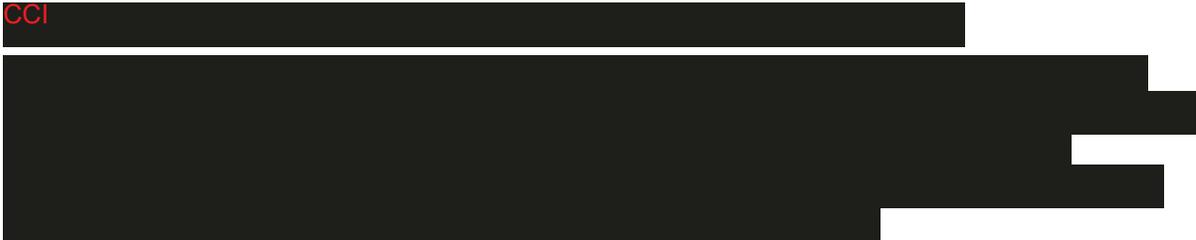
### **9.2.3. Immunogenicity Population for Comparison of Cohorts 2 and 3 to Cohort 1**

A third evaluable immunogenicity population, evaluable-20 immunogenicity population, is defined for the comparisons of subjects 60 through 64 years of age from Cohort 1 to the other 2 younger age cohorts (Cohort 2: 50 through 59 years of age; and Cohort 3: 18 through 49 years of age), limited to subjects receiving 20vPnC. This population will generally include any subject who:

1. receives the vaccine (Vaccination 1 for Cohort 1) as randomized,
2. is enrolled in the appropriate cohort based on age on the day of first vaccination (ie, 60 through 64 years of age for Cohort 1, 50 through 59 years of age for Cohort 2, and 18 through 49 years of age for Cohort 3),
3. has Visit 2 blood collection within an appropriate window for Visit 2,
4. has at least 1 valid and determinate OPA titer for any of the 20 serotypes for Visit 2,
5. does not receive any prohibited vaccinations after the vaccination at Visit 1 and before Visit 2, and
6. has no other major protocol deviations as determined by the clinician.

The evaluable-20 immunogenicity population will also be the primary analysis population for immunogenicity results from Cohort 2 and Cohort 3. Subjects will be included in the vaccine group as randomized in the analysis based on the evaluable-20 immunogenicity population.

CCI



### **9.2.5. Analysis of Demographic and Clinical Characteristics**

The demographic characteristics, which will include sex, race, ethnicity, age at the time of randomization, and smoking history, will be summarized using descriptive statistics. Demographic characteristics will be summarized for each vaccine group separately for each cohort.

### **9.3. Immunogenicity Analyses**

All statistical analyses for serotype-specific OPA titers will be done on the natural log scale, and the results will be reported on the original scale after back transformation.

Missing assay results will not be replaced or imputed. OPA LLOQ values and conventions to handle OPA titers below the LLOQ or below the limit of quantitation will be described in the SAP.

CCI [REDACTED]

### **9.3.1. Immunogenicity Analysis Comparing 20vPnC/Saline to 13vPnC/PPSV23 in Cohort 1**

#### **Analyses of OPA GMTs and GMRs**

Serotype-specific OPA GMTs will be calculated based on sera collected before study vaccination and 1 month after each vaccination. Geometric means and their 2-sided CIs will be derived by calculating means and CIs on the natural log scale, then exponentiating the results. CIs will be based on the t-distribution.

For each of the 20 primary endpoints corresponding to the serotype-specific OPA titers, the GMRs of the 20vPnC/saline GMT to the 13vPnC/PPSV23 GMT will be provided. GMRs and their 2-sided CIs will be derived by calculating differences in means and CIs on the natural log scale, then exponentiating the results.

The difference in means, on the natural log scale, will be 20vPnC/saline minus 13vPnC/PPSV23 for the 13 matched serotypes at Visit 2 or 20vPnC/saline at Visit 2 minus 13vPnC/PPSV23 at Visit 3 for the 7 additional serotypes. CIs will be based on the t-distribution. CCI [REDACTED]

CCI [REDACTED]

#### **Other Immunogenicity Analyses Based on OPA Titer**

OPA GMFRs will be summarized for each vaccine serotype from Visit 1 to Visit 2 for the 13 matching serotypes. For the 7 additional serotypes, the GMFR will be summarized from Visit 1 to Visit 2 for the 20vPnC/saline vaccine group and from Visit 1 to Visit 3 for the 13vPnC/PPSV23 vaccine group. GMFRs will be limited to subjects with nonmissing values both before any vaccination and after the indicated vaccination. Two-sided CIs will be included.

The proportion of subjects with OPA titers  $\geq$  LLOQ will be provided for time points and serotypes noted in the paragraph above. The associated 2-sided CIs will be obtained using the Clopper-Pearson method.

The proportion of subjects with a  $\geq$ 4-fold rise in serotype-specific OPA titer from Visit 1 to Visit 2 (20vPnC/saline group for all 20 serotypes, and 13vPnC/PPSV23 group for the 13 matching serotypes) or Visit 3 (13vPnC/PPSV23 group for the 7 additional serotypes) will be provided. The assessment of a 4-fold rise will be based on the increase from Visit 1 to Visit 2 for the 20 serotypes in subjects receiving 20vPnC as well as for the 13 matched serotypes in subjects receiving 13vPnC, and on the increase from Visit 1 to Visit 3 for the 7 additional serotypes in subjects receiving 13vPnC/PPSV23. The associated 2-sided CIs will be obtained using the Clopper-Pearson method.

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### **9.3.2. Immunogenicity Analysis Comparing Younger Cohorts (Subjects 50 Through 59 Years of Age and Subjects 18 Through 49 Years of Age) to Subjects 60 Through 64 Years of Age From Cohort 1, Limited to Subjects Receiving 20vPnC (Bridging Analyses)**

The analyses of all 20 serotypes will be based on subjects who received 20vPnC.

Serotype-specific OPA GMTs will be calculated from sera collected before study vaccination and 1 month after vaccination (Visit 2). Geometric means and their 2-sided 95% CIs will be derived by calculating means and CIs on the natural log scale, then exponentiating the results. CIs will be based on the t-distribution.

The GMRs of the younger-cohort GMT to the older-cohort GMT will be provided for OPA responses. “Younger” refers to either Cohort 3 (subjects 18 through 49 years of age) or Cohort 2 (subjects 50 through 59 years of age). “Older” refers to subjects 60 through 64 years of age from Cohort 1. The responses from the 20 serotypes will be obtained from Visit 2. Two-sided 95% CIs will be included.

GMRs and their 2-sided 95% CIs will be derived by calculating differences in means and CIs on the natural log scale, then exponentiating the results. The difference in means, on the natural log scale, will be the younger cohort (Cohort 2 or Cohort 3) minus the older cohort (Cohort 1). CIs will be based on the t-distribution. The OPA results from the younger cohort will be declared noninferior to those from subjects 60 through 64 years of age from Cohort 1 for a specific serotype if the lower 2-sided 95% confidence limit for the serotype-specific OPA GMR exceeds 0.5.

### **9.3.3. Other Immunogenicity Analyses for Cohorts 2 and 3 Based on OPA Titer of 20vPnC**

OPA GMFRs will be summarized for each vaccine serotype in the 20vPnC group in Cohorts 2 and Cohort 3 from Visit 1 to Visit 2. GMFRs will be limited to subjects with nonmissing values both before and after vaccination.



### 9.3.7. Other Immunogenicity Analyses

Descriptive statistics of serotype-specific OPA results may be provided for subpopulations (ie, different age groups). Descriptive statistics may include GMTs, GMFRs, and percentages with OPA titers  $\geq$  LLOQ.

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CCI [Redacted]

[Redacted]

[Redacted]

## 9.4. Safety Analysis

### 9.4.1. Adverse Events

AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by vaccine group within cohort. A 3-tier approach will be used to summarize AEs. Under this approach AEs are classified into 1 of 3 tiers:

- Tier 1 events: These are prespecified events of clinical importance and are identified in a list in the product's safety review plan. p-Values and 95% CIs for between-group comparisons (risk differences) will be provided for Tier 1 events. At this development stage for 20vPnC, no Tier 1 events have been identified.
- Tier 2 events: These are events that are not Tier 1, but are considered "relatively common." A MedDRA preferred term is defined as a Tier 2 event if there is an incidence of at least 4 events in any AE in any vaccine group and any cohort. 95% CIs for between-group comparisons (risk differences) will be provided for Tier 2 events.
- Tier 3 events: These are events that are neither Tier 1 nor Tier 2 events. Counts and percentages for each vaccine group will be provided for Tier 3 events.

The Miettinen and Nurminen method will be used to derive a 95% CI for the risk difference between vaccine groups.<sup>74</sup>

Descriptive summary statistics will be provided for SAEs and NDCMCs for each vaccine group and each cohort.

### 9.4.2. Reactogenicity

Reactogenicity results will be analyzed separately for each cohort. Descriptive statistics will be provided for each reactogenicity endpoint for each vaccine group separately within each cohort. In each group/cohort, local reactions from Day 1 through Day 10 and systemic events from Day 1 through Day 7 after the first vaccination will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include proportions of subjects with the indicated endpoint and the associated Clopper-Pearson 95% CIs.

CCI [REDACTED]

CCI [REDACTED]

[REDACTED]

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CCI [REDACTED]

[REDACTED]

[REDACTED]

## 10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

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

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

## **11. DATA HANDLING AND RECORD KEEPING**

### **11.1. Case Report Forms/Electronic Data Record**

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

## **11.2. Record Retention**

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed ICDs, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

## **12. ETHICS**

### **12.1. Institutional Review Board/Ethics Committee**

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, ICDs, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

### **12.2. Ethical Conduct of the Study**

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences [CIOMS] 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

### **12.3. Subject Information and Consent**

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

measures will include omitting subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic form and will be password protected 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, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed and will be replaced by a single, specific, numerical code based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with the CSA and applicable privacy laws.

The ICDs and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The ICDs used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study, the sharing of data relating to the study, and possible risks associated with participation, including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each study subject is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

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

#### **12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP**

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

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

### **13. DEFINITION OF END OF TRIAL**

#### **13.1. End of Trial in All Participating Countries**

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

### **14. SPONSOR DISCONTINUATION CRITERIA**

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of 20vPnC at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 30 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

### **15. PUBLICATION OF STUDY RESULTS**

#### **15.1. Communication of Results by Pfizer**

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on [www.clinicaltrials.gov](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 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 Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

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

## EudraCT

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

[www.pfizer.com](http://www.pfizer.com)

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has 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).

### **15.2. Publications by Investigators**

Pfizer supports the exercise of academic freedom and has no objection to publication by the PI of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, “publication”) before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, <http://www.icmje.org/index.html#authorship>, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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**Appendix 1. Abbreviations**

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

<b>Abbreviation</b>	<b>Term</b>
7vPnC	7-valent pneumococcal conjugate vaccine
13vPnC	13-valent pneumococcal conjugate vaccine
20vPnC	20-valent pneumococcal conjugate vaccine
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
ALT	alanine aminotransferase
AOM	acute otitis media
AST	aspartate aminotransferase
CAP	community-acquired pneumonia
CAPiTA	Community-Acquired Pneumonia Immunization Trial in Adults
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatinine kinase
COPD	chronic obstructive pulmonary disease
CRF	case report form
CRM <sub>197</sub>	cross-reactive material 197
CSA	clinical study agreement
CT	clinical trial
DILI	drug-induced liver injury
DU	dispensable unit
EC	ethics committee
e-diary	electronic diary
CCI	
EDP	exposure during pregnancy
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document

<b>Abbreviation</b>	<b>Term</b>
ICH	International Council for Harmonisation
ID	identification
CCI	
IND	investigational new drug application
INR	international normalized ratio
IP manual	Investigational Product Manual
IPD	invasive pneumococcal disease
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWR	interactive Web-based response
LFT	liver function test
LLOQ	lower limit of quantitation
LRI	lower respiratory tract infection
LSLV	last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
OPA	opsonophagocytic activity
PCD	primary completion date
PI	principal investigator
PPSV23	23-valent pneumococcal polysaccharide vaccine
PT	prothrombin time
CCI	
SAE	serious adverse event
SAP	statistical analysis plan
SoA	Schedule of Activities
SRM	study reference manual
SRSD	single reference safety document
TBili	total bilirubin
ULN	upper limit of normal
US	United States
USPI	US package insert
VT	vaccine-type
WHO	World Health Organization
WOCBP	woman of childbearing potential

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