



**A PHASE 3, RANDOMIZED, DOUBLE-BLIND TRIAL TO EVALUATE THE
SAFETY AND IMMUNOGENICITY OF A 20-VALENT PNEUMOCOCCAL
CONJUGATE VACCINE (20VPNC) WHEN COADMINISTERED WITH
SEASONAL INACTIVATED INFLUENZA VACCINE (SIIV) IN ADULTS
≥65 YEARS OF AGE**

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Adults ≥65 Years of Age

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1. PROTOCOL SUMMARY

1.1. Synopsis

Pfizer is developing a new 20vPnC candidate to expand protection against pneumococcal disease beyond that covered by current pneumococcal vaccines in children and adults. 20vPnC has the same composition as 13vPnC (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 and contains the same excipients as 13vPnC. 20vPnC is in late-stage clinical development, and data from Phase 3 studies in adults 18 years of age and above provide evidence that the safety profile is acceptable and similar to 13vPnC, and induces immune responses that are expected to support licensure for an adult (≥ 18 years of age) indication.

Annual seasonal influenza vaccination is recommended in a number of countries around the world to prevent influenza in adults, particularly adults with risk factors for increased influenza morbidity and mortality, such as those ≥ 65 years of age. Currently, 13vPnC is also recommended for vaccination of adults in that same age group, based on shared decision-making between an individual and their healthcare practitioner. Therefore, upon introduction of 20vPnC for immunization of adults, it is possible that it may be administered with influenza vaccine during influenza season.

The purpose of this study is to assess the safety and immunogenicity of 20vPnC and SIIV when given together at the same visit compared to the vaccines given 1 month apart (SIIV followed 1 month later by 20vPnC) in adults ≥ 65 years of age. Adults in this age group may be naïve to pneumococcal vaccine or have received prior pneumococcal vaccines, such as PPSV23, 13vPnC, or both; this study will endeavor to enroll participants with these vaccine histories.

Short Title:

Safety and Immunogenicity of 20vPnC Coadministered With SIIV in Adults ≥ 65 Years of Age

Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Safety Objective:	Primary Safety Estimands:	Primary Safety Endpoints:
To describe the safety profile of 20vPnC when coadministered with or 1 month after SIIV	In participants receiving 1 dose of 20vPnC or SIIV or saline and having safety follow-up after vaccination from each vaccine group: <ul style="list-style-type: none"> The percentage of participants reporting prompted local reactions within 10 days after each vaccination The percentage of participants reporting prompted systemic events within 7 days after each vaccination The percentage of participants reporting AEs within 1 month after each vaccination The percentage of participants reporting SAEs from the first vaccination up to 6 months after the last vaccination The percentage of participants reporting any NDCMCs up to 6 months after the last vaccination 	<ul style="list-style-type: none"> Prompted local reactions (redness, swelling, and pain at the injection site) Prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) AEs SAEs NDCMCs
Primary Pneumococcal Immunogenicity Objective:	Primary Pneumococcal Immunogenicity Estimand:	Primary Pneumococcal Immunogenicity Endpoint:
To demonstrate that the OPA GMTs elicited by 20vPnC when coadministered with SIIV (20vPnC+SIIV) are noninferior to those elicited by 20vPnC when administered 1 month after SIIV	In participants in compliance with the key protocol criteria (evaluable participants): <ul style="list-style-type: none"> GMR of the serotype-specific OPA titers 1 month after vaccination with 20vPnC from the coadministration group to the serotype-specific OPA titers 1 month after vaccination with 20vPnC from the separate-administration group 	<ul style="list-style-type: none"> Pneumococcal serotype-specific OPA titers
Primary SIIV Immunogenicity Objective:	Primary SIIV Immunogenicity Estimand:	Primary SIIV Immunogenicity Endpoint:
To demonstrate that the HAI GMTs elicited by SIIV when coadministered with 20vPnC (20vPnC+SIIV) are noninferior to those elicited by SIIV alone	In evaluable participants: <ul style="list-style-type: none"> GMR of the strain-specific HAI titers 1 month after vaccination with SIIV from the coadministration group to the corresponding strain from the separate-administration group 	<ul style="list-style-type: none"> Strain-specific HAI titers

Objectives	Estimands	Endpoints
Secondary Pneumococcal Immunogenicity Objective:	Secondary Pneumococcal Immunogenicity Estimands:	Secondary Pneumococcal Immunogenicity Endpoint:
To describe the fold rises of immune responses to 20vPnC when coadministered with or 1 month after SIIV	In evaluable participants from each vaccine group: <ul style="list-style-type: none"> • GMFR in serotype-specific OPA titers from before vaccination to 1 month after vaccination • The percentage of participants with a ≥ 4-fold rise in serotype-specific OPA titers from before vaccination to 1 month after vaccination 	<ul style="list-style-type: none"> • Pneumococcal serotype-specific OPA titers
Secondary SIIV Immunogenicity Objective:	Secondary SIIV Immunogenicity Estimands:	Secondary SIIV Immunogenicity Endpoint:
To describe the fold rises of immune responses to SIIV when coadministered with 20vPnC or administered alone	In evaluable participants from each vaccine group: <ul style="list-style-type: none"> • GMFR in strain-specific HAI titers from before vaccination to 1 month after vaccination 	<ul style="list-style-type: none"> • Strain-specific HAI titers

Overall Design

This Phase 3, multicenter, randomized, double-blind study with a 2-arm parallel design will be conducted at investigator sites in the United States. The purpose of this study is to assess the safety and immunogenicity of 20vPnC and SIIV given together at the same visit compared to the vaccines given separately 1 month apart (SIIV followed by 20vPnC). The study design and assessments are modeled after prior concomitant studies of pneumococcal conjugate vaccine and influenza vaccine. A single lot of SIIV is proposed for the study, and ideally this SIIV would be specifically indicated for use in adults ≥ 65 years of age; however, ultimately the SIIV used may be determined by supply availability.

Local reactions (redness, swelling, and pain at the injection site) occurring at the 20vPnC or saline injection site within 10 days and systemic events (fever, headache, fatigue, muscle pain, and joint pain) occurring within 7 days after each vaccination visit (Visit 1 and Visit 2) will be prompted for and collected daily by the participant in an e-diary device or application. Use of antipyretic/pain medications will also be prompted for and collected daily in the e-diary for 7 days after vaccination.

AEs will be collected from the signing of informed consent through Visit 3 (approximately 1 month after Visit 2). SAEs and NDCMCs will be collected from the signing of informed consent through 6 months after Visit 2.

To assess immunogenicity, blood will be collected at 3 study visits: at Visit 1 (prior to vaccination); at Visit 2 (prior to vaccination), 1 month after Visit 1; and at Visit 3, 1 month after Visit 2.

Number of Participants

Approximately 1780 participants (890 per group) will be randomized for a total of approximately 1600 evaluable participants (assuming a 10% dropout rate).

Intervention Groups and Duration

Each participant will participate in the study for approximately 7 months. Based on an estimated 3-month enrollment, the study duration will be approximately 10 months. All participants will receive SIIV, 20vPnC, and saline via intramuscular injection.

Statistical Methods

The primary pneumococcal and SIIV immunogenicity objectives will be evaluated by formal hypothesis tests for NI of coadministration of SIIV and 20vPnC (coadministration group) to administration of SIIV followed by 20vPnC 1 month later (separate-administration group), based on serotype-specific OPA GMTs and the strain-specific HAI GMTs 1 month after vaccination respectively. NI of the coadministration group to the separate-administration group for a pneumococcal serotype or an influenza strain will be declared if the lower bound of the 2-sided 95% CI for the GMR (coadministration group to separate-administration group) 1 month after vaccination is greater than 0.50 (2-fold criterion) or 0.67 (1.5-fold criterion), respectively. CCI

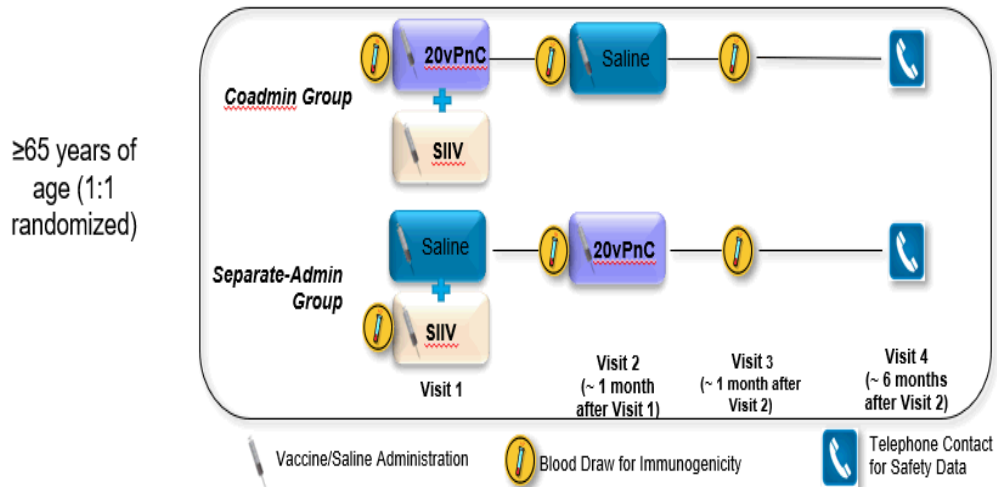
Strain-specific HAI GMFR from before vaccination to 1 month after vaccination,

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The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, and AEs (including SAEs and NDCMCs) for each vaccine group. A 3-tier approach will be used to summarize AEs.

1.2. Schema

Figure 1. Schema



1.3. Schedule of Activities

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

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

Visit Number	1	2	3	4
Visit Description	Vaccination 1	Vaccination 2	Follow-up After Vaccination 2	6-Month Safety Collection
Visit Type	Clinic Visit	Clinic Visit	Clinic Visit	Telephone Contact
Visit Window (Days)	Day 1	28 to 42 Days After Vaccination 1	28 to 42 Days After Vaccination 2	168 to 196 Days After Vaccination 2
Obtain informed consent	X			
Assign participant number via the IRT	X			
Record demography	X			
Perform clinical assessment, including medical history and smoking history	X			
Record pneumococcal vaccine history ^a	X			
Record nonstudy vaccinations		X	X	
Record concomitant medications ^b	X	X	X	X
Obtain prevaccination oral temperature	X	X		
Contraception check, if applicable ^c	X	X		
Review inclusion and exclusion criteria	X			
Review temporary delay criteria	X	X		
Review continued eligibility		X	X	
Assign randomization number	X			

Visit Number	1	2	3	4
Obtain blood sample for immunogenicity (~30 mL)	X ^d	X ^d	X	
Administer investigational product(s) ^e	X	X		
Observe and record acute reactions for 30 minutes after investigational product administration	X	X		
Provide a participant contact card	X			
Provide participant with an e-diary (device or application), thermometer, and measuring device and instruct to collect prompted local reactions, systemic events, and use of pain/antipyretic medications ^f	X			
Review e-diary ^g		X	X	
Record and report AEs ^h	X-----X			
Record and report SAEs and NDCMCs ^{i,j}	X-----X			

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

- a. The name and date of administration of any prior pneumococcal vaccines will be collected and recorded in the CRF. The names and dates must be obtained from sources, such as vaccination cards or medical records.
- b. Record concomitant medications used to treat SAEs or NDCMCs.
- c. The investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly until 28 days after the last dose of investigational product and document the conversation and the participant’s affirmation in the participant’s chart.
- d. Blood sample will be collected prior to vaccination.
- e. Remind the participant that the use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).
- f. Participants will record prompted local reactions and systemic events in an e-diary occurring within 10 and 7 days, respectively, after vaccination. Use of antipyretic/pain medications will also be prompted for and collected daily in an e-diary for 7 days after vaccination. Participants will be instructed to contact the study staff or investigator if they experience redness or swelling measuring ≥ 20 measuring device units or severe pain at the 20vPnC/saline injection site or any Grade 4 prompted systemic event.
- g. Designated site staff will review e-diary data online at frequent intervals (daily is optimal) for the 10 days following each vaccination to evaluate participant compliance and reported events as part of the ongoing safety review. Any e-diary devices given to participants are to be collected no later than Visit 3.
- h. AEs include nonserious AEs, SAEs, and NDCMCs.
- i. An NDCMC is defined as a disease or medical condition, not previously identified, that is expected to be persistent or otherwise long-lasting in its effects.
- j. If the participant consents, participants withdrawn from the study will receive a 6-month telephone safety follow-up after their last vaccination for collection of any SAEs and NDCMCs.

2. INTRODUCTION

2.1. Pneumococcal Disease

Streptococcus pneumoniae are gram-positive encapsulated cocci that have been a leading cause of bacteremia, bacterial meningitis, pneumonia, and AOM and continue to be a major global public health concern.^{1,2,3} Serious pneumococcal disease may occur at any age; however, children <5 and adults ≥ 65 years of age are at particularly increased risk.⁴ Individuals with certain comorbidities and immunocompromising conditions are also at increased risk, including persons with chronic heart, lung, liver, and renal disease, and those with functional asplenia.

Surveillance studies conducted in 2010 to 2012 by the CDC found that *S pneumoniae* were among the most common bacterial pathogens identified in CAP requiring hospitalization in both children and adults in the United States.^{5,6} Bacteremic pneumococcal pneumonia (accounting for the majority of IPD in adults) is less common than nonbacteremic pneumococcal pneumonia (an estimated 3 to 10 or more cases of nonbacteremic pneumococcal pneumonia occur for every 1 case of bacteremic pneumonia); both bacteremic and nonbacteremic pneumococcal pneumonia are associated with significant morbidity and mortality in all age groups.^{1,7} Pneumococcal disease in older adults represents a high clinical and economic healthcare burden. In Australia, the incidence of hospitalization for all-cause pneumonia in adults aged ≥ 65 years from 2011 through 2012 corresponded to an incidence rate of 1347/100,000 population.⁸ Incidence rates were higher in adults ≥ 85 years of age (3507/100,000). Pneumococcal pneumonia accounted for 20.6% of hospitalization with an incidence of 274/100,000 population.⁸ In a study of the global burden of LRIs using data from 195 countries, it was estimated that in 2016, LRIs were among the leading causes of death in people of all ages and pneumococcal LRIs accounted for approximately 50% of LRI deaths (1.2 million deaths) across all ages in 2016.⁹ The CDC estimated that in 2017, there were 31,000 cases and 3590 deaths due to IPD in the United States.¹⁰ As these numbers suggest, *S pneumoniae* remains an important cause of serious disease in the United States and worldwide.

S pneumoniae has been identified as one of the main pathogens in influenza-related secondary bacterial pneumonia. A review of Emerging Infections Network data identified *S pneumoniae* in 16% of both pediatric and adult patients with laboratory-confirmed influenza and secondary bacterial infection.¹¹ Coinfection with influenza and *S pneumoniae* may cause more severe disease than infection with either alone.^{12,13} Both pneumococcal pneumonia and IPD (eg, *S pneumoniae* isolated from a normally sterile site) have been associated with severe and fatal cases of influenza during influenza pandemics, including the influenza A(H1N1)pdm09 pandemic in 2009.^{14,15,16,17,18}

In addition to the burden of pneumococcal pneumonia among adults, influenza is an important contributor to adult morbidity and mortality.¹⁹ In the United States, annual influenza vaccination is recommended for adults as the primary method for preventing influenza illness and its complications (which may include bacterial pneumonia).²⁰

2.2. Vaccines to Prevent Pneumococcal Disease

2.2.1. Pneumococcal Polysaccharide Vaccines

The polysaccharide capsule has been identified as an important virulence factor for this pathogen. While more than 95 pneumococcal serotypes, differentiated by their capsular polysaccharide composition, have been identified, serious disease is generally caused by a smaller subset of serotypes.^{21,22} Anticapsular antibodies, directed against the specific serotype, bind to the capsule and promote complement-mediated opsonophagocytic killing and clearance of the organism.²³ Pneumococcal disease can be prevented with polysaccharide-based vaccines that induce antibody responses with functional (opsonophagocytic) activity and target the capsular serotypes responsible for disease.²⁴

Vaccines containing free polysaccharides have been licensed since the 1970s. One such vaccine, PPSV23, has been licensed in the United States since 1983.²⁵ 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), nor do they generate immunologic memory, so their protective effect wanes over 2 to 5 years.^{4,26,27,28} Moreover, their ability to prevent nonbacteremic pneumonia and AOM is limited or lacking.^{24,28,29,30} They also do not have an impact on nasopharyngeal carriage and, therefore, do not afford herd protection.³¹ 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.^{32,33,34} 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 VT pneumococcus.³⁵ Despite waning immunity, these concerns of hyporesponsiveness, as well as other factors, have led most recommending bodies to restrict PPSV23 to a single lifetime dose in adults ≥ 65 years of age and 1 to 2 doses in most other high-risk populations.^{35,36,37}

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.^{27,38} Prevnar® (7vPnC) was the first pneumococcal conjugate vaccine to be licensed (2000) and was indicated for prevention of pneumococcal disease in infants and young children on the basis of efficacy studies. 7vPnC contained capsular polysaccharide conjugates for 7 pneumococcal serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), each covalently linked to 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).^{39,40,41,42,43} These serotypes also accounted for a high proportion of antibiotic-resistant strains.⁴⁴ 7vPnC demonstrated efficacy against

VT IPD, pneumonia, and AOM in large, randomized controlled efficacy studies in infants.^{45,46} The 7vPnC components contained in a related pneumococcal conjugate vaccine also were demonstrated to be efficacious against clinically/radiographically-defined pneumonia.^{47,48} Following the introduction of 7vPnC, a reduction of nasopharyngeal carriage and transmission has resulted in indirect herd effects, with a 92% reduction of 7vPnC VT IPD in older adults ≥ 65 years of age.⁴⁹

Prevnar 13® (13vPnC) was developed to expand serotype coverage and was licensed in the United States in 2010. 13vPnC includes the same *S pneumoniae* serotypes as 7vPnC and an additional 6 polysaccharide conjugates for serotypes 1, 3, 5, 6A, 7F, and 19A.^{38,42,50} The vaccine was licensed for use in infants and young children based on comparisons of serotype-specific IgG to 7vPnC, with supportive data to demonstrate the functional activity of the immune responses. 13vPnC was subsequently licensed in adults based on an accelerated approval pathway demonstrating comparable serotype-specific OPA responses to PPSV23, followed by traditional approval based on demonstration of efficacy against VT CAP in CAPiTA, a randomized controlled study of adults ≥ 65 years of age.⁵¹ 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 the evidence that protection against IPD wanes significantly over time.²⁶ 13vPnC has replaced 7vPnC and is licensed in the United States and many other countries, with national recommendations for use in children and older adults.^{52,53,54,55} It has also been prequalified by WHO for use in national infant immunization programs in lower- and middle-income countries.^{56,57} Surveillance data from several countries following the introduction of 13vPnC into the routine infant immunization program have demonstrated vaccine effectiveness against VT IPD in the vaccinated population.^{58,59,60}

Prevnar 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.^{37,61,62,63} 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 Prevnar 13 into the routine infant immunization schedule, suggesting potential value in direct immunization of adults rather than reliance solely on the herd effect.⁶⁴ 13vPnC is currently recommended for adults ≥ 65 years of age, based on shared decision-making between the individual and their healthcare practitioner. The prevalence of IPD due to most of the serotypes contained only in PPSV23 has remained stable or slightly increased in the United States and other countries, despite continued recommendation and use of PPSV23 in adults ≥ 65 years of age and high-risk adults.^{65,66,67} These serotypes account for a significant amount of pneumococcal disease and their continued presence highlights the need for a better vaccine than PPSV23 to expand protection.

2.3. 13vPnC and Influenza Vaccine

Because 13vPnC and influenza vaccine have similar target populations and might be given at the same visit, 3 Pfizer-sponsored trials previously evaluated the safety and immunogenicity of 13vPnC coadministered with SIIV.^{68,69,70} One trial evaluated the safety and immunogenicity of 13vPnC coadministered with TIV among healthy adults 50 to 59 years of age naïve to PPSV23.⁶⁸ Another trial evaluated the safety and immunogenicity of 13vPnC coadministered with TIV among healthy adults ≥ 65 years of age who were PPSV23-naïve.⁶⁹ A third trial evaluated the safety and immunogenicity of 13vPnC coadministered with QIV among adults ≥ 50 years of age who received at least 1 dose of PPSV23 before study enrollment.⁷⁰

The safety profile of 13vPnC when coadministered with SIIV was generally consistent with the known safety profile of 13vPnC. Serotype-specific pneumococcal antibody responses generally appeared to be slightly lower when 13vPnC was coadministered with SIIV compared to 13vPnC administered alone, but NI was demonstrated for all (2 studies),^{68,70} or almost all (12 of 13 serotypes in 1 study),⁶⁹ vaccine serotypes in the studies. The immune responses to the influenza vaccine strains were comparable whether 13vPnC was coadministered or given separately.^{68,69,70}

See Section 2.4 for more details about the safety and immunogenicity results for the 13vPnC+SIIV studies.

2.4. Development of 20vPnC

The 20vPnC candidate is modeled after 7vPnC and 13vPnC. 20vPnC contains the polysaccharides of capsular serotypes present in 13vPnC and 7 new capsular polysaccharides (for serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F) individually conjugated to CRM₁₉₇. The 7 additional serotypes were selected based on their relative prevalence as a cause of IPD, their generalized geographic distribution, and other factors that would support inclusion, such as the presence of antibiotic resistance (11A, 15B), association with outbreaks (8, 12F), and greater disease severity (eg, meningitis, mortality) (10A, 11A, and 22F).^{71,72,73,74,75,76,77,78,79,80,81,82,83,84} These 7 serotypes have a long-standing association with serious pneumococcal disease and are responsible for a substantial burden of remaining pneumococcal disease.

The 20vPnC clinical development program in adults has included several trials, including: 2 Phase 1 trials in healthy adults; 1 Phase 2 trial in adults 60 through 64 years of age; and, 3 Phase 3 trials in adults ≥ 18 years of age.

In Phase 1 and Phase 2 trials, 20vPnC induced immune responses to the pneumococcal serotypes in the vaccine. The Phase 3 pivotal trial (B7471007) met its primary immunogenicity objectives of NI for all serotypes in common with licensed Prevnar 13 and 6 of the 7 additional serotypes when compared PPSV23; 1 of the new 7 serotypes missed NI criteria by a small margin. Secondary immunogenicity objectives for adults 18 to 59 years of age compared to those 60 to 64 years of age met NI for all 20 serotypes. This suggests that protective antibodies against all 20 serotypes were elicited by 20vPnC, and that protection

against pneumococcal disease will be similar to 13vPnC. The safety objectives were met in adults ≥ 18 years of age, demonstrating that the safety and tolerability of 20vPnC were comparable to licensed pneumococcal vaccines.

Additionally, the Phase 3 program has demonstrated equivalence of immunogenicity among 3 different lots of 20vPnC in a clinical lot consistency trial, and 20vPnC has acceptable safety and elicits immune responses to the 20 vaccine serotypes in adults previously vaccinated with pneumococcal vaccines.

Additional description of the clinical trial results, epidemiology of the 7 serotypes, and clinical (and nonclinical) program are described in the 20vPnC IB.

2.5. Indication

20vPnC is being developed in adults for the prevention of pneumococcal disease (including pneumonia and invasive disease) caused by *S pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F in adults ≥ 18 years of age.

2.6. Study Rationale

When an individual interacts with a healthcare provider to obtain an influenza vaccination, there may also be an opportunity to administer other recommended vaccines for which the individual may be eligible, such as pneumococcal conjugate vaccine. Therefore, assessing the safety and immunogenicity of coadministration with the influenza vaccine will help inform potential use of 20vPnC.

The purpose of this study is to assess the safety and immunogenicity of 20vPnC and SIIV when given together at the same visit compared to the vaccines given 1 month apart (SIIV followed 1 month later by 20vPnC) in adults ≥ 65 years of age. Adults in this age group may be naïve to pneumococcal vaccine or have received prior pneumococcal vaccines, such as PPSV23, 13vPnC, or both. Therefore, this study will enroll participants with these diverse vaccine histories, although no specific proportions will be targeted. The study described in this protocol uses a similar design, and will perform similar assessments, as in prior studies of SIIV coadministration with other pneumococcal conjugate vaccines.^{68,69,70}

2.7. Background

20vPnC is being developed to further expand protection beyond 13vPnC against the global burden of vaccine-preventable pneumococcal disease in children and adults. The clinical development program in adults has been generally modeled on the 13vPnC program. The clinical program is currently in late-stage development. To date, 2 Phase 1, 1 Phase 2, and 3 Phase 3 studies in adults have been conducted to support licensure for an adult indication. These are all safety and immunogenicity studies. An application to support licensure of 20vPnC in adults 18 years of age and above is anticipated to be submitted in late 2020.

Upon introduction of 20vPnC in adults, healthcare providers may seek the opportunity during influenza season to provide 20vPnC when individuals present for their influenza vaccination. Therefore, data on the safety and immunogenicity of coadministration of these 2 vaccines will be helpful for that situation. This Phase 3 study is designed to provide data on the safety profile and immunogenicity of 20vPnC and SIIV when administered at the same visit.

2.7.1. Clinical Overview

Data from Phase 1 and Phase 2 studies in adults 18 to 64 years of age found that 20vPnC induces immune responses to the 20 vaccine serotypes and had a safety profile consistent with other pneumococcal conjugate vaccines. Additionally, safety data from 3 Phase 3 adult studies (B7471006, B7471007, and B7471008) have shown safety profiles consistent with other pneumococcal conjugate vaccines. Immunogenicity data from the pivotal Phase 3 studies demonstrated that 20vPnC induces OPA GMTs that are noninferior to 13vPnC for the 13 matched serotypes and noninferior to PPSV23 for 6 of the 7 additional serotypes. The remaining serotype demonstrated strong immune responses. See the 20vPnC IB for additional details.

2.8. Benefit/Risk Assessment

The safety profile of 20vPnC is expected to be similar to 13vPnC, but AEs may be different with the investigational 20vPnC. The safety profiles are expected to be similar because 20vPnC contains the same components and excipients as 13vPnC, along with the polysaccharide conjugates for 7 additional pneumococcal serotypes, and to date, 20vPnC has demonstrated a safety profile similar to 13vPnC in clinical trials. The most common AEs noted in adults after vaccination are primarily related to local reactions (injection site pain, redness, and swelling) and systemic events (fever, headache, fatigue, joint pain, and muscle pain). Safety review of data from the 3 completed Phase 3 adult trials have not revealed any unexpected safety concerns. See the 20vPnC IB for additional details.

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

Additional potential risks of clinical significance are presented in the table in [Section 2.8.1](#)

More detailed information about the known and expected benefits and risks and reasonably expected AEs of 20vPnC may be found in the IB, which is the SRSD for this study. The SRSD for the SIIV agent is the USPI.

2.8.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): Vaccinations with 20vPnC and SIIV		
<p>20vPnC</p> <p>The relevant key risks associated with 20vPnC include: local reactions (injection site pain, redness, and swelling); systemic events (fever, headache, fatigue, joint pain, and muscle pain); and allergic reactions, including skin rash, face or lip swelling, wheezing, shortness of breath, or severe allergic reaction (eg, anaphylactic shock).</p>	<p>The risks are based on the 20vPnC IB.</p>	<p>Eligibility criteria have been selected to ensure that only appropriate participants are included in the study (see Section 5).</p> <p>E-diary and AE data will be monitored by the investigator (or designee) and sponsor.</p> <p>Participants who develop exclusionary conditions during study conduct or participants with significant reactions after Visit 1 vaccination or AEs considered by the investigator to present increased risk to the participant if he/she received additional study vaccinations will be excluded from further vaccinations.</p>
<p>SIIV</p> <p>The relevant key risks associated with SIIV include: injection site pain, tenderness at the injection site, headache, fatigue, myalgia, and malaise.</p>	<p>The risks are based on the SIIV USPI.</p>	<p>Eligibility criteria have been selected to ensure that only appropriate participants are included in the study (see Section 5).</p> <p>Participants who develop exclusionary conditions during study conduct or participants with significant reactions after Visit 1 vaccinations or AEs considered by the investigator to present increased risk to the participant if he/she received additional study vaccinations will be excluded from further vaccinations.</p>
<p>Conjugate pneumococcal vaccine coadministered with SIIV.</p> <p>Anticipated risks of coadministration of 20vPnC and SIIV are based on risks of coadministration of 13vPnC and SIIV and include: possible increased incidence of local reactions at the 20vPnC injection site compared with placebo, higher proportion of participants reporting systemic events (eg, fatigue, headache, muscle pain, chills, rash, decreased appetite).</p>	<p>The risks are based on 3 clinical trials.^{68,69,70}</p>	<p>E-diary and AE data will be monitored by the investigator (or designee) and sponsor.</p> <p>Participants who develop exclusionary conditions during study conduct or participants with significant reactions after Visit 1 vaccinations or AEs considered by the investigator to present increased risk to the participant if he/she received additional study vaccinations will be excluded from further vaccinations.</p>

Study Procedure: Venipuncture		
There is the risk of fainting, and pain, swelling, bruising, and infection at the venipuncture site.	Venipuncture is required to collect immunogenicity data from participants.	Only qualified nurses, physicians, nurse practitioners, physician assistants, phlebotomists, or medical assistants certified or otherwise authorized to draw blood per the standards and procedures of the investigative site, as allowed by institutional, local, and country guidance, will be allowed to draw blood to minimize local complications.
Other: N/A		

2.8.2. Benefit Assessment

As described in [Section 2](#), adults ≥ 65 years of age are at particularly increased risk of pneumococcal disease, and pneumococcal conjugate vaccines have been shown to elicit T-cell-dependent immune responses, which have been shown to be protective in older adults. A safe and immunogenic pneumococcal conjugate vaccine with expanded pneumococcal serotype coverage would fulfill an unmet need for expanded protection against pneumococcal disease.

If 20vPnC is successful in Phase 3 studies and is approved, it is anticipated to provide a benefit to a participant in the prevention of pneumonia and invasive disease caused by vaccine serotypes.

The SIIV in this study is licensed by the FDA for the prevention of influenza disease due to the influenza strains; therefore, administration of this vaccine may help protect against influenza disease.

2.8.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks of vaccination with 20vPnC or SIIV (eg, transient, mild-to-moderate local reactions and systemic events and risks of minor complications from intramuscular injections or venipuncture) are justified by the anticipated benefits that participants might receive (eg, possible protective immunity against vaccine-serotype *S pneumoniae* and influenza).

Pfizer considers that the available information in clinical studies conducted to date with 20vPnC, the available safety profile of similar pneumococcal conjugate vaccines (ie, Prevnar and Prevnar 13), and the limited risks from study procedures support a favorable benefit-risk profile for 20vPnC and this study.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary Safety Objective:	Primary Safety Estimands:	Primary Safety Endpoints:
To describe the safety profile of 20vPnC when coadministered with or 1 month after SIIV	In participants receiving 1 dose of 20vPnC or SIIV or saline and having safety follow-up after vaccination from each vaccine group: <ul style="list-style-type: none"> • The percentage of participants reporting prompted local reactions within 10 days after each vaccination • The percentage of participants reporting prompted systemic events within 7 days after each vaccination • The percentage of participants reporting AEs within 1 month after each vaccination • The percentage of participants reporting SAEs up to 6 months after the last vaccination • The percentage of participants reporting any NDCMCs up to 6 months after the last vaccination 	<ul style="list-style-type: none"> • Prompted local reactions (redness, swelling, and pain at the injection site) • Prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) • AEs • SAEs • NDCMCs
Primary Pneumococcal Immunogenicity Objective:	Primary Pneumococcal Immunogenicity Estimand:	Primary Pneumococcal Immunogenicity Endpoint:
To demonstrate that the OPA GMTs elicited by 20vPnC when coadministered with SIIV (20vPnC+SIIV) are noninferior to those elicited by 20vPnC when administered 1 month after SIIV	In participants in compliance with the key protocol criteria (evaluable participants): <ul style="list-style-type: none"> • GMR of the serotype-specific OPA titers 1 month after vaccination with 20vPnC from the coadministration group to the serotype-specific OPA titers 1 month after vaccination with 20vPnC from the separate-administration group 	<ul style="list-style-type: none"> • Pneumococcal serotype-specific OPA titers
Primary SIIV Immunogenicity Objective:	Primary SIIV Immunogenicity Estimand:	Primary SIIV Immunogenicity Endpoint:
To demonstrate that the HAI GMTs elicited by SIIV when coadministered with 20vPnC (20vPnC+SIIV) are noninferior to those elicited by SIIV alone	In evaluable participants: <ul style="list-style-type: none"> • GMR of the strain-specific HAI titers 1 month after vaccination with SIIV from the coadministration group to the corresponding strain from the separate-administration group. 	<ul style="list-style-type: none"> • Strain-specific HAI titers

Objectives	Estimands	Endpoints
Secondary Pneumococcal Immunogenicity Objective:	Secondary Pneumococcal Immunogenicity Estimands:	Secondary Pneumococcal Immunogenicity Endpoint:
To describe the fold rises of immune responses to 20vPnC when coadministered with or 1 month after SIIV	In evaluable participants from each vaccine group: <ul style="list-style-type: none"> • GMFR in serotype-specific OPA titers from before vaccination to 1 month after vaccination • The percentage of participants with a ≥ 4-fold rise in serotype-specific OPA titers from before vaccination to 1 month after vaccination 	<ul style="list-style-type: none"> • Pneumococcal serotype-specific OPA titers
Secondary SIIV Immunogenicity Objective:	Secondary SIIV Immunogenicity Estimand:	Secondary SIIV Immunogenicity Endpoint:
To describe the fold rises of immune responses to SIIV when coadministered with 20vPnC or administered alone	In evaluable participants from each vaccine group: <ul style="list-style-type: none"> • GMFR in strain-specific HAI titers from before vaccination to 1 month after vaccination 	<ul style="list-style-type: none"> • Strain-specific HAI titers
CCI [REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

4. STUDY DESIGN

4.1. Overall Design

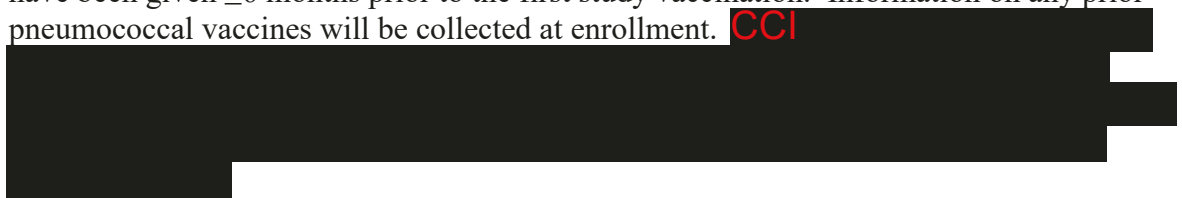
This Phase 3, multicenter, randomized, double-blind study, with a 2-arm parallel design, will be conducted at investigator sites in the United States. The purpose of this study is to assess the safety and immunogenicity of 20vPnC and SIIV when given together at the same visit ([SIIV+20vPnC]/saline group) compared to 20vPnC given 1 month after SIIV ([SIIV+saline]/20vPnC group). The study design and assessments are modeled from prior studies of pneumococcal conjugate vaccine coadministered with influenza vaccine.^{68,69,70}

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Approximately 1780 healthy adults ≥ 65 years of age will be stratified by prior pneumococcal vaccine status (no previous pneumococcal vaccine [naïve], receipt of at least 1 dose of PPSV23 only, receipt of at least 1 dose of 13vPnC only, or receipt of at least 1 dose each of PPSV23 and 13vPnC) and randomized in 1:1 ratio to 1 of 2 groups by center-based randomization. The coadministration group ([SIIV+20vPnC]/saline) will receive SIIV and 20vPnC at the same visit (Visit 1), followed 1 month later by administration of saline (Visit 2). The separate-administration group ([SIIV+saline]/20vPnC) will receive SIIV and saline at Visit 1, followed 1 month later with 20vPnC administered at Visit 2.

Refer to [Section 4.2](#) for the rationale behind this stratification.

If participants have received prior pneumococcal vaccination(s), the most recent dose must have been given ≥ 6 months prior to the first study vaccination. Information on any prior pneumococcal vaccines will be collected at enrollment. **CCI**



On Day 1 (Visit 1), participants will be assessed for eligibility (including medical history and pneumococcal vaccine history). If eligible, participants will have blood drawn for immunogenicity assessments and be randomized to receive either SIIV and 20vPnC ([SIIV+20vPnC]/saline) or SIIV and saline ([SIIV+saline]/20vPnC). The 20vPnC and saline will be prepared and administered by an unblinded investigator site staff member. Participants will be observed for 30 minutes after vaccination by blinded investigator site staff, and any reactions occurring during that time will be recorded as AEs.

At Visit 2, (28 to 42 days after Visit 1 [Study Days 29 to 43]), participants will return to the investigator site and be assessed for continued eligibility. Participants will be asked to provide information on any AEs (including nonserious AEs, SAEs, and NDCMCs), and on any needed e-diary follow-up. Participants will also be asked for information on concomitant medications used to treat any SAEs or NDCMCs and on any nonstudy vaccines they received since Visit 1. Blood will be drawn for immunogenicity assessments. Participants will receive a vaccination with either saline (if the participant was in the [SIIV+20vPnC]/saline group) or 20vPnC (if the participant was in the [SIIV+saline]/20vPnC group) and be observed for 30 minutes after vaccination by blinded investigator site staff; any reactions occurring during this time will be recorded as AEs.

At Visit 1, participants will receive an e-diary (device or mobile-device application), thermometer, and measuring device (caliper) and will be instructed at each vaccination visit (Visit 1 and Visit 2) to record prompted local reactions (redness, swelling, and pain at the injection site) occurring at the 20vPnC/saline injection site within 10 days after vaccination (Days 1 through 10, where Day 1 is the day of vaccination) and prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain) occurring within 7 days after vaccination (Days 1 through 7, where Day 1 is the day of vaccination) daily in the e-diary.

Participants will also be instructed to record any use of antipyretic/pain medications in the e-diary daily for 7 days after vaccination. Participants will be instructed to contact the study staff if the participant experiences redness or swelling at the 20vPnC/saline injection site measuring >20 measuring device units (>10 cm) or severe injection site pain (prevents daily activity) in the 10 days after vaccination or has an emergency room visit or hospitalization.

AEs (nonserious AEs, SAEs, and NDCMCs) will be collected for each participant from the time informed consent is obtained through and including Visit 3.

At Visit 3 (28 to 42 days after Visit 2), participants will return to the investigator site and be assessed for continued eligibility. Information will be collected from the participants on AEs, SAEs, NDCMCs, and e-diary follow-up (as needed). Blood will be drawn for immunogenicity assessment.


At Visit 4 (approximately 6 months [168 to 196 days] after Visit 2), the site will contact the participant via telephone to inquire about SAEs and NDCMCs and concomitant medications used to treat SAEs or NDCMCs since the last visit.

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

4.2. Scientific Rationale for Study Design

The purpose of this study is to assess the safety and immunogenicity of 20vPnC and SIIV given together at the same visit compared to the vaccines given separately. This study uses a similar design and includes similar assessments as in prior studies of SIIV coadministration with other pneumococcal conjugate vaccines (13vPnC and an investigational 15-valent pneumococcal conjugate vaccine).^{68,69,70,85}

Additionally, this study design accounts for potential effect of prior pneumococcal vaccine on subsequent pneumococcal responses. Adults ≥ 65 years of age may be naïve to pneumococcal vaccines or have been vaccinated with PPSV23 or 13vPnC in the past. Previous studies have found lower pneumococcal responses to pneumococcal conjugate vaccines among individuals vaccinated with PPSV23 compared to naïve individuals, and variable responses after a second dose of 13vPnC compared to naïve individuals were also observed.^{68,86} CCI



4.3. Justification for Dose

The 20vPnC candidate is modeled after 7vPnC and 13vPnC, and contains capsular polysaccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F individually conjugated to CRM₁₉₇. The vaccine formulation contains 2.2 µg of each saccharide, except for 4.4 µg of 6B, per 0.5-mL dose. In adults, administration of 1 dose of pneumococcal conjugate vaccine induces immune responses. The SIIV will be a licensed vaccine, provided in a commercially available presentation, and the indicated dose will be administered.

For these products the term “dose” refers to an injection of a vaccine.

4.4. End of Study Definition

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

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female participants ≥ 65 years of age at the time of consent.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Adults determined by clinical assessment, including medical history and clinical judgment, to be eligible for the study, including adults with preexisting stable disease, defined as disease not requiring significant change in therapy in the previous 6 weeks or hospitalization for worsening disease within 12 weeks before receipt of investigational product.
4. Expected to be available for the duration of the study and can be contacted by telephone during study participation.

5. Male participant who is able to father children and willing to use a highly effective method of contraception, as outlined in this protocol, for at least 28 days after the dose of investigational product; or female participant not of childbearing potential; or male participant not able to father children. Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

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6. Adults who have no history of ever receiving a pneumococcal vaccine (ie, pneumococcal vaccine-naïve), or have a history of receiving a licensed pneumococcal vaccination ≥ 6 months prior to the first vaccination in the study.

Note: For participants with a history of receiving a licensed pneumococcal vaccination, documentation of date(s) and type(s) of prior pneumococcal vaccination(s) will be obtained.

Informed Consent:

7. Capable of giving signed informed consent, as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions:

1. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of 20vPnC, any other diphtheria toxoid-containing vaccine, or SIIV.
2. Allergy to egg proteins (egg or egg products) or chicken proteins.
3. Serious chronic disorder, including metastatic malignancy, severe COPD requiring supplemental oxygen, end-stage renal disease with or without dialysis, cirrhosis of the liver, clinically unstable cardiac disease, or any other disorder that in the investigator's opinion would make the participant inappropriate for entry into the study.
4. History of Guillain-Barré syndrome.
5. History of microbiologically proven invasive disease caused by *S pneumoniae*.
6. Known or suspected immunodeficiency or other conditions associated with immunosuppression, including, but not limited to, immunoglobulin class/subclass deficiencies, generalized malignancy, HIV infection, leukemia, lymphoma, or organ or bone marrow transplant.

7. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
8. Congenital, functional, or surgical asplenia.
9. Other medical or psychiatric condition, including recent (within the past year) or active suicidal ideation/behavior, or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

10. Previous vaccination with any investigational pneumococcal vaccine, or planned receipt of any licensed or investigational pneumococcal vaccine through study participation.
11. Vaccination with any influenza vaccine <6 months before investigational product administration, or planned receipt of any licensed or investigational nonstudy influenza vaccine during study participation.
12. Currently receives treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, or planned receipt through the last blood draw (Visit 3). If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before investigational product administration. Inhaled/nebulized, intraarticular, intrabursal, or topical (skin, eyes, or ears) corticosteroids are permitted.
13. Receipt of blood/plasma products or immunoglobulin within the 60 days before investigational product administration, or planned receipt through the last planned blood draw in the study (through Visit 3).

Prior/Concurrent Clinical Study Experience:

14. Participation in other studies involving investigational drugs, investigational vaccines, or investigational devices within 28 days prior to study entry and/or during study participation. Participation in purely observational studies is acceptable.

Diagnostic Assessments:

Not applicable.

Other Exclusions:

15. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

5.3.1. Contraception

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

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs and SAEs.

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

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

The following conditions may allow a participant to be vaccinated once the conditions have resolved and the participant is otherwise eligible:

5.5.1. Temporary Delay Criteria

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

The Visit 1 and Visit 2 blood draws prior to vaccination should take place on the same day as the vaccination.

5.5.1.1. Criteria for Temporarily Delaying Vaccine Administration

- Current febrile illness (body temperature $\geq 100.4^{\circ}\text{F}$ [$\geq 38.0^{\circ}\text{C}$]) or other acute illness within 48 hours before investigational product administration.
- Receipt of any inactivated or otherwise nonlive vaccine within 14 days or any live vaccine within 28 days before investigational product administration.

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

6. STUDY INTERVENTION

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

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

6.1. Study Intervention(s) Administered

20vPnC and saline will be provided by the sponsor to the study sites (see Section 6.1.1 for SIIV supply).

20vPnC and saline will be packed and labeled as investigational product in accordance with current guidelines and applicable local and legal regulatory requirements. The formulations of the investigational products are described below.

20vPnC is a sterile liquid suspension formulation containing saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F individually conjugated to CRM₁₉₇. CCI

20vPnC will be supplied to the site as packaged, single-use prefilled syringes.

The saline control will consist of a sterile normal saline solution for injection (0.9% sodium chloride injection) and will be supplied to the site as packaged single-use prefilled syringes.

6.1.1. Concomitant Vaccines/Medications

Licensed SIIV containing strains of influenza viruses that are antigenically equivalent to the annually recommended strains will be supplied to the site as packaged, single-use prefilled syringes after required regulatory and legal documents have been received by the sponsor. Pfizer will provide this vaccine. CCI

CCI

Administration of SIIV will be recorded in the CRF.

6.1.2. Administration

At Visit 1, all participants will receive a single dose of SIIV injected intramuscularly into the right deltoid. The SIIV will be administered in an open-label fashion. Participants randomized to the (SIIV+20vPnC)/saline group will receive 0.5 mL of 20vPnC injected intramuscularly into the left deltoid, and participants randomized to the (SIIV+saline)/20vPnC group will receive 0.5 mL of saline injected intramuscularly into the left deltoid.

At Visit 2, participants randomized to the (SIIV+20vPnC)/saline group will receive 0.5 mL of saline intramuscularly into the left deltoid, and participants randomized into the (SIIV+saline)/20vPnC group will receive 0.5 mL of 20vPnC injected intramuscularly into the left deltoid.

The 20vPnC and saline vaccines will be administered by an unblinded third-party site staff member at Visit 1 and Visit 2.

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

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

Study intervention administration details will be recorded on the CRF.

6.1.3. Medical Devices

In this study, medical devices being deployed are the prefilled syringes containing 20vPnC, saline, or SIIV. Instructions for medical device use are provided in the IP manual or in the package insert.

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the unblinded study personnel throughout the study.

CCI

6.2. Preparation/Handling/Storage/Accountability

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational 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.

CCI

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CCI

[REDACTED]

[REDACTED]

CCI [REDACTED]

6.2.1. Preparation and Dispensing

See the IP manual or applicable SRSD for instructions on how to prepare the study intervention for administration. Study interventions 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. The 20vPnC and saline will be prepared and administered by an unblinded staff member (see Section 6.2.2).

6.2.2. Preparation/Handling by Unblinded Staff

The 20vPnC and saline will be prepared by qualified unblinded site personnel according to the IP manual and will be administered by an unblinded site staff member at Visit 1 and Visit 2. All other site staff members, including the PI, and the participant will be blinded. The PI will assign the responsibility of administering 20vPnC and saline to unblinded persons who will not participate in the evaluation of any study participant. More than 1 unblinded site staff member will be assigned. A site staff member or clinic pharmacy should fulfill this role and must be an appropriately qualified and experienced member of the study staff as described in Section 6.2.1. Contact between the unblinded site staff member who will administer 20vPnC and saline and study participants should be kept to a minimum.

6.3. Measures to Minimize Bias: Randomization and Blinding

As the appearances of 20vPnC and saline are different, the investigational products will be prepared and administered by a designated third-party unblinded site staff member. All other study personnel, including the PI, and the participant will be blinded. The unblinded site staff member(s) will not participate in participant assessments. Because all participants will receive SIV at Visit 1, SIV will be an open-label vaccination but can still be prepared and administered by the same designated third-party unblinded site staff member. See [Section 6.3.2](#) and [Section 6.3.3](#) for more details on blinding of site staff members and sponsor.

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site staff (study coordinator or specified designee) will be required to enter or select information, including, but not limited to, the user's ID and password, the protocol number, and the participant number. The site staff will then be

provided with a vaccine assignment, randomization number, and DU or container number when the investigational product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

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

Participants will be stratified by prior pneumococcal vaccine status (no previous pneumococcal vaccine [naïve], receipt of at least 1 dose of PPSV23 only or at least 1 dose of 13vPnC only, or receipt of at least 1 dose of both PPSV23 and 13vPnC) and randomized in a 1:1 ratio to each of the 2 vaccine groups, either the coadministration group ([SIIV+20vPnC]/saline) or the separate-administration group ([SIIV+saline]/20vPnC group), by center-based randomization. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, an otherwise uninvolved third party will be responsible for the preparation and dispensing of all study intervention and will endeavor to ensure that there are no differences in time or effort taken to administer the study intervention and no blinded site staff are able to view the administration.

This third party will instruct the participant to avoid discussing the packaging of the study intervention with the investigator.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

6.3.2. Blinding of Site Personnel

Site staff taking part in any participant randomization, assessments, interviews, data collection, or CRF data entry, including the investigator and investigator staff, will be blinded to investigational product assignments during the study.

The investigational products will be prepared and administered by a designated third-party unblinded site staff member (see [Section 6.2.2](#) for details).

6.3.3. Blinding of the Sponsor

Sponsor personnel directly involved in evaluating participant data will be blinded to vaccine assignment **CCI** following the principles outlined in the ICH E9 Statistical Principles for Clinical Trials.⁸⁷ A data blinding plan will be created to describe the blinding requirements and unblinding events. Laboratory personnel performing the immunologic assays will be blinded until all assays have been completed and assay results finalized. As noted in [Section 6.3.4](#), the investigator site staff will remain blinded for the duration of the study.

6.3.4. Breaking the Blind

The study will be participant- and investigator-blinded through the duration of the study.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's vaccine assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

6.4. Study Intervention Compliance

The date and time of each dose administered will be recorded in the source documents and recorded in the CRF. The blinded study intervention and study participant ID will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

6.5.1. Prohibited During the Study

- Receipt of any investigational vaccines, drugs, or medical devices is prohibited during study participation.
- Receipt of nonstudy pneumococcal or influenza vaccine is prohibited during study participation.
- Receipt of any other licensed nonstudy vaccine is prohibited until after Visit 3, unless medically necessary, in which case every effort should be made to separate inactivated vaccines by 14 days and live vaccines by 28 days from the study vaccination visits.
- Receipt of blood/plasma products, immunoglobulins, and/or immunosuppressive therapy (including a ≥ 14 -day course of systemic corticosteroids) is prohibited through Visit 3.

6.5.2. Permitted During the Study

- Prescription and nonprescription medications, vitamins, minerals, and herbal remedies are permitted during participation in the study.
- The use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).

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

6.6. Recording Prior and Concomitant Vaccines and Concomitant Treatments

The name and date of administration of any prior pneumococcal vaccines will be collected and recorded in the CRF. The name(s) and date(s) of administration are to be obtained from sources, such as medical records or vaccination cards.

The name and date of administration for all nonstudy vaccinations received from the time of signing of the ICD to Visit 3 will be collected and recorded in the CRF.

Medications taken to treat SAEs or NDCMCs from the time of signing of the ICD to Visit 4 will be recorded in the CRF.

6.7. Dose Modification

Not applicable.

6.8. Intervention After the End of the Study

There is no intervention at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

If a participant no longer meets the eligibility criteria during the vaccination period of the study, further vaccinations should be discontinued, but the participant may remain in the study. If a participant is discontinued from vaccination and the participant consents, safety follow-up will be conducted as per [Section 8.3](#) (AEs will be collected for 1 month after the last study vaccination and SAEs will be collected for 6 months after the last study vaccination).

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following: participant no longer meets eligibility criteria, specific protocol deviations, withdrawal by participant, and certain AEs or SAEs.

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is discontinued, the participant will remain in the study to be evaluated for safety. See the [SoA](#) for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

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

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for withdrawal from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AE;
- Physician decision;
- Pregnancy;
- Protocol deviation;
- Screen failure;
- Withdrawal by participant;
- Medication error without associated AE;
- No longer meets eligibility criteria;
- Other.

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, compliance, or administrative reasons.

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

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

Participants should ideally notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. Participants should be questioned regarding their reason for withdrawal. The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

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

A final telephone contact 6 months after the last vaccination ([Section 8.3](#)) for the collection of safety information should be completed for all participants who have been withdrawn after administration of investigational product, unless consent for further contact has been withdrawn, or the participant is lost to follow-up. Participant withdrawal should be explained in the source documents and should include whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or postvaccination study follow-up.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, but data already generated from the samples will continue to be available and may be used to protect the integrity of existing analyses; the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see [Section 7.2.1](#)) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

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

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

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to

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

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of [Section 10.1.8](#) (Appendix 1).

8. STUDY ASSESSMENTS AND PROCEDURES

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

The date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in [Section 8.11](#) and in the [SoA](#). Protocol waivers or exemptions are not allowed.

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

Adherence to the study design requirements, including those specified in [Section 4](#) and in the [SoA](#), is essential and required for study conduct.

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

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

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

The total blood-sampling volume for individual participants in this study is approximately 90 mL.

8.1. Efficacy and/or Immunogenicity Assessments

8.1.1. Immunogenicity Assessments

Blood samples (approximately 30 mL) will be collected from all participants at Visit 1 (prior to administration of SIIV and blinded vaccine), Visit 2 (1 month [28 to 42 days] after administration of vaccines at Visit 1, and prior to blinded vaccine at Visit 2), and Visit 3 (1 month [28 to 42 days] after vaccination at Visit 2). Sample collection, processing, storage, and shipping information can be found in the SRM or equivalent manual.

Pneumococcal Responses

OPA Responses to the 20vPnC Serotypes

OPA titers for the 20vPnC serotypes will be measured in sera collected at Visits 1, 2, and 3.

SIIV Responses

HAI titers to the influenza strains in the SIIV administered will be determined on sera collected at Visits 1 and 2 (prior to and 1 month [28 to 42 days] after SIIV administration).

CCI [REDACTED]

8.1.2. Biological Samples

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

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

The participant 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 participant's genetic material is performed.

8.2. Safety Assessments

A clinical assessment, including medical history and measurement of oral temperature, will be performed on all participants prior to any vaccination at Visit 1 to determine participant eligibility and to establish a clinical baseline. Significant medical history and significant findings from any physical examination (if performed) will be recorded as medical history in the CRF. Temperature measurement prior to vaccination at Visits 1 and 2 will be documented and recorded in the CRF.

The participant will be observed for 30 minutes after each study vaccination and any reactions occurring during that time will be recorded as AEs.

Prompted e-diary events, including local reactions (redness, swelling, and pain at the injection site) at the site of the 20vPnC or saline injection and systemic events (fever, headache, fatigue, muscle pain, and joint pain) that occur 10 and 7 days, respectively, after each vaccination at Visit 1 and Visit 2 (where Day 1 is the day of vaccination), are graded as described in [Section 8.2.2.1](#) and [Section 8.2.2.2](#). Furthermore, AEs, SAEs, and NDCMCs will be collected as defined in [Section 8.3](#).

Planned time points for all safety assessments are provided in the [SoA](#). Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

8.2.1. Participant Electronic Diary

Participants will be asked to monitor and record local reactions and systemic events using an e-diary (in a provisioned device or an application on a personal device). Use of antipyretic/pain medication will also be collected. This allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience. Data reported in the e-diary will be transferred electronically to the e-diary vendor, where they will be available for review by investigators, their appropriately qualified designees, and sponsor staff at all times via an internet-based portal. At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically to Pfizer for analysis and reporting.

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

The investigator or designee must obtain stop dates for any local reactions and specific systemic events that were ongoing on the last day that the e-diary was completed. The stop dates should be entered in the CRF. Because chronic use of antipyretic/pain medication is very common in this population and is not being used as a surrogate for an adverse sign/symptom, a stop date will not be sought if antipyretic/pain medication use is present on the last day that the e-diary was completed.

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

8.2.2. Grading Scale for Prompted Events

The grading scales used in this study to assess prompted events as described below are based on concepts outlined in the FDA CBER guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.⁸⁸

8.2.2.1. Local Reactions

For the first 10 days following each study vaccination (Days 1 through 10, where Day 1 is the day of vaccination), the participants will be asked to assess redness, swelling, and pain at the blinded vaccine (20vPnC or saline) injection site and to record the symptoms in the e-diary in the evening. Redness and swelling will be measured and recorded in measuring device (caliper) units (range: 1 to 21+) and then categorized during analysis as mild, moderate, or severe based on the grading scale in [Table 1](#). Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. Pain at the vaccine injection site will be assessed by the participant as mild, moderate, or severe according to the grading scale in [Table 1](#). The participant will be prompted to contact the investigator if he/she experiences a severe (Grade 3 or above) local reaction to assess the reaction and perform an unscheduled assessment or visit as appropriate.

Only an investigator is able to classify a participant’s local reaction as Grade 4, after physical examination of the participant or documentation from another medically qualified source (eg, emergency room or hospital record). If a participant experiences a Grade 4 local reaction, the investigator must immediately notify the sponsor. Site staff will educate the participants regarding signs and symptoms that would prompt site contact. Grade 4 reactions will be collected as an AE on the CRF. The event will be graded using the AE severity grading scale ([Section 10.3.4](#)).

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

Table 1. Grading Scales for Local Reactions

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

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

Note: If the size of the redness and/or swelling falls between 2 measuring device units, the higher measuring device unit number will be recorded in the e-diary.

- Participants experiencing Grade 3 local reactions are required to contact the investigator site. In the event that the participant does not call, the investigator will call the participant.
- Grade 4 assessment should be made by the investigator; Grade 4 local reactions will not be collected in the e-diary but will be collected as AEs on the CRF. The severity of the local reaction should be graded using the AE severity grading scale in [Section 10.3.4](#).
- Prevents daily activity, eg, results in missed days of work or is otherwise incapacitating.

8.2.2.2. Systemic Events – Systemic Symptoms and Fever

From Day 1 through Day 7 following vaccination at Visit 1 and Visit 2, where Day 1 is the day of vaccination, participants 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 participant as mild, moderate, or severe according to the grading scale in [Table 2](#) below. Participants will also be instructed to contact site staff or the investigator if they experience any possible Grade 4 prompted systemic event (ie, emergency room visit or hospitalization for severe headache, severe fatigue, severe muscle pain, or severe joint pain)

within 7 days after vaccination. Study staff may also contact the participant to obtain additional information on Grade 3 events entered into the e-diary.

Only an investigator is able to classify a participant’s systemic event as Grade 4, after physical examination of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant. If a participant experiences a Grade 4 systemic event, the investigator must immediately notify the sponsor. Grade 4 events will be collected as an AE on the CRF. The event will be graded using the AE severity grading scale (See [Section 10.3.4](#)).

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

Table 2. Grading Scales for Systemic Events

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

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

- a. Prevents daily routine activity, eg, results in missed days of work or is otherwise incapacitating; includes use of narcotics for analgesia.
- b. Grade 4 assessment should be made by the investigator; Grade 4 systemic events will not be collected in the e-diary but will be collected as AEs on the CRF. The severity of the systemic event should be graded using the AE severity grading scale in [Section 10.3.4](#).

8.2.2.2.1. Fever

In order to record information on fever, a digital thermometer will be given to the participant with instructions on how to measure oral temperature at home. Temperature will be collected in the evening daily for 7 days following each vaccination (Days 1 through 7, where Day 1 is the day of vaccination) and at any time during the 7 days that fever is suspected. Fever is defined as an 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 the fever has resolved (1 day of temperature <100.4°F [$<38.0^{\circ}\text{C}$]) in order to collect a stop date in the CRF. Participants reporting a fever >40.0°C will be prompted to contact the study site. Study staff may also contact the participant to obtain additional information if a temperature of >102.0°F is entered into an e-diary. Temperature will be measured and recorded to 1 decimal place.

Temperatures reported in degrees Fahrenheit will be programmatically converted to degrees Celsius for reporting. Fever will be grouped into ranges for the analysis according to Table 3.

Table 3. Ranges for Fever

38.0°C to 38.4°C
>38.4°C to 38.9°C
>38.9°C to 40.0°C
>40.0°C ^a

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

a. Participants reporting a fever >40.0°C will be prompted to contact the study site.

8.2.2.3. Use of Antipyretic/Pain Medication

The participant will be asked to record the use of antipyretic/pain medication (yes/no) in the e-diary in the evening, daily, for 7 days following each vaccination (Days 1 through 7, where Day 1 is the day of vaccination). Antipyretic/pain medication includes chronic use of NSAIDs; however, use of low-dose aspirin (<325 mg) should not be recorded in the e-diary.

8.2.3. Participant Clinical Safety Laboratory Assessments

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

8.2.4. Suicidal Ideation and Behavior Risk Monitoring

Not applicable.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in [Section 10.3](#).

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see [Section 7.1](#)).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

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

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each participant begins from the time the participant provides informed consent, which is obtained before the participant’s participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 3. At Month 7 (Visit 4, final telephone contact), the participant will be contacted by telephone to inquire about SAEs, including hospitalizations and NDCMCs, since Visit 3. Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

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

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

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

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Reporting Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period, as described in Section 8.3.1, are reported to Pfizer Safety on the Vaccine SAE Reporting Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in [Appendix 3](#). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators, as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate, according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental EDP:
 - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by injection.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Reporting Form and EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until the final telephone contact (Visit 4).
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting Form is maintained in the ISF.

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

preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

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

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

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

8.3.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.7. Adverse Events of Special Interest

Not applicable.

8.3.7.1. Lack of Efficacy

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

8.3.8. Medical Device Deficiencies (Including Malfunctions)

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

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

Note: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in [Section 8.3.1](#) through [8.3.4](#) and [Appendix 3](#) of the protocol.

8.3.8.1. Time Period for Detecting Medical Device Deficiencies

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

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

The method of documenting medical device deficiencies is provided in [Appendix 8](#).

8.3.8.2. Follow-up of Medical Device Deficiencies

All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see [Section 8.3.3](#)). Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on a follow-up form with all changes signed and dated by the investigator.

8.3.8.3. Prompt Reporting of Device Deficiencies to Sponsor

Device deficiencies will be reported to the sponsor within 1 day after the investigator determines that the event meets the protocol definition of a medical device deficiency. Information will be provided to the sponsor as described in the IP manual.

Any device deficiency that is associated with an SAE must be reported to Pfizer Safety within 24 hours upon the investigator's awareness as outlined in [Section 8.3.1.1](#) and [8.3.1.2](#).

The sponsor will be the contact for the receipt of device deficiency information.

8.3.8.4. Regulatory Reporting Requirements for Device Deficiencies

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/EC.

8.3.9. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

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

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

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

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

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

Other examples include, but are not limited to:

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

8.4. Treatment of Overdose

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

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

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

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

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

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[REDACTED]
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[REDACTED]

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in [Section 8.1](#).

8.10. Health Economics

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

8.11. Study Procedures

The study procedures are summarized in the SoA. The day of Dose 1 is considered to be Day 1. The timing of visit procedures (ie, prior to vaccination and after vaccination) must be maintained; however, there is flexibility in the order in which the procedures can be conducted at each visit. The only exception is that at Visit 1, the ICD must be signed prior to the start of any study procedure.

8.11.1. Visit 1 (Vaccination 1 – Day 1)

Prior to randomization:

- Obtain a personally signed and dated ICD indicating that the participant has been informed of all pertinent aspects of the study before performing any study-specific procedures.
- Assign a participant number via the IRT.
- Obtain and record the participant's demographic information (including date of birth, sex, race, and ethnicity). The complete date of birth (ie, DD-MMM-YYYY) will be collected to critically evaluate the immune response and safety profile by age.
- Obtain and record significant medical history, including the presence of chronic conditions (eg, diabetes, asthma, cardiac disease, COPD), and/or medical history of significance, such as relevant surgical procedures.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if significant, record such findings on the medical history CRF.
- Record pneumococcal vaccine history, including name(s) of the vaccine(s) received and date(s) given (dates may be approximate but minimally sufficient to confirm eligibility and appropriate stratification).
- Assess and record smoking history.
- If applicable, instruct the participant to use appropriate contraceptives until 28 days after administration of the last dose of investigational product, and document the conversation and the participant's affirmation in the participant's source document.
- Measure and record the participant's oral temperature (°F/°C).
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met and that none of the temporary delay criteria are met.
- Assign a randomization number and an investigational product container number via the IRT. This must be the last step before proceeding. An 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.
- Administer a single 0.5-mL injection of SIIV into the right deltoid muscle.
- An unblinded site staff member will administer a single 0.5-mL injection of 20vPnC or saline into the left deltoid muscle.
- Blinded site staff will observe the participant for 30 minutes after administration of 20vPnC or saline for any reactions. Record any AEs on the CRF and on the Vaccine SAE Reporting Form, as applicable. Record concomitant medications used to treat SAEs and NDCMCs.
- Issue the participant a measuring device to measure 20vPnC or saline injection site reactions and a digital thermometer and provide instructions on their use.
- Issue the participant an e-diary (device or application) and provide instructions on its use and completion. Ask the participant to complete the e-diary from Day 1 to Day 10, with Day 1 being the day of vaccination.
- Ask the participant to contact the investigator site staff or investigator as soon as possible during the 10-day postvaccination period if the participant has redness and/or swelling at the 20vPnC or saline injection site measuring >20 measuring device units (>10 cm), or severe 20vPnC or saline injection site pain (prevents daily activity) to determine if the event requires further assessment by the investigator (refer to [Section 8.2](#)).
- Ask the participant to contact the investigator site staff or the investigator as soon as possible if they experience any possible Grade 4 prompted local reaction in their left arm within 10 days, or systemic event within 7 days, after vaccination (refer to [Section 8.2](#)).
- Ask the participant to contact the site staff or investigator immediately if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs.
- Provide the participant with the participant contact card containing the study and investigator information (see [Section 10.1.10](#)).
- Inform the participant that they may be contacted by site staff to obtain additional information on reports of fever >102.0°F or Grade 3 events entered into the e-diary.
- Inform the participant that the use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).

- Remind the participant to use appropriate contraceptives until 28 days after vaccination, if applicable.
- The investigator or an authorized designee completes the CRF and the source documents 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 (Day 1 is the day of vaccination) following vaccination to evaluate participant compliance and as part of the ongoing safety review.

8.11.2. Visit 2 (Vaccination 2 – 28 to 42 Days After Visit 1 [Study Days 29 to 43])

Prior to vaccination:

- Ensure and document that the participant continues to be eligible for the study (see [Section 7](#) for participant discontinuation/withdrawal) and that none of the temporary delay criteria are met.
- Record nonstudy vaccinations as described in [Section 6.6](#).
- Perform a contraception check (see [Section 10.4](#)), if applicable.
- Review the participant's e-diary data. Collect stop dates of any e-diary events (local reactions or systemic events) ongoing on the last day that the e-diary was completed and record stop dates in the CRF.
- Determine if any AEs (includes nonserious AEs, SAEs, and NDCMCs) have occurred since the previous visit, follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing), record as described in [Section 8.2](#), and record concomitant medications used to treat NDCMCs and SAEs.
- Measure and record the participant's oral temperature (°F/°C).
- Collect a blood sample of approximately 30 mL for immunogenicity assessments prior to vaccination.

After vaccination (including investigational product administration):

- An unblinded site staff member will administer a single 0.5-mL injection of 20vPnC or saline into the deltoid muscle of the left arm.
- Blinded site staff will observe the participant for 30 minutes after investigational product administration for any acute (immediate) reactions. Record any acute (immediate) reactions on the AE CRF and on an SAE form, as applicable.

- Confirm that the e-diary is working and review instructions, if necessary. Ask the participant to complete the e-diary from Day 1 to Day 10, with Day 1 being the day of vaccination. Provide thermometer or measuring device, if needed.
- Ask the participant to contact the investigator site staff or investigator as soon as possible during the 10-day postvaccination period if the participant has redness and/or swelling at the 20vPnC or saline injection site measuring >20 measuring device units (>10.0 cm), or severe 20vPnC or saline injection site pain (prevents daily activity) to determine if the event requires further assessment by the investigator (refer to [Section 10.3](#)).
- Ask the participant to contact the investigator site staff or the investigator as soon as possible if they experience any possible Grade 4 prompted local reaction in their left arm within 10 days, or systemic event within 7 days, after vaccination (refer to [Section 8.3](#)).
- Ask the participant to contact the site staff or investigator immediately if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs.
- Inform the participant that they may be contacted by site staff to obtain additional information on reports of fever >102.0°F or Grade 3 events entered into the e-diary.
- Inform the participant that use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).
- Remind the participant to use appropriate contraceptives until 28 days after vaccination, if applicable.
- The investigator or an authorized designee completes the CRF and the source documents 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 (Day 1 is the day of vaccination) following vaccination to evaluate participant compliance and as part of the ongoing safety review.

8.11.3. Visit 3 (Follow-up – 28 to 42 Days After Vaccination 2 [Study Days 57 to 85])

- Ensure and document that the participant continues to be eligible for the study (see [Section 7](#) for participant discontinuation/withdrawal).
- Record nonstudy vaccinations as described in [Section 6.6](#).
- Review the participant's e-diary data. Collect stop dates of any e-diary events (local reactions or systemic events) ongoing on the last day that the e-diary was completed and record stop dates in the CRF.

- Collect the e-diary (if applicable).
- Determine if any AEs (includes nonserious AEs, SAEs, and NDCMCs) have occurred since the previous visit, follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing), record as described in [Section 8.3](#), and record concomitant medications used to treat NDCMCs and SAEs.
- Collect a blood sample of approximately 30 mL for immunogenicity assessments.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs.
- The investigator or an authorized designee completes the CRF and the source documents.

8.11.4. Visit 4 (6-Month Safety Collection [Telephone Contact] – 168 to 196 Days After Last Vaccination)

- Contact the participant by telephone approximately 6 months after the last study vaccination; this contact should be attempted for all participants who have received at least 1 study vaccination, unless the participant has withdrawn consent.
- Determine whether any SAEs and NDCMCs have occurred since the previous visit, follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing), record as described in [Section 8.3](#), and record concomitant medications used to treat NDCMCs and SAEs.
- The investigator or an authorized designee completes the CRF and the source documents.

8.12. Unscheduled Visits

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

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

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

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

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

- Measure oral temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in [Section 8.2.2.1](#).
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

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

Participants will also be instructed to contact site staff or the investigator if they experience any possible Grade 4 prompted systemic event (ie, emergency room visit or hospitalization for headache, fatigue, muscle pain, or joint pain) or fever >104.0°F (>40.0°C) within 7 days, or local reaction in the 20vPnC/saline injection site (ie, necrosis, exfoliative dermatitis, or emergency room visit/hospitalization for injection site pain) within 10 days after vaccination.

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

Additionally, site staff may contact the participant to obtain additional information on fever >102.0°F or Grade 3 events entered into the e-diary.

9. STATISTICAL CONSIDERATIONS

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

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimands corresponding to each primary, secondary, CCI objective are described in the table in Section 3. The estimands to evaluate the immunogenicity objectives for NI) are based on the evaluable populations (see Section 9.3 for definition). The estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. The estimands address the objective of estimating the maximum potential difference between 2 groups, since the impact of noncompliance is likely to diminish the observed difference between the 2 groups. Missing serology results will not be imputed. Immunogenicity results that are below the LLOQ will be set to $0.5 \times \text{LLOQ}$ in the analysis. In the primary safety objective evaluations, missing e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer Safety rules. No other missing information will be imputed in the safety analysis.

9.1.2. Statistical Hypotheses

There are 2 primary immunogenicity objectives (Section 3). Hypothesis testing will be used to assess those 2 NI objectives.


The null hypotheses (H_{01}) for each pneumococcal serotype is:

$$H_{01}: \ln(\mu_A) - \ln(\mu_B) \leq \ln(0.5)$$

where $\ln(0.5)$ corresponds to a 2-fold margin for the assessment of NI with respect to the immune responses to 20vPnC and

- $\ln(\mu_A)$ is the natural log of the serotype-specific OPA GMT 1 month after coadministration of SIIV and 20vPnC for the (SIIV+20vPnC)/saline group;
- $\ln(\mu_B)$ is the natural log of the serotype-specific OPA GMT 1 month after 20vPnC administration for the (SIIV+saline)/20vPnC group.

NI for serotype-specific OPA titers will be formally evaluated by a 2-sided 95% CI for the ratio of serotype-specific OPA GMTs (SIIV+20vPnC)/saline group over (SIIV+saline)/20vPnC group. The null hypothesis (H_{01}) will be rejected and NI for a serotype will be declared if the lower bound of the 2-sided 95% CI for the GMR of the coadministration group to the separate-administration group is greater than 0.5 (2-fold criterion). CCI



The null hypotheses (H_{02}) for each influenza strain-specific antibody is:

$$H_{02}: \ln(\mu_C) - \ln(\mu_D) \leq \ln(0.67)$$

where $\ln(0.67)$ corresponds to a 1.5-fold margin for assessment of NI with respect to the immune responses to SIIV and

- $\ln(\mu_C)$ is the natural log of the strain-specific HAI GMT 1 month after coadministration of SIIV and 20vPnC for the (SIIV+20vPnC)/saline group;
- $\ln(\mu_D)$ is the natural log of the strain-specific HAI GMT 1 month after SIIV administration for the (SIIV+saline)/20vPnC group.

NI for strain-specific HAI titers will be formally evaluated by a 2-sided 95% CI for the ratio of strain-specific HAI GMTs ([SIIV+20vPnC]/saline group over [SIIV+saline]/20vPnC group). The null hypothesis (H_{02}) will be rejected and NI for strain-specific HAI will be declared if the lower bound of the 2-sided 95% CI for the GMR of the coadministration group to the separate-administration group is greater than 0.67 (1.5-fold criterion).

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9.1.3. Multiplicity Considerations

For the primary immunogenicity assessment of NI of coadministration of SIIV and 20vPnC ([SIIV+20vPnC]/saline group) to administration of SIIV followed by 20vPnC 1 month later ([SIIV+saline]/20vPnC group) for all 20 OPA serotypes in 20vPnC and all the HAI strains in SIIV, a 2-sided test for each of the 20 OPA serotypes and each of the HAI strains is performed only once at an alpha level of 0.05. The primary immunogenicity objectives of the study will be achieved if the 2-fold NI criterion is met for each of the 20 OPA serotypes and the 1.5-fold NI criterion is met for each of the HAI strains. Therefore, the type I error rate for the immunogenicity assessments is well controlled.

9.2. Sample Size Determination

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Sample size and power are based on simulations with assumptions supported by the OPA results from a Phase 3 pivotal study (B7471007) of 20vPnC and a Phase 4 study (B1851138) of 13vPnC evaluating the immune response when 13vPnC was given concomitantly and separately. With 800 evaluable participants in each vaccine group, the study has approximately 99%, 95%, and 75% power to demonstrate NI for at least 18 out of 20, for at least 19 out of 20, and for all 20 serotypes, respectively. Assuming a nonevaluable rate of 10%, the study will randomize approximately 1780 participants to achieve 800 evaluable participants in each group.

CCI

[REDACTED]

[REDACTED]	[REDACTED]	+	[REDACTED]
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CCI

[REDACTED]

CCI [REDACTED] Assuming the GMR of the (SIIV+20vPnC)/saline group to the (SIIV+saline)/20vPnC group is 0.9 for each HAI strain and standard deviations are the same as those observed in Study B1851138, 800 evaluable participants in each vaccine group provide approximately 99% power to demonstrate NI for all HAI strains.

CCI [REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
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[REDACTED]

9.3. Analysis Sets

Participant Analysis Set	Description
Enrolled	All participants who sign the ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Evaluable pneumococcal immunogenicity	All randomized participants who receive the assigned investigational products at Visit 1 for the (SIIV+20vPnC)/saline group or receive the assigned investigational products at both Visit 1 and Visit 2 for the (SIIV+saline)/20vPnC group; have the blood collection within an appropriate window 1 month after 20vPnC (Visit 2 for [SIIV+20vPnC]/saline group, Visit 3 for [SIIV+saline]/20vPnC group); have at least 1 valid and determinate OPA result from 1 month after vaccination with 20vPnC; and have no other major protocol deviations as determined by the clinician.
Evaluable HAI immunogenicity	All randomized participants who receive the assigned investigational products at Visit 1, have Visit 2 blood collection within an appropriate window for Visit 2, have at least 1 valid and determinate HAI titer for any of the HAI strains in SIIV at Visit 2, and have no other major protocol deviations as determined by the clinician.
CCI [REDACTED]	[REDACTED]
Safety	All randomized participants who receive 1 dose of 20vPnC or SIIV or saline and have safety follow-up after vaccination.

9.4. Statistical Analyses

The SAP will be developed and finalized before any planned analyses (Section 9.5.1) are performed. The SAP will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary, CCI [REDACTED] endpoints.

9.4.1. Immunogenicity Analysis

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in Section 9.3.

CCI [Redacted]

Missing serology results will not be imputed. Titers below LLOQ or denoted as BLQ will be set to $0.5 \times \text{LLOQ}$ for analysis.

Endpoint	Statistical Analysis Methods
Primary pneumococcal immunogenicity	<ul style="list-style-type: none"> For the 20 serotypes in 20vPnC, 1 month after vaccination refers to 1 month after vaccination with 20vPnC and SIIV (Visit 2) for the (SIIV+20vPnC)/saline group and 1 month after vaccination with 20vPnC (Visit 3) for the (SIIV+saline)/20vPnC group. For each of the 20 serotype-specific OPA titers, the GMRs of the (SIIV+20vPnC)/saline group GMT to the (SIIV+saline)/20vPnC group GMT at 1 month after vaccination will be provided. GMRs and their 2-sided 95% CIs will be derived by calculating differences in means and CIs on the natural log scale, then exponentiating the results. The difference in means, on the natural log scale, will be the (SIIV+20vPnC)/saline group at Visit 2 minus the (SIIV+saline)/20vPnC group at Visit 3 for the 20 serotypes in 20vPnC. <p>As the primary approach to calculate the GMR and CI for each serotype of OPA titer, a linear regression model that includes terms for prior pneumococcal vaccine status, age (at the time of randomization), corresponding baseline OPA titer, sex, smoking status, and vaccine group will be used to calculate the serotype-specific OPA GMR and 95% CI, along with the model-based least squares GMTs and associated 2-sided 95% CIs for each vaccine group. NI for a serotype will be declared if the lower bound of the 2-sided 95% CI for the GMR of the (SIIV+20vPnC)/saline group over the (SIIV+saline)/20vPnC group exceeds 0.5. CCI [Redacted]</p> <p>CCI [Redacted]</p>

	<p>This analysis will be based on the evaluable pneumococcal immunogenicity populations in order to provide a comparison that has the greatest chance of identifying a difference between the groups with respect to immunogenicity, if a meaningful difference in vaccine effect actually exists.</p>
Primary SIIV immunogenicity	<ul style="list-style-type: none">• For the HAI strains in SIIV, 1 month after vaccination refers to 1 month after vaccination with SIIV (Visit 2) for both vaccine groups.• For each of the HAI strains, the GMRs of the (SIIV+20vPnC)/saline group GMT to the (SIIV+saline)/20vPnC group GMT at 1 month after vaccination will be provided. GMRs and their 2-sided 95% CIs will be derived by calculating differences in means and CIs on the natural log scale, then exponentiating the results. The difference in means, on the natural log scale, will be the (SIIV+20vPnC)/saline group at Visit 2 minus the (SIIV+saline)/20vPnC group at Visit 2 for all HAI strains in SIIV. <p>As the primary approach to calculate the GMR and CI for each strain of HAI titer, a linear regression model that includes terms for prior pneumococcal vaccine status, age (at the time of randomization), corresponding baseline HAI titer, sex, smoking status, and vaccine group will be used to calculate the strain-specific HAI GMR and 95% CI, along with the model-based least squares GMTs and associated 2-sided 95% CIs for each vaccine group. NI for a strain will be declared if the lower bound of the 2-sided 95% CI for the GMR of the (SIIV+20vPnC)/saline group over the (SIIV+saline)/20vPnC group exceeds 0.67. CCI [REDACTED]</p> <p>CCI [REDACTED]</p> <p>This analysis will be based on the evaluable HAI immunogenicity populations in order to provide a comparison that has the greatest chance of identifying a difference between the groups with respect to immunogenicity, if a meaningful difference in vaccine effect actually exists.</p>

Secondary pneumococcal immunogenicity	<ul style="list-style-type: none">• GMFRs and associated 2-sided 95% CIs will be provided for each OPA serotype from before vaccination to 1 month after vaccination for each vaccine group. GMFRs will be limited to participants with nonmissing values both before and after vaccination. The GMFR will be calculated as the mean of the difference of logarithmically transformed serotype-specific OPA titer (after vaccination minus before vaccination for each participant) and transformed back to the original units. 2-Sided 95% CIs will be obtained by exponentiating CIs using Student's t distribution for the mean difference of measures on the logarithmically transformed assay results.• The point estimate and exact 2-sided 95% CI will be calculated for each vaccine group using the Clopper-Pearson method for the percentage of participants with a ≥ 4-fold rise in serotype-specific OPA titers from before vaccination to 1 month after vaccination.
Secondary SIIV immunogenicity	<ul style="list-style-type: none">• HAI GMFRs and associated 2-sided 95% CIs will be provided for each HAI strain from before vaccination to 1 month after vaccination for each vaccine group, using the same method described above for serotype-specific OPA GMFRs and CIs.
CCI [REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

9.4.2. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	<ul style="list-style-type: none"> • Descriptive statistics will be provided for each reactogenicity endpoint for each vaccine group. In each vaccine group, prompted local reactions from Day 1 through Day 10 and prompted systemic events from Day 1 through Day 7 after each vaccination will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated 2-sided Clopper-Pearson 95% CIs. • AEs, SAEs, and NDCMCs will be categorized according to MedDRA terms. A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers: <ol style="list-style-type: none"> (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product’s safety review plan; (2) Tier 2 events are those that are not Tier 1 but are considered “relatively common”; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. <p>For both Tier 1 and Tier 2 events, the 2-sided 95% CIs for the difference in percentage of participants reporting the events between the (SIIV+20vPnC)/saline group and the (SIIV+saline)/20vPnC group will be calculated using the Miettinen and Nurminen method. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference in percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed.</p> <p>There is no Tier 1 event identified for 20vPnC at this stage. For Tier 2 AEs, the between-group difference and 95% CIs will be calculated for 1 month after vaccination with SIIV and 20vPnC for the (SIIV+20vPnC)/saline group vs 1 month after vaccination with SIIV and saline for the (SIIV+saline)/20vPnC group, and for 1 month after vaccination with SIIV and 20vPnC for the (SIIV+20vPnC)/saline group vs 1 month after vaccination with 20vPnC for the (SIIV+saline)/20vPnC group. Descriptive summary statistics (counts and percentages and associated 2-sided Clopper-Pearson 95% CIs) will be provided for Tier 3 events, SAEs, and NDCMCs for each vaccine group.</p>

	<ul style="list-style-type: none">The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing e-diary data will not be imputed. Missing AE dates will be handled according to the Pfizer safety rules.
Secondary	N/A
CCI [REDACTED]	[REDACTED]

9.5. Interim Analyses

No interim analysis is planned in this study.

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CCI [REDACTED]

[REDACTED]

[REDACTED]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

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

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

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

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.4. Data Protection

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

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

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

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

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

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the EMA Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of “bona-fide scientific research” that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

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

10.1.6. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.7. Source Documents

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

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

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

A description of the use of computerized systems is documented in the Data Management Plan.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

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

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

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

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

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

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

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

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the ISF. To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

Not applicable.

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

10.3.1. Definition of AE

AE Definition

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

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 - Is associated with accompanying symptoms.
 - Requires additional diagnostic testing or medical/surgical intervention.
 - Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE and meet the requirements as per [Section 8.3.7.1](#). Also, “lack of efficacy” or “failure of expected pharmacological action” does constitute an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of an NDCMC

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

10.3.3. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity <ul style="list-style-type: none">• The term disability means a substantial disruption of a person’s ability to conduct normal life functions.• This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: <ul style="list-style-type: none">• Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

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

AE and SAE Recording/Reporting		
<p>The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the Vaccine SAE Reporting Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.</p> <p>It should be noted that the Vaccine SAE Reporting Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Reporting Form for reporting of SAE information.</p>		
Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.	All AEs/SAEs associated with EDP or breastfeeding. Occupational exposure is not recorded.	All (and EDP Supplemental Form for EDP) Note: Include all SAEs associated with EDP or breastfeeding. Include all AEs/SAEs associated with occupational exposure.
<ul style="list-style-type: none"> • When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is not acceptable for the investigator to send photocopies of the participant’s medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Reporting Form/AE/SAE CRF page. 		

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as “related to study intervention” for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Reporting Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

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

10.3.5. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

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

SAE Reporting to Pfizer Safety via the Vaccine SAE Reporting Form

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

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10.5. Appendix 5: Genetics

Not applicable.

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

Potential Cases of Drug-Induced Liver Injury

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

LFTs are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations ($>2 \times \text{ULN}$) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above $3 \times \text{ULN}$ (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values $>3 \times \text{ULN}$ AND a TBili value $>2 \times \text{ULN}$ with no evidence of hemolysis and an alkaline phosphatase value $<2 \times \text{ULN}$ or not available.
- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
 - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND $>3 \times \text{ULN}$; or $>8 \times \text{ULN}$ (whichever is smaller).
 - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least $1 \times \text{ULN}$ **or** if the value reaches $>3 \times \text{ULN}$ (whichever is smaller).

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

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

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a

coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

Not applicable.

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

Definitions of a Medical Device Incident

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

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

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see [Section 6.1.3](#) for the list of sponsor medical devices).

10.8.1. Definition of AE and ADE

AE and ADE Definition

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

10.8.2. Definition of SAE, SADE, and USADE

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

An SAE is an AE that:
a. Led to death.
b. Led to serious deterioration in the health of the participant, that either resulted in: <ul style="list-style-type: none">• A life-threatening illness or injury. The term “life-threatening” in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.• A permanent impairment of a body structure or a body function.• Inpatient or prolonged hospitalization. Planned hospitalization for a preexisting condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.• Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect.
SADE Definition
<ul style="list-style-type: none">• An SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE.
USADE Definition
<ul style="list-style-type: none">• A USADE is an SADE which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.8.3. Definition of Device Deficiency

Device Deficiency Definition
<ul style="list-style-type: none">• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

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

AE, SAE, and Device Deficiency Recording

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

Assessment of Intensity

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

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

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

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

Follow-up of AE/SAE/Device Deficiency

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

10.8.5. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

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

SAE Reporting to Pfizer Safety via Vaccine SAE Reporting Form

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

10.8.6. Reporting of SADEs

SADE Reporting to Pfizer Safety

NOTE: There are additional reporting obligations for medical device incidents that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

10.9. Appendix 9: Country-Specific Requirements

Not applicable.

10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
7vPnC	7-valent pneumococcal conjugate vaccine
13vPnC	13-valent pneumococcal conjugate vaccine
20vPnC	20-valent pneumococcal conjugate vaccine
ACIP	Advisory Committee on Immunization Practices
ADE	adverse device effect
AE	adverse event
ALT	alanine aminotransferase
AOM	acute otitis media
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
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
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatinine kinase
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CRF	case report form
CRM ₁₉₇	cross-reactive material 197
CRO	contract research organization
CSA	clinical study agreement
DILI	drug-induced liver injury
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
e-diary	electronic diary
CCI	
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise

Abbreviation	Term
GMR	geometric mean ratio
GMT	geometric mean titer
HAI	hemagglutination inhibition assay
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
CCI	
IND	investigational new drug application
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IPD	invasive pneumococcal disease
IRB	institutional review board
IRT	interactive response technology
ISO	International Organization for Standardization
ISF	investigator site file
IWR	interactive Web-based response
LFT	liver function test
LLOQ	lower limit of quantitation
LRI	lower respiratory tract infection
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
NI	noninferiority
NSAID	nonsteroidal antiinflammatory drug
OPA	opsonophagocytic activity
PI	principal investigator
PPSV23	23-valent pneumococcal polysaccharide vaccine
PT	prothrombin time
QIV	quadrivalent inactivated influenza vaccine
CCI	
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SIIV	seasonal inactivated influenza vaccine
SoA	Schedule of Activities
SOP	standard operating procedure

Abbreviation	Term
SRM	study reference manual
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TIV	trivalent inactivated influenza vaccine
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
USPI	US package insert
VT	vaccine-type
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

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