



**A PHASE 2, RANDOMIZED, DOUBLE-BLIND TRIAL TO EVALUATE THE
SAFETY AND IMMUNOGENICITY OF A MULTIVALENT PNEUMOCOCCAL
CONJUGATE VACCINE IN ADULTS 60 THROUGH 64 YEARS OF AGE**

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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. Centers for Disease Control and Prevention (CDC) data estimated that in 2015 there were 29,500 cases and 3350 deaths due to invasive pneumococcal disease (IPD) in the United States. In 2008, the World Health Organization (WHO) estimated that 1.6 million people die from pneumococcal disease each year. *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. 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, such as the licensed 23-valent pneumococcal polysaccharide vaccine (PPSV23), containing free 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.

Prevnar[®] (7-valent pneumococcal conjugate vaccine), which was licensed in the United States in 2000, and Prevnar 13[®] (13-valent pneumococcal conjugate vaccine [13vPnC]), which was licensed in the United States in 2010, are pneumococcal conjugate vaccines containing 7 and 13, respectively, pneumococcal capsular polysaccharides individually conjugated to cross-reactive material 197 (CRM₁₉₇), 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) 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. A Phase 1 study is being conducted in healthy adults 18 to 49 years of age to support further development of 20vPnC. The purpose of the proposed Phase 2 study in older adults is to generate a safety and immunogenicity data set with 20vPnC to support and inform the design of the Phase 3 clinical development program for adults.

Study Design

This is a Phase 2, multicenter, randomized, active-controlled, double-blind study with a 2-arm parallel design. A total of 440 adults 60 through 64 years of age with no history of pneumococcal vaccination will be enrolled and randomized equally to receive an initial vaccination with either:

- a single dose of 20vPnC followed 1 month later by saline (placebo) administration in the active vaccine group (20vPnC/saline group), or
- a single dose of 13vPnC followed 1 month later by a dose of PPSV23 in the control group (13vPnC/PPSV23 group).

13vPnC will serve as a control for safety, as well as immunogenicity of the 13 serotypes in common with 20vPnC. PPSV23 will serve as a control for immunogenicity of the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) in 20vPnC.

Blood samples will be collected on the day of investigational product administration prior to each study vaccination (Vaccination 1 and Vaccination 2), 1 month after Vaccination 2, and 12 months after Vaccination 1 for immunogenicity assessments. Prompted local reactions at the injection site and prompted systemic events will be collected daily for 10 and 7 days, respectively, after Vaccination 1. Adverse events (AEs) occurring from signed informed consent through 1 month after Vaccination 2 will be collected and serious adverse events (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) will be collected from signed informed consent through 12 months after Vaccination 1.

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Primary Objective and Endpoints

Primary Objective

- To describe the safety profile of 20vPnC in the study population.

Primary Endpoints

- Proportions of subjects reporting prompted local reactions within 10 days after vaccination (redness, swelling, and pain at the injection site).
- Proportions of subjects reporting prompted systemic events within 7 days after vaccination (fever, headache, fatigue, muscle pain, and joint pain).
- Proportions of subjects reporting adverse events (AEs) within 1 month after vaccination.
- Proportions of subjects reporting serious adverse events (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) within 6 months and 12 months after vaccination.

Secondary Objective and Endpoints

Secondary Objective

- To describe the immunogenicity of 20vPnC in the study population.

Secondary Endpoints

- Pneumococcal serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) 1 month after vaccination.
- Pneumococcal serotype-specific OPA geometric mean fold rises (GMFRs) from before vaccination to 1 month after vaccination.

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Statistical Methods

An analysis of safety and immunogenicity data will be conducted when data are available as described in [Section 9](#) and the statistical analysis plan (SAP). All analyses will be descriptive. No formal hypothesis tests between vaccine groups are planned; therefore, no power calculations for comparison of vaccine groups are included; however, the probabilities of at least 1 AE are calculated for range of assumed true event rates.

[REDACTED]

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.

Visit Number	1	2	3	4	5
Visit Description	Vaccination 1	Vaccination 2	Follow-up Vaccination 2	6-Month Safety Collection	Persistence Blood Draw and 12-Month Safety Collection
Visit Type	Clinic Visit	Clinic Visit	Clinic Visit	Telephone Contact	Clinic Visit
Visit Window (Days)	Day 1	28 to 35 Days After Visit 1	28 to 35 Days After Visit 2	168 to 196 Days After Visit 1	350 to 378 Days After Visit 1
Obtain informed consent	X				
Record demography	X				
Obtain medical history data and record tobacco usage	X				
Perform physical examination and measure height and weight	X				
Measure prevaccination oral temperature	X	X			
Contraception check, if applicable ^a	X	X	X		
Record nonstudy vaccinations and concomitant medications ^b	X	X	X	X	X
Review inclusion and exclusion criteria	X				
Review continued eligibility		X	X		X
Review temporary delay criteria	X	X	X		X
Assign a subject number	X				

Visit Number	1	2	3	4	5
Visit Description	Vaccination 1	Vaccination 2	Follow-up Vaccination 2	6-Month Safety Collection	Persistence Blood Draw and 12-Month Safety Collection
Visit Type	Clinic Visit	Clinic Visit	Clinic Visit	Telephone Contact	Clinic Visit
Visit Window (Days)	Day 1	28 to 35 Days After Visit 1	28 to 35 Days After Visit 2	168 to 196 Days After Visit 1	350 to 378 Days After Visit 1
Assign randomization number	X				
Obtain blood sample (~30 or ~50 mL per blood sample)	X ^{c,d}	X ^{c,e}	X ^d		X ^c
Administer investigational vaccine (20vPnC/saline or 13vPnC /PPSV23)	X (20vPnC or 13vPnC)	X ^f (saline or PPSV23)			X ^f
Assess and record acute reactions for at least 30 minutes after investigational vaccine administration	X	X			
Provide subject with an e-diary, thermometer and measuring device and instruct how to collect prompted local reactions through Day 10 and systemic events through Day 7 ^g	X				
Review and/or collect e-diary ^h	X	X			
Record and report adverse events ⁱ	X-----X				

Visit Number	1	2	3	4	5
Visit Description	Vaccination 1	Vaccination 2	Follow-up Vaccination 2	6-Month Safety Collection	Persistence Blood Draw and 12-Month Safety Collection
Visit Type	Clinic Visit	Clinic Visit	Clinic Visit	Telephone Contact	Clinic Visit
Visit Window (Days)	Day 1	28 to 35 Days After Visit 1	28 to 35 Days After Visit 2	168 to 196 Days After Visit 1	350 to 378 Days After Visit 1
Record and report serious adverse events and newly diagnosed chronic medical conditions ^j			X-----X		

- a. The investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly until 28 days after vaccine administration and document the conversation and the subject's affirmation in the subject's chart.
- b. Record nonstudy vaccinations and concomitant medications as described in [Section 5.10.3](#).
- c. Blood sample will be collected prior to vaccination.
- d. Obtain blood sample (~30 mL) for immunologic assessments.
- e. [REDACTED]
- f. Subjects who received 20vPnC on Day 1 will receive saline; subjects who received 13vPnC on Day 1 will receive PPSV23.
- g. Subjects will record prompted local reactions and systemic events in an electronic diary (e-diary) for the 10 and 7 days, respectively, following the first vaccination. Subjects will be requested to contact the study staff if they experience redness or swelling measuring ≥ 21 caliper units or severe pain at the injection site or a fever $>104.0^{\circ}\text{F}$ ($>40.0^{\circ}\text{C}$) or any Grade 4 prompted systemic event.
- h. Designated site staff will review e-diary data online at frequent intervals (daily is optimal) for the 10 days following vaccination to evaluate subject compliance and as part of the ongoing safety review and will collect the e-diary at Visit 2
- i. Adverse events include nonserious adverse events, serious adverse events, and newly diagnosed chronic medical conditions.
- j. 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.^{1,2,3} Serious pneumococcal disease may occur at any age; however, children <5 years and adults ≥65 years of age are at particularly increased risk.⁴ Individuals with certain comorbidities and immunocompromising conditions are also at risk. The annual burden of pneumococcal disease in children and adults in the United States has been estimated, using 2004 healthcare utilization and disease data. There were approximately 445,000 hospitalizations, 2.3 million hospital days, 5.0 million outpatient visits, and 22,000 annual deaths, including 19,000 from pneumonia annually, with the majority of the deaths (18,000) having occurred in persons ≥65 years of age.³ These data represent disease burden after a relatively short period of Prevnar[®] (7-valent pneumococcal conjugate vaccine) use in the infant vaccine schedule (<5 years). A preliminary update of estimates in adults after introduction of Prevnar 13[®] (13-valent pneumococcal conjugate vaccine [13vPnC]) suggests that although there has been a reduction in disease burden, 207,000 hospitalizations for pneumococcal pneumonia, meningitis, and sepsis (plausibility range of 106,000-308,000) and 283,000 cases of pneumococcal disease (plausibility range of 145,000-422,000) occurred in US adults in 2015.⁵ Surveillance studies conducted in 2010-2012 by the Centers for Disease Control and Prevention (CDC) found that *S pneumoniae* remains among the most common pathogens identified in community-acquired pneumonia (CAP) requiring hospitalization in the United States in both children and adults.^{6,7} 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), but it is associated with significant morbidity and mortality¹ in all age groups. The CDC estimated that in 2015 there were 29,500 cases and 3350 deaths due to IPD in the United States.⁸ In many regions of the world the disease burden is much higher, reflected in an assessment by the World Health Organization (WHO) in 2008 estimating that 1.6 million people die from pneumococcal disease each year.⁹ 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.^{10,11} Anticapsular antibodies directed against the specific serotype bind to the capsule and promote complement-mediated opsonophagocytic killing and clearance of the organism.¹² 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.¹³

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.^{14,15} 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.^{4,15,16,17} Moreover, their ability to prevent nonbacteremic pneumonia, CAP, AOM, and nasopharyngeal carriage is limited or lacking.^{13,17,18,19,20} 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.^{21,22,23} 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.²⁴ Despite these limitations, a number of national vaccine policy expert bodies recommend PPSV23 vaccination of adults ≥65 years of age and/or in persons with substantial risk factors for pneumococcal disease, to provide some degree of protection against IPD due to serotypes not covered by existing pneumococcal conjugate vaccines.²⁵ However, in the United States, the Advisory Committee on Immunization Practices (ACIP) recommends that adults ≥65 years of age, or those with certain immunocompromising conditions, receive 13vPnC first, followed by PPSV23 1 year later. Other countries have similar recommendations for certain risk groups. In contrast, because of concerns of hyporesponsiveness, as well as other factors, most recommendations restrict PPSV23 to a single lifetime dose in adults ≥65 years of age and 1 to 2 doses in most other high-risk populations.^{25,26,27}

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.^{16,28} Prevnar was the first pneumococcal conjugate vaccine to be licensed (2000) and was indicated for prevention of pneumococcal disease in infants and young children on the basis of efficacy studies. Prevnar contained capsular polysaccharide conjugates for 7 pneumococcal serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), each covalently linked to cross-reactive material 197 (CRM₁₉₇), a nontoxic variant of diphtheria toxin. These 7 serotypes were responsible for approximately 80% to 90% of IPD in children <5 years of age in the United States and approximately 60% to 80% of IPD in the same age group in Europe at that time (1998-2000).^{29,30,31,32,33} These serotypes also accounted for a high proportion of antibiotic-resistant strains.³⁴ Prevnar demonstrated efficacy against VT IPD, pneumonia, and AOM in large randomized controlled efficacy studies in infants.^{35,36} The Prevnar components contained in a related pneumococcal conjugate vaccine also were demonstrated to be efficacious against clinically/radiographically defined pneumonia.^{37,38,39,40} Following introduction of Prevnar, reduction of nasopharyngeal carriage and transmission has resulted in indirect herd effects, with a 92% reduction of Prevnar VT IPD in older adults ≥65 years of age.^{41,42}

Prevnar 13 was developed to expand serotype coverage and was licensed in the United States in 2010. Prevnar 13 includes the same *S pneumoniae* serotypes as Prevnar and an additional 6 polysaccharide conjugates for serotypes 1, 3, 5, 6A, 7F, and 19A.^{28,32,43} The vaccine was licensed for use in infants and young children based on comparisons of serotype-specific immunoglobulin G (IgG) to Prevnar, with supportive data to demonstrate the functional activity of the immune responses. Prevnar 13 was later 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 CAP⁴⁴ in CAPiTA (Community-Acquired Pneumonia Immunization Trial in Adults), a randomized controlled study of adults 65 years of age and older. 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.¹⁵ Prevnar 13 has replaced Prevnar and is licensed in the United States and many other countries, with national recommendations for use in children and older adults.^{45,46,47,48} It has also been prequalified by WHO for use in national infant immunization programs in lower- and middle-income countries.^{49,50} Surveillance data from several countries following introduction of Prevnar 13 into the routine infant immunization program have demonstrated vaccine effectiveness against VT IPD in the vaccinated population.^{51,52,53}

Prenar 13 was licensed for adults ≥ 50 years of age in 2011, and recommended by the ACIP for use in adults with immunocompromising conditions in 2012. In July 2016, it was also licensed for use in adults 18 to 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 Pevnar into the routine infant immunization schedule, suggesting potential value in direct immunization of adults rather than reliance solely on the herd effect.⁵⁴ The data on disease burden, combined with the results of the CAPiTA study, led to the August 2014 ACIP recommendation for all adults aged ≥ 65 years to receive Pevnar 13, followed by PPSV23 six to twelve months later (except for those who had already received PPSV23 and for whom an additional dose was not indicated). In 2015, a ≥ 12 -month interval between vaccinations was recommended, based on demonstrated higher frequency of local reactions with short intervals, and theoretical immunogenicity considerations.^{27,55} The recommendation for Pevnar 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 Pevnar 13. However, the prevalence of IPD due to most of the serotypes contained only in PPSV23 has remained stable or slightly increased over the past 15 years, despite continued recommendation and use of PPSV23 in adults ≥ 65 years of age and high-risk adults.^{56,57,58} The continued presence of IPD due to serotypes contained only in PPSV23 is likely due to a combination of intrinsic population factors including age and comorbidities, limitations in the ability of PPSV23 to prevent disease and reduce carriage, limited duration of PPSV23 protection, and lack of boosting with subsequent doses, which highlights the need for a better vaccine than PPSV23 and expanded coverage.

1.2.2.3. Rationale for 20vPnC

Because of the number of serotypes that may cause pneumococcal disease among different geographic regions, different age populations, and different environmental backgrounds, there remains value in expanding serotype coverage.

20vPnC is being developed to further expand protection against the global burden of vaccine-preventable pneumococcal disease in children and adults over that of Pevnar 13. 20vPnC contains the serotypes present in Pevnar 13 plus 7 new serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F), as well as the same excipients as the currently licensed conjugate vaccine. The polysaccharides of the 20 capsular serotypes of *S. pneumoniae* are each covalently linked to CRM₁₉₇. These 7 additional serotypes were selected based on their relative prevalence as a cause of IPD, their generalized geographic distribution, and other factors that would support inclusion, such as the presence of antibiotic resistance and greater disease severity (eg, meningitis, mortality).^{59,60,61,62,63,64,65,66,67,68,69,70} These 7 serotypes are also present in PPSV23.⁷¹ Adding these additional serotypes to the 13 serotypes in Pevnar 13 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 Prevnar and Prevnar 13, and contains polysaccharides of capsular serotypes of *S pneumoniae*, each covalently linked to CRM₁₉₇.

CCI



A Phase 1 study is being conducted in healthy adults 18 to 49 years of age to support further development of 20vPnC. The details of this study can be found in the IB.

The purpose of this study is to assess the safety, tolerability, and immunogenicity of 20vPnC in adults 60 to 64 years of age and to generate a safety and immunogenicity data set with 20vPnC to support and inform the design of the Phase 3 clinical development program for adults. The targeted age of the population for this study, adults 60 through 64 years of age, has been selected as this approximates the population (≥ 65 years of age) who are recommended for vaccination with 13vPnC and PPSV23 by ACIP, but are unlikely to have already received a pneumococcal vaccine. All subjects will receive either 20vPnC or 13vPnC for the initial vaccination. 13vPnC will serve as a reference vaccine for safety and tolerability assessments and for immunogenicity of the 13 common serotypes in 20vPnC. At the second vaccination, 1 month later, the 20vPnC recipients will receive saline and the 13vPnC recipients will receive PPSV23. PPSV23 will provide a reference for the immune responses to the 7 additional serotypes in the 20vPnC. Subjects will also return 12 months after Vaccination 1 for measurement of circulating antibodies at that time.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the 20vPnC IB. The SRSD for 13vPnC and PPSV23 are the US package inserts (USPIs).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objective and Endpoints

2.1.1. Primary Objective

- To describe the safety profile of 20vPnC in the study population.

2.1.2. Primary Endpoints

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

- Proportions of subjects reporting adverse events (AEs) within 1 month after vaccination.
- Proportions of subjects reporting serious adverse events (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) within 6 months and 12 months after vaccination.

2.2. Secondary Objective and Endpoints

2.2.1. Secondary Objective

- To describe the immunogenicity of 20vPnC in the study population.

2.2.2. Secondary Endpoints

- Pneumococcal serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) 1 month after vaccination.
- Pneumococcal serotype-specific OPA geometric mean fold rises (GMFRs) from before vaccination to 1 month after vaccination.

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3. STUDY DESIGN

This will be a Phase 2, multicenter, randomized, active-controlled, double-blind study with a 2-arm parallel design, conducted at investigative sites in the United States. A total of 440 adults 60 through 64 years of age with no history of pneumococcal vaccination will be enrolled and randomized equally to receive an initial vaccination with either:

- a single dose of 20vPnC followed 1 month later by saline (placebo) administration in the active vaccine group (20vPnC/saline group), or
- a single dose of 13vPnC followed 1 month later by a dose of PPSV23 in the control group (13vPnC/PPSV23 group).

13vPnC will serve as a control for safety, as well as immunogenicity of the 13 serotypes in common with 20vPnC. PPSV23 will serve as a control for immunogenicity of the 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) in 20vPnC as described in [Table 1](#).

Table 1. Time Points for Key Safety and Immunogenicity Objectives by Investigational Product

	20vPnC	Control – 13vPnC ^a	Control – PPSV23 ^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 eventsc	X (1 month after Visits 1 and 2)	X (1 month after Visit 1)	X (1 month after Visit 2)
Immune responses to serotypes in common with 13vPnC: 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 additional 7 serotypes: 8, 10A, 11A, 12F, 15B, 22F, 33F	X (1 month after Visit 1)		X (1 month after Visit 2)

- Control group from enrollment and vaccination with 13vPnC at Visit 1 until vaccination with PPSV23 at Visit 2.
- Control group after vaccination with PPSV23 at Visit 2.
- SAEs and newly diagnosed chronic medical conditions (NDCMCs) will be collected through Visit 5 (12 months after Visit 1).

On Day 1 (Visit 1), subjects will have blood drawn for immunogenicity assessments, receive an investigational product (20vPnC or 13vPnC; the investigational products have the same appearance and can be administered by unblinded or blinded site staff), be observed for 30 minutes after vaccination, and receive safety follow-up and electronic diary (e-diary) instructions. Local reactions (pain, redness, and swelling) at the injection site will be prompted for and collected daily in an e-diary from Day 1 through Day 10 after the Visit 1 vaccination. Systemic events (fever, fatigue, headache, muscle pain, and joint pain) and use of antipyretic medications will be prompted for and collected daily in an e-diary from Day 1 through Day 7 after the Visit 1 vaccination. AEs (including nonserious AEs, SAEs, and NDCMCs) will be assessed for approximately 1 month after the Visit 1 vaccination (through Visit 2). Refer to [Section 8.1.4](#) for the definition of an NDCMC.

At Visit 2 (28-35 days after Visit 1), subjects will return for follow-up. Information will be collected from the subjects on AEs and e-diary follow-up (as needed), blood will be drawn for immunogenicity assessments (this represents the 1-month post–Vaccination 1 time point), a dose of saline will be administered to subjects who received 20vPnC at Visit 1, and PPSV23 will be administered to subjects who received 13vPnC at Visit 1. The subjects will be observed for 30 minutes and will receive safety follow-up instructions. The investigational product will be prepared at this visit by a designated unblinded site staff member. AEs (including nonserious AEs, SAEs, and NDCMCs) will be assessed for approximately 1 month after the Visit 2 vaccination (through Visit 3).

At Visit 3 (28-35 days after Visit 2), subjects will return for safety follow-up and a blood draw for immunogenicity assessments.

At Visit 4 (approximately 6 months after the first vaccination), the sites will contact the subject via telephone to inquire about SAEs and NDCMCs.

At Visit 5 (12 months [350 to 378 days] after the first vaccination), subjects will return to have a blood draw for immunogenicity assessments. SAEs and NDCMCs will also be collected at this visit.

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3.1. Duration of Subject Participation

Each subject will participate in the study for approximately 12 months.

3.2. Duration of Study

The study duration will be approximately 16 months.

3.3. Number of Subjects

Approximately 440 subjects (220 per group) will be randomized for a total of approximately 400 evaluable subjects (assuming a 10% dropout rate). 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 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, laboratory tests, and other study procedures including completion of the e-diary.
3. Expected to be available for the duration of the study and can be contacted by telephone during study participation.
4. Male or female adults ≥ 60 to ≤ 64 years of age (from the 60th birthday up to, but not including, the 65th birthday) at enrollment.
5. Healthy adults, including adults with preexisting stable disease, defined as disease not requiring significant change in therapy or requiring hospitalization within 3 months before receipt of investigational product, as determined by medical history, physical examination, laboratory screening, and clinical judgment of the investigator.
6. Female subjects who are not of childbearing potential must (ie, meet at least 1 of the following criteria):
 - a. Have achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;
 - b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;
 - c. Have medically confirmed ovarian failure.

All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

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. 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.
4. 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.
5. Previous vaccination with any licensed or investigational pneumococcal vaccine, or planned receipt through study participation.
6. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of 13vPnC, 20vPnC, or PPSV23.
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 postvaccination 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; breastfeeding female subjects; female subjects of childbearing potential and fertile male subjects with partners of childbearing potential who are, in the opinion of the investigator, sexually active and at risk of pregnancy with their partners and are unwilling or unable 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.

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 Vaccinations 1 and 2 and the respective vaccinations should take place on the same day (Visit 1 and Visit 2).

4.3.1. Criteria for Temporarily Delaying Vaccine Administration (Visits 1 and 2)

- Febrile illness (oral 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 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 Blood Draw (Visits 1, 2, 3, and 5)

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

4.4. Lifestyle Requirements

4.4.1. Contraception

All male subjects who are able to father children and who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his partner from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects needs to affirm their or their partners consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the subject or male subject's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
2. Correctly placed copper-containing intrauterine device (IUD).
3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.
4. Male sterilization with absence of sperm in the postvasectomy ejaculate.
5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).
6. Female partner who meets the criteria for nonchildbearing potential, as described below:
 - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having an FSH level confirming the postmenopausal state;
 - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
 - Have medically confirmed ovarian failure.

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

All sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose of investigational product.

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, 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 retained in the site 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 the Site Personnel

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

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

Vaccination 2 will be prepared by an unblinded site staff member. Vaccination 2 will be administered to blinded subjects; the 2 investigational products will have an identical

appearance after preparation. The study staff administering the vaccines can be blinded or unblinded, but only the designated unblinded site staff member assigned to prepare Vaccination 2 will be unblinded (see [Section 5.6.2](#)). All other study personnel including the principal investigator (PI), and the subject, will be blinded. The PI will assign the responsibility of preparing Vaccination 2 to unblinded persons who will not participate in the evaluation of any study subject. More than 1 unblinded site staff member may be assigned. A member of the study site staff or clinic pharmacy should fulfill this role. Contact between the unblinded staff member who will prepare Vaccination 2 and study subjects should be kept to a minimum.

The investigator, study coordinator, and any site staff other than the unblinded site staff member must not be allowed to know the investigational product assigned to any study subject and must not be allowed to see the inner packaging containing the investigational product. The outer investigational product cartons will be blinded.

5.3. Blinding of the Sponsor

Sponsor personnel directly involved in evaluating subject data will be blinded to vaccine assignment until the analysis of all available data through Visit 2 is available, following the principles outlined in ICH E9 guideline on Statistical Principles for Clinical Trials. A data blinding plan will be created to describe the blinding requirements and unblinding events. The plan to control distribution of unblinded data among designated Pfizer personnel and core study team members will be specified in the data dissemination plan. 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 CRM₁₉₇. CCI [REDACTED]

[REDACTED]

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[REDACTED]

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 (Pneumovax, Merck) and is a clear, sterile solution consisting of a mixture of purified capsular polysaccharides from 23 types 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

All subjects will receive a single dose (0.5 mL) of investigational product administered intramuscularly into the deltoid muscle, preferably in the nondominant arm, at Visit 1 and Visit 2.

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.

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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 unblinded dispenser/administrator at 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 unblinded site staff and then may be destroyed after the sponsor's unblinded site staff 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)

5.10.1. Prohibited During the Study

- Receipt of any investigational vaccines, drugs, or medical devices is prohibited during subject participation in the study.

- Receipt of any nonstudy pneumococcal vaccine is prohibited during subject participation in the study.
- Receipt of any licensed vaccine, with the exception of licensed inactivated influenza vaccine, is prohibited from Visit 1 to Visit 4 (6 months after Vaccination 1).
- Receipt of blood/plasma products, immunoglobulins, and/or immunosuppressive therapy (including a ≥ 14 -day course of systemic corticosteroids) is prohibited during subject participation in the study.

5.10.2. Permitted During the Study

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

5.10.3. Recording Concomitant Treatments

The name and date of administration for all nonstudy vaccinations received from the time of signing of the informed consent document to Visit 5 will be collected and recorded in the CRF (per [Section 5.10.1](#) and [Section 5.10.2](#)).

Medications taken to treat SAEs or NDCMCs from the time of signing of the informed consent document to Visit 5 will be recorded in the CRF.

6. STUDY PROCEDURES

The study procedures are summarized in the Schedule of Activities. The day of vaccination is considered to be Day 1.

6.1. Visit 1 (Vaccination 1 – Day 1)

Prior to vaccination:

- Obtain written informed consent before performing any study-specific procedures.
- 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 subject number via the IRT.
- Obtain and record the subject demography (sex, birth date, ethnicity, race, racial designation).
- Assess and record tobacco usage.
- Obtain and record the medical history including the presence of chronic conditions (eg, diabetes, hypertension, atherosclerosis, COPD) and/or medical history of significance such as relevant surgical procedures).
- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes. Abnormal results will be recorded in the CRF.
- Measure and record the subject's height, weight, and oral temperature (°F/°C).
- Record nonstudy vaccinations and medications as described in [Section 5.10.3](#).
- Assign a randomization number and an investigational product container number via the IRT. This must be the last step before proceeding. A blinded or unblinded site staff member will prepare the investigational product according to the IP manual.

After randomization:

- Collect a blood sample of approximately 30 mL for immunogenicity assessments prior to vaccination.
- The blinded/unblinded dispenser/administrator will administer a single 0.5-mL injection of investigational product into the deltoid muscle (preferably in the nondominant arm).
- Blinded site staff will observe the subject for at least 30 minutes after investigational product administration for any acute reactions. Record any acute 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 investigator site staff or investigator immediately during the 10-day postvaccination period if he or she experiences redness or swelling at the injection site measuring ≥ 21 measuring device units (≥ 10.5 cm), severe injection site pain

(prevents daily activity), a fever of $>104^{\circ}\text{F}$, or any Grade 4 prompted systemic event to determine if the event requires further assessment by the investigator.

- Ask the subject to contact the investigator or investigator site staff immediately if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs during the study period.
- Remind the 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.
- Record AEs, SAEs, and NDCMCs as described in [Section 8](#).
- 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 (daily is optimal) for the 10 days following vaccination to evaluate subject compliance and as part of the ongoing safety review.

6.2. Visit 2 (Vaccination 2 – 28 to 35 Days After Visit 1)

Prior to vaccination:

- 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.
- Measure and record the subject's oral temperature ($^{\circ}\text{F}/^{\circ}\text{C}$).
- Record nonstudy vaccinations and medications as described in [Section 5.10.3](#).
- Collect a blood sample of approximately 50 mL for immunogenicity assessments prior to vaccination.
- 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 whether any AEs, SAEs, or NDCMCs have occurred since Visit 1 and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in [Section 8](#).
- An unblinded site staff member will prepare the investigational product according to the IP manual.

After vaccination (including investigational product administration):

- The blinded/unblinded dispenser/administrator will administer a single 0.5-mL injection of investigational product into the deltoid muscle (preferably in the nondominant arm).
- Blinded investigator site staff will observe the subject for at least 30 minutes after investigational product administration for any acute reactions. Record any acute reactions on the AE CRF and on an SAE form as applicable.
- Remind the subject to contact the investigator or investigator site staff immediately if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs during the study period.
- Remind the 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.
- The investigator or an authorized designee completes the CRF.

6.3. Visit 3 (Follow-up Vaccination 2 – 28 to 35 Days After Visit 2)

- 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.
- Record nonstudy vaccinations and medications as described in [Section 5.10.3](#).
- Perform a contraception check, if applicable, and document the conversation and the subject's affirmation in the subject's chart.
- Collect a blood sample of approximately 30 mL for immunogenicity assessments.
- Determine whether any AEs, SAEs, or NDCMCs have occurred since Visit 2 and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in [Section 8](#).
- Remind the subject to contact the investigator or investigator site staff immediately if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs during the study period.
- The investigator or an authorized designee completes the CRF.

6.4. Visit 4 (6-Month Safety Collection by Telephone – 168 to 196 Days After Visit 1)

- Record nonstudy vaccinations and medications as described in [Section 5.10.3](#).
- Determine whether any SAEs or NDCMCs have occurred since Visit 3 and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in [Section 8](#).

- Remind the subject to contact the investigator or investigator site staff immediately if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs during the study period.
- The investigator or an authorized designee completes the CRF.

6.5. Visit 5 (Persistence Blood Draw and 12-Month Safety Collection – 350 to 378 Days After Visit 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.
- Record nonstudy vaccinations and medications as described in [Section 5.10.3](#).
- Determine whether any SAEs or NDCMCs have occurred since Visit 4 and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in [Section 8](#).
- Collect a blood sample of approximately 50 mL for immunogenicity assessments.
- The investigator or an authorized designee completes the CRF.

6.6. Unscheduled Visits

If the subject reports redness or swelling at the injection site measuring ≥ 21 measuring device units (≥ 10.5 cm) or severe injection site pain during the 10-day post-Vaccination 1 period, a telephone contact must occur as soon as possible between the investigator or medically qualified designee and subject to assess if an unscheduled investigator site visit is required. An investigator site visit should 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 Visit 2.

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

- Measure 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 7.1.2.1](#).
- 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 investigator site staff if they experience a fever >104.0°F or any possible Grade 4 prompted systemic event (ie, emergency room visit or hospitalization for headache, fatigue, muscle pain, joint pain) within 7 days after vaccination.

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

Additionally, study staff may contact the subject to obtain additional information on Grade 3 events entered into the e-diary.

6.7. 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 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 CRF for all subjects and a 6-month post-Vaccination 1 follow-up telephone contact for the collection of safety information should be completed for all subjects who have been withdrawn after administration of investigational product unless the subject has withdrawn consent for any future contact.

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 Withdrawal From the Study Due to Adverse Events, [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 investigator 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 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. 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 posttreatment study follow-up. 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 investigator site may 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 investigator 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 investigator site staff and representative may 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. Serum samples should be processed and stored as indicated in the study reference manual (SRM) or equivalent document.

7.1. Safety Parameters

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

A medical history, physical examination, and measurement of oral temperature will be performed on all subjects prior to Vaccination 1 to determine subject eligibility and to establish a clinical baseline. Significant medical history and observations from the physical examination and temperature measurement will be documented and recorded in the CRF.

Acute reactions 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 at Visit 1, are graded as described in [Section 7.1.2](#). In addition, AEs, SAEs, and NDCMCs will be collected as defined in [Section 8](#).

7.1.1. Subject Electronic Diary

The subject will be asked to monitor and record local reactions for 10 days and systemic events and antipyretics/pain medication used to treat symptoms for 7 days, each evening following Vaccination 1 (Day 1 through Day 10 or Day 7, respectively, where Day 1 is the day of vaccination) on a system that uses a personal digital assistant (PDA) or other technology. This system, hereafter referred to as the subject's e-diary, 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, systemic events, and antipyretics/pain medication used to treat symptoms reported in the e-diary will be transferred electronically to the e-diary vendor, where they will be available for review by investigators, their qualified designees, and sponsor staff at all times via an internet-based portal. At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically to Pfizer for analysis and reporting.

The e-diary data do not need to be reported by the investigator 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.

Investigators (or an appropriately qualified designee) are required to review the e-diary data online at frequent intervals (daily is optimal) to evaluate subject compliance and 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 at Visit 2.

7.1.2. Grading Scale for Prompted Events

The grading scales used in this study to assess prompted 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.⁷²

7.1.2.1. Local Reactions

From Day 1 through Day 10, where Day 1 is the day of Vaccination 1, 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 then categorized during analysis as mild, moderate, or severe based on the grading scale in [Table 2](#) 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 2. 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. Investigator site staff must educate the subject regarding signs and symptoms that would prompt investigator site contact.

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

Table 2. Grading Scales for Local Reactions

	Mild Grade 1	Moderate Grade 2	Severe Grade 3^a	Grade 4^b
Redness (synonymous with erythema)	5 to 10 measuring device units = 2.5 to 5.0 cm	11 to 20 measuring device units = 5.5 to 10.0 cm	≥21 measuring device units = ≥10.5 cm	Necrosis or exfoliative dermatitis
Swelling (synonymous with edema)	5 to 10 measuring device units = 2.5 to 5.0 cm	11 to 20 measuring device units = 5.5 to 10.0 cm	≥21 measuring device units = ≥10.5 cm	Necrosis
Pain at injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity ^c	Emergency room visit or hospitalization

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 will be asked 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 as an AE on the CRF. The severity of the local reaction should be graded using the AE severity grading scale in [Section 8.3](#).
- Prevents daily activity, ie, results in missed days of work or school or is otherwise incapacitating.

7.1.2.2. Systemic Events

From Day 1 through Day 7, where Day 1 is the day of Vaccination 1, 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 3](#) below. Subjects will also be instructed to contact investigator site staff if they experience any possible Grade 4 prompted systemic event (ie, emergency room visit or hospitalization for headache, fatigue, muscle pain, or 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.

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

Table 3. Grading Scales for Systemic Events

	Mild Grade 1	Moderate Grade 2	Severe Grade 3^a	Grade 4^b
Fatigue (synonymous with tiredness)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization
Muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization

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

- Prevents daily routine activity, ie, results in missed days of work or school or is otherwise incapacitating.
- 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](#).

7.1.2.3. 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 less than 100.4°F [38.0°C]) in order to collect a stop date in the CRF. A subject with a fever $>104.0^{\circ}\text{F}$ ($>40.0^{\circ}\text{C}$) will be prompted to contact the investigator to assess the fever. Study staff may also contact the subject to obtain additional information if a temperature of $>102^{\circ}\text{F}$ is entered into an e-diary. Temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis according to Table 4 below.

Table 4. Ranges for Fever

100.4°F to 101.1°F (38.0°C to 38.4°C)
101.2°F to 102.0°F (38.5°C to 38.9°C)
102.1°F to 104.0°F (39.0°C to 40.0°C)
>104.0°F (>40.0°C)

7.1.2.4. Use of Antipyretic/Pain Medication

From Day 1 through Day 7, where Day 1 is the day of Vaccination 1, the subject will be asked to record the use of antipyretic and/or pain medication used to treat symptoms (yes/no) in the e-diary in the evening.

7.2. Immunogenicity

Blood samples (approximately 30 or 50 mL/visit) for immunogenicity assessments will be collected from all subjects prior to Vaccination 1, prior to Vaccination 2 (post-Vaccination 1/pre-Vaccination 2), approximately 1 month (28 to 35 days) after Vaccination 2, and approximately 1 year after Vaccination 1. Sample collection, processing, storage, and shipping information can be found in the SRM or equivalent manual.

The total volume of blood collected from each subject completing participation through Visit 5 will be approximately 160 mL. Sera will be used for immunogenicity assessments and vaccine development research (eg, assay development to support vaccine programs).

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

7.3. 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. If allowed by the informed consent document, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. 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 ^a	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), except occupational exposure	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

a. Nonserious AEs will be recorded from the time the subject provides informed consent through and including Visit 3. After Visit 3, only newly diagnosed chronic medical conditions (can be nonserious) and SAEs will be reported.

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 or her first awareness of the event.

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), through and including Visit 3. Between Visit 3 and Visit 5, only NDCMCs and SAEs will be reported. 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. At Visit 4 (6 months after Vaccination 1), the subject will be contacted by telephone to inquire about SAEs, including hospitalizations and NDCMCs since Visit 3. At Visit 5 (12 months after Vaccination 1), the subject will be asked about SAEs, including hospitalizations and NDCMCs since Visit 4.

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

An SAE 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

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with subject's usual function.
2	MODERATE	Interferes to some extent with subject's usual function.
3	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 $>3 \times$ ULN AND a TBili value $>2 \times$ ULN with no evidence of hemolysis and an alkaline phosphatase value $<2 \times$ 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

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
 - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

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.

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

- a. For lack of efficacy (particularly for studies conducted with vaccines, contraceptives, and products used in the treatment of life-threatening diseases or conditions [eg, anti-infectives]), see the Lack of Efficacy section below.

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, 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.

9. DATA ANALYSIS/STATISTICAL METHODS

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

9.1. Sample Size Determination

The study size is not based on any formal statistical hypothesis test. Approximately 220 adults per vaccine group are planned to be randomized. No formal statistical comparisons between vaccine groups are planned. Therefore, no power calculations for comparison of vaccine groups are included; however, the probabilities of at least 1 AE are calculated for range of assumed true event rates.

With approximately 200 subjects per vaccine group, the probabilities of observing at least 1 AE, local reaction, or systemic event where the true rate is 0.1%, 0.5%, 1%, and $\geq 5\%$ are 0.198, 0.668, 0.890, and >0.999 , respectively.

9.2. Analysis Populations

The safety population will include all subjects who receive 1 dose of 20vPnC or 13vPnC. Subjects will be assigned to vaccine groups corresponding to the vaccine actually received. The safety population will be the only analysis population for the primary endpoints.

The evaluable immunogenicity population will generally include any subject:

1. who receives the assigned vaccine as randomized,
2. whose has either Visit 2 or Visit 3 blood collection within 27 to 49 days, inclusive, after vaccination, and

3. who has CCI OPA titers CCI for at least 1 serotype for either the Visit 2 time point (which is 1 month after Vaccination 1) or the Visit 3 time point (which is 1 month after Vaccination 2); however, at least 1 nonmissing value must be obtained 27 to 49 days, inclusive, after the indicated vaccination.

A subject may be included in the evaluable population even if one of the Visit 2 or Visit 3 blood collections is outside the window. However, titers CCI obtained outside the window will be excluded from the evaluable population analysis. Additional criteria (eg, without major protocol violations) are described in the SAP.

The evaluable immunogenicity population will be the primary analysis population for immunogenicity results.

The all-available immunogenicity population will include all subjects who receive 20vPnC or 13vPnC and have CCI 1 valid and determinate OPA titer CCI after either vaccination. The all-available immunogenicity population will be the secondary analysis population for immunogenicity results. Subjects will be assigned to their randomized vaccine.

9.3. Immunogenicity Analysis

Geometric means (GMs) will be calculated for OPA results at every time point by vaccine group, as well as the 95% confidence intervals (CIs). Each serotype will be analyzed separately.

GMFRs will be calculated for the OPA CCI results. GMFRs will be calculated for change in value from before the first vaccination until 1 month after the first vaccination (Visit 2), from before the first vaccination (Visit 1) until 1 month after the second vaccination (Visit 3), CCI. GMFRs will be defined as the latter result divided by the earlier result.

GMs and their confidence intervals (CIs) will be obtained by taking log transforms of titers CCI, calculating the 95% CI with reference to the t-distribution, then exponentiating the mean and the limits. The GMFR and its CI will be calculated using the same method.

The proportions of subjects with OPA titers \geq the lower limit of quantitation (LLOQ) will be calculated for each time point and each serotype. The 95% CIs will be obtained using the Clopper-Pearson method.

Reverse cumulative distribution curves (RCDCs) will be compiled for each serotype. The visits in each RCDC will depend on the serotype. RCDCs for the 13 shared serotypes will be limited to before vaccination, 1 month after Vaccination 1, CCI

. RCDCs for the additional 7 serotypes will be limited to before vaccination, 1 month after Vaccination 1 or 1 month after Vaccination 2 (depending on the investigational products received), CCI. Further details will be specified in the SAP.

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9.4. Safety Analysis

Descriptive statistics will be compiled for each safety endpoint for each vaccine group separately. In each group, local reactions and systemic events from Day 1 to Day 10 and from Day 1 to Day 7, respectively, after Vaccination 1 only, will be presented by severity and cumulatively across severity levels. Descriptive statistics will include proportions of subjects with the indicated endpoint and the associated Clopper-Pearson 95% CIs.

AEs (including nonserious AEs, SAEs, and NDCMCs) with causality and severity will be summarized from Vaccination 1 until Visit 2, approximately 1 month (up to 35 days) after Vaccination 1. AEs will also be summarized from Vaccination 2 until Visit 3, approximately 2 months after 20vPnC (and 1 month after saline) administration in the 20vPnC/saline group, and 1 month after PPSV23 administration in the 13vPnC/PPSV23 group. Additionally, SAEs and NDCMCs will be presented for 2 intervals: from Vaccination 1 until Visit 4 (6 months after 20vPnC administration) and from Vaccination 1 until Visit 5 (12 months after 20vPnC administration). The descriptive statistics for AEs will be summarized as the number and percentage of subjects reporting at least 1 event of each preferred term with the associated Clopper-Pearson 95% CIs, arranged by system organ class, and will also be summarized as the number of occurrences of the event.

9.5. Analysis Timing

1. Unblinded descriptive analyses of safety data for the first 30 subjects through 10 days of follow-up after Vaccination 1. These analyses will be performed by a designated unblinded statistician.
2. Unblinded safety and immunogenicity data from Visit 1 through Visit 2 will be analyzed when available. The analyses will be descriptive. This analysis will inform internal program development decisions and potentially support regulatory interactions.
3. Unblinded safety and immunogenicity data from Visit 2 to Visit 3 will be analyzed when available. The analyses will be descriptive. This analysis will also inform internal program development decisions and potentially support regulatory interactions.
4. Safety data from Visit 3 through Visit 4 (6-month telephone call) will be analyzed when available.
5. Safety CCI data from Visit 4 through Visit 5 will be analyzed when available. These will be the final analyses.

There will be no alpha adjustments for these analyses.

Laboratory personnel directly conducting the immunogenicity assays will remain blinded until the last subject completes the 12-month visit.

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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 institutional review board (IRB)/ethics committee (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 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 informed consent documents, 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.

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, informed consent documents, 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 ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. 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 applicable privacy laws.

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

The informed consent documents 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 and possible risks associated with participation.

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 the Participating Country

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 (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on 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

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 for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to 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.

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

Abbreviation	Term
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 ₁₉₇	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
E-DMC	external data monitoring committee
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
GM	geometric mean
CCI	
GMFR	geometric mean fold rise
GMT	geometric mean titer
HIV	human immunodeficiency virus
IB	investigator's brochure
ICH	International Council for Harmonisation

Abbreviation	Term
ID	identification
IgG	immunoglobulin G
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IPD	invasive pneumococcal disease
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IWR	interactive Web-based response
LFT	liver function test
LLOQ	lower limit of quantitation
LSLV	last subject last visit
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
OPA	opsonophagocytic activity
PCD	primary completion date
PDA	personal digital assistant
PI	principal investigator
PPSV23	23-valent pneumococcal polysaccharide vaccine
PT	prothrombin time
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SAP	statistical analysis plan
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

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