A PHASE 3, MULTICENTER, SINGLE-ARM, OPEN-LABEL STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A SINGLE DOSE OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN JAPANESE SUBJECTS AGED 6 TO 64 YEARS WHO ARE CONSIDERED TO BE AT INCREASED RISK OF PNEUMOCOCCAL DISEASE AND WHO ARE NAIVE TO PNEUMOCOCCAL VACCINES

Investigational Product Number:	PF-05208760
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Document	Version Date	Summary of Changes and Rationale
Original protocol	20 March 2018	Not applicable (N/A)

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PROTOCOL SUMMARY

Disease caused by *Streptococcus pneumoniae* is a major global public health concern. While the burden of invasive pneumococcal disease (IPD) is predominantly borne by the very young, very old, and immunocompromised, manifestations of pneumococcal disease are a considerable cause of morbidity and mortality in all age groups.

In Japan, 13-valent pneumococcal conjugate vaccine (13vPnC) was approved for children aged ≥2 months to <6 years in 2013 and for adults aged ≥65 years in 2014. 13vPnC has not been approved for individuals between the ages of 6 and 64 years in Japan, which is in contrast to the situation in the United States, countries in Europe, and many other countries globally where 13vPnC is approved for these ages. This situation is despite the fact that the 6- to 64-year age group has a not-insignificant proportion of individuals with underlying medical conditions who are considered to be at increased risk for developing pneumococcal disease (PD) based on the epidemiological data in Japan. Furthermore, the 5- to 64-year age group represented 27% of reported IPD cases in Japan in 2013, and many IPD patients are individuals with underlying medical conditions.

Pfizer-sponsored clinical studies conducted outside Japan in healthy individuals and in immunocompetent individuals with underlying stable medical conditions aged 6 years and older demonstrated that a single dose of 13vPnC was safe and well tolerated. In addition, the safety and immunogenicity of 13vPnC have been confirmed in overseas clinical studies involving immunocompromised populations, ie, subjects with sickle-cell disease (SCD), human immunodeficiency virus (HIV)-infected subjects, and recipients of hematopoietic stem cell transplant (HSCT). Furthermore, more than 642 million doses of Prevenar 13®/Prevnar 13® (13vPnC) have been administered to individuals across the age spectrum globally and more than 15 million doses have been administered in Japan to children aged <6 years and adults aged ≥65 years, without specific safety concerns.

Therefore, the unmet medical need for protection against PD that could be provided by 13vPnC, the large database of safety data from clinical studies in Japan and globally, and the extensive postmarketing experience support the conduct of the present study, Phase 3 Study B1851172, in Japan. This study will assess the safety, tolerability, and immunogenicity of a single dose of 13vPnC in Japanese individuals aged 6 to 64 years who are considered to be at increased risk of pneumococcal disease and who are naive to pneumococcal vaccine.

STUDY OBJECTIVES AND ENDPOINTS

Primary Objective:	**Primary Endpoints:**
• To assess the safety and tolerability of a single dose of 13vPnC as measured by the incidence of local reactions, systemic events, adverse events (AEs), and serious adverse events (SAEs).	• Number and proportion of subjects reporting local reactions (redness, swelling, pain at injection site) and severity of the local reactions occurring within the 7-day period following study vaccination in the 6- to <18-year age group. • Number and proportion of subjects reporting local reactions (redness, swelling, pain at injection site) and severity of the local reactions occurring within the 14-day period following study vaccination in the 18- to <65-year age group. • Number and proportion of subjects reporting systemic events (fever, fatigue, headache, vomiting, diarrhea, muscle pain, joint pain) and severity of the systemic events occurring within the 7-day period following study vaccination in the 6- to <18-year age group. • Number and proportion of subjects reporting systemic events (fever, fatigue, headache, vomiting, diarrhea, muscle pain, joint pain) and severity of the systemic events occurring within the 14-day period following study vaccination in the 18- to <65-year age group. • Number and proportion of subjects reporting AEs and SAEs until Visit 2 categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) in all age groups.
Secondary Objective:	**Secondary Endpoints:**
• To describe the immune responses elicited by a single dose of 13vPnC.	• Serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) 1 month after vaccination in all age groups. • Geometric mean fold rises (GMFRs) in serotype-specific OPA titers from before vaccination to 1 month after vaccination in all age groups. • Serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) 1 month after vaccination in all age groups. • GMFRs in serotype-specific IgG from before vaccination to 1 month after vaccination in all age groups.

STUDY DESIGN

This is a Phase 3, multicenter, single-arm, open-label study to assess the safety, tolerability, and immunogenicity of single dose of 13vPnC in Japanese subjects aged 6 to 64 years who are considered to be at increased risk of pneumococcal disease and who are naive to pneumococcal vaccines.

Approximate Duration of Subject Participation

Subjects will participate in the study for approximately 1 month (29 to 43 days).

Approximate Duration of the Study

The study will be completed in approximately 6 months. Study duration is from first subject first visit (FSFV) to last subject last visit (LSLV).

Approximate Number of Subjects

Approximately 200 subjects will be enrolled: approximately 50 subjects in the 6- to <18-year age group and approximately 150 subjects in the 18- to <65-year age group.

For the purpose of ensuring a minimum number of subjects in each of the age categories, at least 15 subjects aged 6 to <12 years and 15 subjects aged 12 to <18 years will be enrolled within the 6- to <18-year age group. Furthermore, at least 50 subjects aged 18 to <50 years and 50 subjects aged 50 to <65 years will be enrolled within the 18- to <65-year age group.

Study Vaccine

The investigational products (13vPnC) will be provided by the sponsor to each study site. The study vaccines will be packed and labeled as investigational products in accordance with current guidelines and applicable local and legal regulatory requirements.

13vPnC contains saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to nontoxic diphtheria toxin cross-reactive material 197 (CRM_{197}). The vaccine is formulated to contain 2.2 µg of each saccharide, except for 4.4 µg of 6B, per 0.5-mL dose. The vaccine contains 5 mM succinate buffer, 0.85% sodium chloride, 0.02% polysorbate 80, and 0.125 mg aluminum as aluminum phosphate, per 0.5-mL dose. The vaccine will be provided as a single-dose prefilled syringe.

Statistical Methods

An analysis of safety and immunogenicity data will be conducted when data are available through 1 month after vaccination. All analyses will be descriptive. No formal hypothesis tests are planned.

SCHEDULE OF ACTIVITIES

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

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

Visit Number	**1**	**2**
Visit ID	**Vaccination**	**Follow-up Visit**
Visit Window[a]	**Day 1**	**Day 29 to Day 43**
Informed consent/assent	X	
Demographics	X	
Medical history	X	
Smoking status	X	
Prior/concomitant vaccination and/or immunosuppressive drugs, including systemic corticosteroids, immune-modifying drugs, or monoclonal antibodies	X	X
Physical examination	X	
Prevaccination axillary temperature	X	
Urine pregnancy test[b]	X	
Inclusion and exclusion criteria	X	
Temporary delay criteria	X	
Immunogenicity blood sampling	X[c]	X
Investigational product administration	X	
30-Minute postvaccination observation and assessment of acute reactions	X	
Train subject or a legally acceptable representative/parent/legal guardian to use e-diary and set up e-diary for the subject	X	
Dispense e-diary, digital thermometer, and caliper	X	
Subjects to record local reactions and systemic events in e-diary	6- to <18-year age group: Day 1 to Day 7 18- to <65-year age group: Day 1 to Day 14	
Review e-diary data[d]	X----------X	
Collect e-diary		X
Serious and nonserious adverse event collection	X----------X	

Abbreviation: e-diary = electronic diary.

a. Day relative to study vaccination (Day 1).
b. For female subjects of childbearing potential. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (28 days after vaccination) (or when potential pregnancy is otherwise suspected).
c. Immunogenicity blood sampling at Day 1 must occur before administration of investigational product.
d. Investigators (or appropriately qualified designees) review the e-diary data online at frequent intervals after Day 1.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

13-valent pneumococcal conjugate vaccine (13vPnC) is indicated for the prevention of disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F in individuals 6 to 64 years of age who are considered to be at increased risk of pneumococcal disease.

1.2. Background and Rationale

1.2.1. Unmet Medical Need

Disease caused by *S pneumoniae* is a major global public health concern. While the burden of invasive pneumococcal disease (IPD) is predominantly borne by the very young, very old, and immunocompromised, manifestations of pneumococcal disease are a considerable cause of morbidity and mortality in all age groups. Globally, pneumococcal pneumonia was estimated to cause 1,517,388 deaths (95% uncertainty interval [UI]: 857,940-2,183,791) in 2015 and, across all ages, accounted for 55.4% (95% UI: 31.5-79.1) of deaths due to lower respiratory tract infections.[1]

In Japan, *S pneumoniae* was the leading causative pathogen of community-onset pneumonia and was responsible for 20% to 28% of community-onset pneumonia.[2] The estimated annual incidence of *S pneumoniae*–associated community-onset pneumonia in Japan was 4.7 per 1000 persons among individuals aged 15 years and older, with the estimated annual incidence ranging from 0.8 to 3.8 per 1000 persons when considering the various age decades between 15 and <65 years old.[2] *S pneumoniae* is also an important cause of invasive disease and the estimated incidence of IPD in Japan in 2013 was 1.18 per 100,000 population.[3] The incidence (per 100,000) was higher at both ends of the age spectrum: 6.32 for the population under 5 years of age, 0.36 for the population 5 to 14 years of age, 0.46 for the population 15 to 64 years of age, and 2.41 for the population 65 years of age and older.[3] In 2013, the number of IPD cases was 1505 in total: 331 (22%) for the population under 5 years of age, 406 (27%) for the population 5 to 64 years of age, and 768 (51%) for the population 65 years of age and older. Thus, the number of IPD cases in the population 5 to 64 years of age was similar to that in the population under 5 years of age.[3]

Individuals with certain underlying medical conditions are considered to be at increased risk for developing pneumococcal disease (PD) and also for experiencing severe IPD and its complications. Predisposing factors for pneumococcal disease include chronic medical conditions such as cardiovascular, pulmonary, hepatic, or renal diseases; diabetes mellitus; asplenia; human immunodeficiency virus (HIV) infection or other immunosuppressive conditions; cochlear implant; cerebrospinal fluid (CSF) leaks; smoking; alcoholism; and residence in certain environments, such as nursing homes. According to a research project conducted in 10 prefectures in Japan, in patients older than 15 years who had IPD, 72% had underlying diseases and the case fatality proportion for all cases was 20%.[4,5,6,7]

In addition, because of an increasing prevalence of *S pneumoniae* strains resistant to antibiotics, including penicillin, other beta-lactam antibiotics, and macrolides, the treatment of pneumococcal infections is becoming more difficult.[8,9,10,11,12]

Therefore, there is a need for an effective vaccine to protect against PD across the spectrum of age groups, including in those individuals with underlying medical conditions that increase the risk of contracting pneumococcal disease.

1.2.2. Development of Investigational Product

23-valent pneumococcal polysaccharide vaccine (PPSV23), which contains purified carbohydrates alone and elicits T-cell–independent immune responses, has been licensed for prevention against PD for individuals 2 years of age and older who are considered to be at increased risks of PD.[13,14] Effectiveness of PPSV23 to prevent IPD has been demonstrated but the duration of protection was reported to be short, and the vaccine has failed to show an impact on the burden of PD at the population level.[15,16,17,18] The vaccine's effectiveness for noninvasive pneumococcal pneumonia has been inconclusive, and inconsistent study results have been reported.[18,19,20,21,22] PPSV23 did not demonstrate efficacy against IPD in the HIV-infected population.[23]

Manufacturing vaccines using glycoconjugate technology, where a carbohydrate antigen (bacterial polysaccharide) is chemically coupled to an immunogenic protein carrier, has overcome the limitation of using carbohydrates as vaccine antigens rooted in T-cell–independent immune responses. By conjugating the purified capsular saccharides of *S pneumoniae* to an immunogenic protein carrier, a nontoxic diphtheria toxoid, the normally T-cell–independent immune response is converted to a T-cell–dependent immune response, leading to immunological memory and boosting upon repeated vaccination and thus overcoming the limitation of using polysaccharides as vaccine antigens.

13vPnC contains the same 7 pneumococcal capsular polysaccharide serotypes as the 7-valent pneumococcal conjugate vaccine (7vPnC; serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) plus 6 additional serotypes (1, 3, 5, 6A, 7F, and 19A), with each polysaccharide individually conjugated to cross-reactive material 197 (CRM_{197}). The vaccine is a sterile liquid formulation. 13vPnC has been shown to be safe and immunogenic. 13vPnC elicits immune responses that are quantitatively and qualitatively distinct from those elicited by PPSV23.

Since 2009, 13vPnC has been approved for use in children 6 weeks through 5 years of age in the United States, Europe, and other countries under the trademarks Prevnar 13® and Prevenar 13® for 1 or more of the following indications: prevention of IPD, pneumonia, and otitis media. The indication has been expanded, and 13vPnC is currently approved for children from 6 weeks of age and for adults of all ages in 75 countries, including the United States and countries in Europe. The US Advisory Committee on Immunization Practices (ACIP) has issued recommendations for the use of 13vPnC for children 6 to 18 years of age and for adults ≥19 years of age with certain medical conditions, including immunocompromising conditions.[4]

In Japan, 13vPnC was approved for children aged ≥2 months to <6 years in 2013 and for adults aged ≥65 years in 2014. Since introduction of 7vPnC to Japan in 2010, a 98% reduction in incidence of vaccine-type IPD was observed in children under 5 years old.[24]

1.2.2.1. Clinical Studies in Japan

Two studies in Japanese infants aged 2 or 3 months to 6 months (6096A1-3003 and 6096A1-3024) and 2 studies in Japanese adults aged 50 or 65 years and older (6115A1-3004 and B1851088) have been conducted in Japan. These studies supported the licensure of 13vPnC for children aged ≥2 months to <6 years and for adults aged ≥65 years in Japan.

In the infant studies, 376 infants received at least 1 dose of 13vPnC subcutaneously; these studies demonstrated that 13vPnC vaccination with a 3-dose infant series followed by a booster dose at 12 to 15 months of age was safe and well tolerated.[25,26] Study 6096A1-3024 demonstrated that immune responses to the pneumococcal antigens in 13vPnC were noninferior to those of 7vPnC for the 7 common serotypes and substantially greater for the 6 additional serotypes.[26]

In the adult studies, 134 adults aged 50 to 64 years and 516 adults aged 65 years and older, who were naive to pneumococcal vaccine, received 1 dose of 13vPnC intramuscularly. Overall, a single dose of 13vPnC was safe and well tolerated.[27,28] The B1851088 study demonstrated that 13vPnC was noninferior to PPSV23 for the 12 common serotypes, and was significantly more immunogenic for most of the common serotypes and for serotype 6A in Japanese elderly adults aged 65 years and older who were naive to pneumococcal vaccines.[28]

1.2.3. Study Rationale

In Japan, 13vPnC has not been approved for individuals between the ages of 6 and 64 years. This situation is despite the fact that this age group has a not-insignificant proportion of individuals with underlying medical conditions who are considered to be at increased risk for developing PD based on the epidemiological data in Japan.[29,30] The 5- to 64-year age group represented 27% of reported IPD cases in Japan in 2013.[3] Furthermore, many IPD patients have underlying medical conditions.[7] In view of the epidemiology and prevalence of IPD cases in Japan, development of 13vPnC in Japanese children, adolescents, and adults between 6 years and <65 years of age has also been advocated by Japanese physicians and their professional associations.[31]

Pfizer-sponsored clinical studies conducted outside Japan in healthy individuals and in immunocompetent individuals with underlying stable medical conditions aged 6 years and older demonstrated that a single dose of 13vPnC was safe and well tolerated. In addition, the safety and immunogenicity of 13vPnC have been confirmed in overseas clinical studies involving immunocompromised populations, ie, subjects with sickle-cell disease (SCD), HIV-infected subjects, and recipients of hematopoietic stem cell transplant (HSCT). Furthermore, more than 642 million doses of Prevenar 13/Prevnar 13 (13vPnC) have been administered to individuals across the age spectrum globally and more than 15 million doses have been administered in Japan to children aged <6 years and adults aged ≥65 years, without specific safety concerns.

Therefore, the unmet medical need for protection against PD that could be provided by 13vPnC, the large database of safety data from clinical studies in Japan and globally, and the extensive postmarketing experience support the conduct of the present study, Phase 3 Study B1851172, in Japan. This study will assess the safety, tolerability, and immunogenicity of a single dose of 13vPnC in Japanese individuals aged 6 to 64 years who are considered to be at increased risk of pneumococcal disease and who are naive to pneumococcal vaccine.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the investigator's brochure.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective:	**Primary Endpoints:**
• To assess the safety and tolerability of a single dose of 13vPnC as measured by the incidence of local reactions, systemic events, adverse events (AEs), and serious adverse events (SAEs).	• Number and proportion of subjects reporting local reactions (redness, swelling, pain at injection site) and severity of the local reactions occurring within the 7-day period following study vaccination in the 6- to <18-year age group. • Number and proportion of subjects reporting local reactions (redness, swelling, pain at injection site) and severity of the local reactions occurring within the 14-day period following study vaccination in the 18- to <65-year age group. • Number and proportion of subjects reporting systemic events (fever, fatigue, headache, vomiting, diarrhea, muscle pain, joint pain) and severity of the systemic events occurring within the 7-day period following study vaccination in the 6- to <18-year age group. • Number and proportion of subjects reporting systemic events (fever, fatigue, headache, vomiting, diarrhea, muscle pain, joint pain) and severity of the systemic events occurring within the 14-day period following study vaccination in the 18- to <65-year age group. • Number and proportion of subjects reporting AEs and SAEs until Visit 2 categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) in all age groups.
Secondary Objective:	**Secondary Endpoints:**
• To describe the immune responses elicited by a single dose of 13vPnC.	• Serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) 1 month after vaccination in all age groups. • Geometric mean fold rises (GMFRs) in serotype-specific OPA titers from before vaccination to 1 month after vaccination in all age groups. • Serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs) 1 month after vaccination in all age groups. • GMFRs in serotype-specific IgG from before vaccination to 1 month after vaccination in all age groups.

3. STUDY DESIGN

This is a Phase 3, multicenter, single-arm, open-label study to assess the safety, tolerability, and immunogenicity of a single dose of 13vPnC in Japanese subjects aged 6 to 64 years who are considered to be at increased risk of pneumococcal disease and who are naive to pneumococcal vaccines.

This study consists of 2 age groups, 6 to <18 years old and 18 to <65 years old. Subjects will be enrolled in 1 of these age groups and will be assigned a container number of investigational product by an interactive web response (IWR) system. For the purposes of subject participation in the study, including data collection procedures, enrollment in the study is considered to occur at the time of investigational product assignment.

3.1. Approximate Duration of Subject Participation

Subjects will participate in the study for approximately 1 month (29 to 43 days).

3.2. Approximate Duration of the Study

The study will be completed in approximately 6 months. Study duration is from first subject first visit (FSFV) to last subject last visit (LSLV).

3.3. Approximate Number of Subjects

Approximately 200 subjects will be enrolled: approximately 50 subjects in the 6- to <18-year age group and approximately 150 subjects in the 18- to <65-year age group.

For the purpose of ensuring a minimum number of subjects in each of the age categories, at least 15 subjects aged 6 to <12 years and 15 subjects aged 12 to <18 years will be enrolled within the 6- to <18-year age group. Furthermore, at least 50 subjects aged 18 to <50 years and 50 subjects aged 50 to <65 years will be enrolled within the 18- to <65-year age group (Table 1).

Table 1. Approximate Number of Subjects in Each Age Group and Minimum Number of Subjects for the Specified Age Categories

Age Group 6 to <18 Years[a]		Age Group 18 to <65 Years[b]		Total Subjects
50		150		200
Minimum number of subjects per age category		Minimum number of subjects per age category		
6 to <12 years[a]	12 to <18 years[a]	18 to <50 years[b]	50 to <65 years[b]	
15	15	50	50	

a. Approximately 50 subjects will be enrolled in the 6- to <18-year age group; at least 15 subjects will be enrolled in each of the 6- to <12-year and 12- to <18-year age groups.
b. Approximately 150 subjects will be enrolled in the 18- to <65-year age group; at least 50 subjects will be enrolled in each of the 18- to <50-year or 50- to <65-year age groups.

4. SUBJECT ELIGIBILITY CRITERIA

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

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

4.1. Inclusion Criteria

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

1. Evidence of a personally signed and dated informed consent document indicating that the subject and/or a legally acceptable representative/parent/legal guardian for subjects considered to be minors in Japan (6 to <20 years old) has/have been informed of all pertinent aspects of the study.

2. Availability for the entire duration of the study, and subjects (and a legally acceptable representative/parent/legal guardian if the subject is 6 to <18 years old) who are willing and able to comply with scheduled visits, vaccination plan, and other study procedures including completion of the electronic diary (e-diary) for 7 days (Day 1 to Day 7) for subjects aged 6 to <18 years or 14 days (Day 1 to Day 14) for subjects aged 18 to <65 years after study vaccination.

3. Japanese males and females aged 6 to <65 years at enrollment.

4. Subjects with an increased risk of pneumococcal disease determined by documented medical history, physical examination, and clinical judgment of the investigator. The risks may include but are not limited to stable chronic heart disease, lung disease, liver disease, or renal disease; diabetes mellitus; hematologic or solid organ malignancy; immunocompromised persons with known or suspected immunodeficiency due to underlying diseases or treatments; subjects with anatomic host defense abnormalities such as cochlear implants or CSF leaks.

5. Subject (and/or a legally acceptable representative/parent/legal guardian if the subject is 6 to <18 years old) must be able to be contacted by telephone during study participation.

6. Male subjects able to father children and female subjects of childbearing potential who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception throughout the study and for at least 28 days after vaccination.

Female subjects of nonchildbearing potential must meet at least 1 of the following criteria:

a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state.

b. Have undergone a documented hysterectomy and/or bilateral oophorectomy.

c. Have medically confirmed ovarian failure.

d. Female subjects who are <9 years old. If the female subject who is <9 years old has experienced menarche at an earlier age, the subject will be considered of childbearing potential.

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

4.2. Exclusion Criteria

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

1. Previous vaccination with any licensed or investigational pneumococcal vaccine, or planned receipt during study participation.

2. Unstable chronic medical condition or disease requiring significant change[a] in therapy or hospitalization for worsening disease within 6 weeks before investigational product administration.

3. End-stage disease including but not limited to metastatic[b] malignancy, severe chronic obstructive pulmonary disease (COPD) requiring supplemental oxygen, or end-stage renal disease with or without dialysis.

4. Graft-versus-host disease (GVHD), history of solid organ transplant within 6 months before investigational product administration or history of HSCT, or potential for solid organ transplant or HSCT during study participation.

[a] Change in dose or therapy within a category (eg, change from 1 nonsteroidal anti-inflammatory drug [NSAID] to another) is allowed. Change to new therapy categories (eg, surgery, or addition of a new pharmacological class) is allowed only if it is not caused by worsening disease. If change to new therapy categories is caused by worsening disease, this would be considered significant.

[b] Subjects with lymph node and/or distant metastases.

5. Receipt of cytotoxic chemotherapy or blood products within 3 months before investigational product administration or anti–B-cell antibodies within 6 months before investigational product administration through completion of study participation.

6. Any contraindication to vaccination or vaccine components, including previous anaphylactic reaction to any vaccine or vaccine-related components.

7. Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate any type of injection.

8. Vaccination with a diphtheria-containing vaccine or toxoid within 6 months before investigational product administration through the completion of the study participation.

9. Documented *S pneumoniae* infection within the past 5 years before investigational product administration.

10. Insufficient muscle mass, in the opinion of the investigator, to receive a vaccination in the deltoid muscle of the arm.

11. Residence in a nursing home or long-term care facility, or requirement for semiskilled nursing care. An ambulatory subject who is a resident of a retirement home or village is eligible for the trial.

12. Severe visual impairment requiring third-party support to read.

13. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

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

15. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

16. Pregnant female subjects as determined by urine pregnancy test (human chorionic gonadotropin [hCG]); breastfeeding females; fertile male and female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after vaccination.

4.3. Criteria for Temporarily Delaying Investigational Product Administration

The following conditions are temporary or self-limiting and an investigational product may be administered to a subject in the study once the condition(s) has/have resolved and no other exclusion criteria are met:

1. Current febrile illness (axillary temperature ≥37.5°C) or other acute illness within 48 hours before investigational product administration.

2. Subject has received systemic antibiotic therapy for an acute illness within 72 hours before investigational product administration.

3. Subject has received any inactivated vaccine within 14 days or any live vaccine within 28 days before investigational product administration.

If a subject meets any delaying criteria for investigational product administration, all study procedures including blood draw at Day 1 should be delayed until the day of investigational product administration.

4.4. Lifestyle Requirements

4.4.1. Contraception

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

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

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal) provided the subject or male subject's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

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

4.5. Sponsor's Qualified Medical Personnel

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

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

5. INVESTIGATIONAL PRODUCTS

For the purposes of this study, and per International Council for Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active

ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product is 13vPnC.

5.1. Allocation to Investigational Product

Subjects will be assigned container number by IWR. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the subject number. The site personnel will then be provided with container number when investigational product is being supplied via the IWR system. The IWR system will provide a confirmation report containing the container number assigned. The confirmation report must be stored in the site's files.

The study-specific IWR reference manual will provide the help desk's contact information and further details on the use of the IWR.

5.2. Subject Compliance

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

5.3. Investigational Product Supplies

5.3.1. Dosage Form(s) and Packaging

The investigational products (13vPnC) will be provided by the sponsor to each study site. The study vaccines will be packed and labeled as investigational products in accordance with current guidelines and applicable local and legal regulatory requirements.

13vPnC contains saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to nontoxic diphtheria toxin CRM_{197}. The vaccine is formulated to contain 2.2 µg of each saccharide, except for 4.4 µg of 6B, per 0.5-mL dose. The vaccine contains 5 mM succinate buffer, 0.85% sodium chloride, 0.02% polysorbate 80, and 0.125 mg aluminum as aluminum phosphate, per 0.5-mL dose. The vaccine will be provided as a single-dose prefilled syringe.

5.3.2. Preparation and Dispensing

Only appropriately qualified personnel must dispense the investigational product.

Preparation and dispensing information will be provided in the study reference manual (SRM).

5.4. Administration

All subjects will receive a single dose (0.5 mL) of 13vPnC intramuscularly into the deltoid muscle of the nondominant arm, unless medically contraindicated, in which case the injection may be administered in the dominant arm, at Visit 1.

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

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

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

5.5. Investigational Product Storage

13vPnC will be shipped at +2°C to +8°C to each study site after required regulatory and legal documents have been received by the sponsor. Upon receipt at the study site, the vaccines should be immediately transferred to a +2°C to +8°C temperature-monitored refrigerator for storage.

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.

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

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

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

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

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

5.6. Investigational Product Accountability

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

5.6.1. Destruction of Investigational Product Supplies

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

5.7. Concomitant Treatment(s)

The following concomitant medications and vaccinations will be recorded in the CRF:

- Immunosuppressive drugs, including systemic corticosteroids; immune-modifying drugs, including, but not limited to, disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and the tumor necrosis factor antagonists; or monoclonal antibodies from 6 months prior to study enrollment until completion of study participation, and their start and stop dates, medication name, dose, and units.

- Nonstudy vaccines administered from 6 months prior to study enrollment until completion of study participation, including name of vaccine and date administered.

5.7.1. Prohibited Prior Treatment

- Previous vaccination with any licensed or experimental pneumococcal vaccine (see Section 4.2).

- Diphtheria-containing vaccine or toxoid within 6 months before investigational product administration (see Section 4.2).

- Cytotoxic chemotherapy or blood products within 3 months before investigational product administration or anti–B-cell antibodies within 6 months before investigational product administration (see Section 4.2).

- Investigational product within 28 days before study participation (see Section 4.2).

- Systemic antibiotic therapy for an acute illness within 72 hours before investigational product administration (see Section 4.3).

- Any inactivated vaccine within 14 days or any live vaccine within 28 days before investigational product administration (see Section 4.3).

5.7.2. Prohibited During the Study

- Any licensed vaccine other than pneumococcal vaccine administered concomitantly with the investigational product.

- Any other licensed and/or experimental pneumococcal vaccine (other than the study vaccine administered at Visit 1).

- Diphtheria-containing vaccine or toxoid.

- Cytotoxic chemotherapy, blood products, or anti–B-cell antibodies.

- Any other investigational product other than the study vaccine administered at Visit 1.

- Prophylactic antipyretics or other pain medication to prevent symptoms such as fever or pain associated with investigational product administration.

5.7.3. Permitted During the Study

- The use of antipyretics and pain medications to treat symptoms.

- Medications, other than those described in Section 5.7.2.

- Any licensed vaccine other than pneumococcal vaccine is permitted but may not be administered concomitantly with the investigational product. Whenever possible, any licensed vaccine should be administered at least 14 days for inactivated vaccines, or at least 28 days for live vaccines, before or after study vaccination.

6. STUDY PROCEDURES

The schedule of procedures is presented in the Schedule of Activities. In order that the study visits are scheduled within the correct time frames, the day of vaccination should be considered Day 1.

6.1. Visit 1 - Vaccination (Day 1)

- Obtain written informed consent and, if applicable, assent (age dependent on local requirement) before performing any study-specific procedures.

- Obtain a subject number from IWR.

- Obtain and record the subject demography including date of birth, sex, race, and ethnicity.

- Obtain and record medical history and current medical conditions, including the presence of chronic conditions, medical history of significance such as cardiac, pulmonary, renal, hepatic, hematologic, neurological, and/or endocrinologic medical history, relevant surgical procedures and/or allergies (drug or nondrug), and their start and stop dates.

- Obtain and record vaccination history within 6 months before the study participation as described in Section 5.7. For diphtheria vaccine, obtain and record the date of last booster vaccination (the date may be beyond 6 months before study participation).

- Obtain and record any immunosuppressive drugs, including systemic corticosteroids, immune-modifying drugs, or monoclonal antibodies, received within 6 months before the study participation as described in Section 5.7.

- Assess and record smoking status as either smoker, ex-smoker, or never smoked during the 6 months prior to the study participation.

- Perform a physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance, skin, head, eyes, ears, nose, throat, heart, lungs, abdomen, musculoskeletal, neurological, and lymph nodes, including worsening of medical history conditions. Record findings of physical examination on the physical examination record and, if appropriate, on the medical history CRF. If the condition started after informed consent was given, the condition should be recorded on the AE CRF.

- Perform a urine pregnancy test on female subjects of childbearing potential. A negative pregnancy test result is required before female subjects of childbearing potential may receive the investigational product.

- On the day of investigational product administration, measure the subject's axillary temperature (°C) using the digital thermometer prior to investigational product administration and record the temperature on the vital signs CRF. When multiple measurements are taken for the same time point, the most out-of-range (eg, highest) value must be reported.

- Ensure that all of the inclusion criteria, none of the exclusion criteria, and none of the criteria for temporarily delaying vaccine administration are met. If a subject meets any

delay criteria for vaccination, all study procedures including the blood draw at Day 1 should be delayed until the day of vaccination.

- After all eligibility criteria are confirmed, obtain the investigational product assignment from IWR. Refer to the SRM for further instructions and requirements for recording screen failure subjects.

- Prior to vaccination, collect a blood sample (approximately 10 mL) for immunogenicity assessments and record sample tracking information on the CRF.

- Administer a single 0.5-mL injection of the investigational product into the deltoid muscle of the nondominant arm, unless medically contraindicated, in which case the injection may be administered in the dominant arm.

- Observe the subject for at least 30 minutes after the investigational product administration for any acute reactions. Record any AEs in the subject's source documents and on the AE CRFs.

- Provide training in the use of the e-diary device.

    - For subjects aged 6 to <18 years:

        - Train the subject's legally acceptable representative/parent/legal guardian to use the e-diary and set up the e-diary for the subject. Specific instructions for the site user and the subject's legally acceptable representative/parent/legal guardian to use the e-diary will be provided under separate cover.

        - Issue an e-diary, measuring device (caliper [range: 1 to 14+ for subjects aged 6 to <12 years or caliper [range: 1 to 21+] for subjects aged 12 to <18 years), and digital thermometer and provide instructions for usage.

        - Ask the subject's legally acceptable representative/parent/legal guardian to complete the e-diary from Days 1 to 7 after investigational product administration, where Day 1 is the day of investigational product administration.

        - Ask the subject's legally acceptable representative/parent/legal guardian to contact the investigator immediately if the subject experiences a severe local reaction (redness or swelling) at the injection site measuring >14 caliper units (greater than 7 cm) for subjects aged 6 to <12 years or >20 caliper units (greater than 10 cm) for subjects aged 12 to <18 years to arrange an unscheduled visit as specified in Section 6.3.

        - Ask the subject's legally acceptable representative/parent/legal guardian to contact the investigator immediately if the subject experiences a severe systemic event or fever ≥39.0°C.

- Ask the subject's legally acceptable representative/parent/legal guardian to make a note of the stop date for any local reactions and systemic events, including the use of antipyretics and pain medication to treat symptoms, ongoing on the last day that the e-diary was completed and to report that to the investigator at the next visit.

- Ask the subject's legally acceptable representative/parent/legal guardian to contact the investigator immediately if any significant illness or hospitalization occurs during the study period.

- Ask the subject's legally acceptable representative/parent/legal guardian to return the completed e-diary at Visit 2 approximately 1 month (28 to 42 days) after vaccination.

- For subjects aged 18 to <65 years:

  - Train the subject to use the e-diary and set up the e-diary for the subject. Specific instructions for the site user and the subject to use the e-diary will be provided under separate cover.

  - Issue an e-diary, measuring device (caliper [range: 1 to 21+]), and digital thermometer and provide instructions for usage.

  - Ask the subject to complete the e-diary from Days 1 to 14 after investigational product administration, where Day 1 is the day of investigational product administration.

  - Ask the subject to contact the investigator immediately if he or she experiences a severe local reaction (redness or swelling) at the injection site measuring >20 caliper units (greater than 10 cm) to arrange an unscheduled visit as specified in Section 6.3.

  - Ask the subject to contact the investigator immediately if the subject experiences a severe systemic event or fever ≥39.0°C.

  - Ask the subject to make a note of the stop date for any local reactions and systemic events, including the use of antipyretics and pain medication to treat symptoms, ongoing on the last day that the e-diary was completed and to report that to the investigator at the next visit.

  - Ask the subject to contact the investigator immediately if any significant illness or hospitalization occurs during the study period.

  - Ask the subject to return the completed e-diary at Visit 2 approximately 1 month (28 to 42 days) after vaccination.

- Schedule an appointment for the next study visit.
- Obtain and record AEs and SAEs as described in Section 8 and the Schedule of Activities.
- Complete the source documents and the CRF.
- Update the investigational product accountability records.
- Investigators or appropriately qualified designee reviews the e-diary data online at frequent intervals during the e-dairy entry period from Day 1.

6.2. Visit 2-Follow-up Visit (28 to 42 Days After Visit 1)

- Collect the subject's e-diary.
- Review the subject's e-diary and follow up on any ongoing symptoms. Record their stop date or confirm that they are still continuing on the CRF.
- Obtain and record AEs and SAEs as described in Section 8 and the Schedule of Activities.
- Obtain and record any nonstudy vaccinations, and/or immunosuppressive drugs, including systemic corticosteroid, immune-modifying drugs, or monoclonal antibodies, received since the last study visit.
- Collect a blood sample (approximately 10 mL) for immunogenicity assessments and record sample tracking information on the CRF.
- Complete the source documents and the CRF.

6.3. Assessment of Postvaccination Severe Reactions and Systemic Events

6.3.1. Severe Local Reaction or Fever Telephone Contact and Unscheduled Visit

Severe redness and/or swelling at the injection site is defined as:

- >14 caliper units (greater than 7 cm) for subjects aged 6 to <12 years.
- >20 caliper units (greater than 10 cm) for subjects aged 12 to <65 years.

If a severe local reaction (redness, swelling, or pain at the injection site) or fever ≥39.0°C is reported in the e-diary, a contact must occur as soon as possible between the investigator and the subject to assess whether an unscheduled site visit is required. A site visit must be scheduled as soon as possible to assess the extent of the reaction unless:

- The subject is unable to attend the unscheduled visit, or
- The reaction is no longer present at the time of the contact, or

- The investigator confirms that the data were entered into the e-diary in error by the subject.

The subject contact will be recorded on the CRF. If the subject is unable to attend the unscheduled visit, a reason must be given why the subject did not attend the unscheduled visit. The investigator must contact the subject by telephone to determine whether the local reaction meets Grade 4 and/or SAE reporting criteria (refer to Table 2, Table 3, and Section 8.2.3).

At the severe local reaction or fever assessment visit, the following procedures will be conducted by the investigator or medically qualified member of the study staff. For the purpose of severe reaction assessment, a medically qualified member of the study staff is a study physician or study nurse, as applicable to the investigator's local practice.

The following study procedures will be performed during an unscheduled visit:

- Measure the subject's axillary temperature (°C).
- Measure the minimum and maximum diameter (cm) of any redness and the swelling at the site of vaccination.
- Assess pain in accordance with the criteria provided in Section 7.2.1.3.
- Complete the source documents with any new or updated information.
- Complete the CRF.
- If applicable, remind the subject to make a note of a stop date of the reaction ongoing on the last day that the e-diary was completed and to report that to the investigator at the next visit.

6.3.2. Severe Systemic Event Telephone Contact

If a severe systemic event (fatigue, headache, vomiting, diarrhea, muscle pain, or joint pain) is reported in the e-diary, the investigator must contact the subject by telephone as soon as possible to determine whether the systemic event meets Grade 4 and/or SAE reporting criteria (refer to Table 4 and Section 8.2.3).

This telephone contact will be recorded in the source documents.

6.4. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

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

Any vaccinated subject who withdraws from the study, provided the subject is agreeable, will receive safety follow-up for at least 28 days after study vaccination. If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

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

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

7.1. Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test, with hCG sensitivity of at least 25 mIU/mL, will be performed immediately before investigational product administration.

A negative pregnancy test result is required before female subjects of childbearing potential may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product.

7.2. Safety Assessments

Safety parameters will be assessed as described in the Schedule of Activities and below.

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

The postvaccination safety parameters include assessments of local reactions and systemic events occurring within 7 days for subjects aged 6 to <18 years or 14 days for subjects aged 18 to <65 years following investigational product administration. The reactogenicity will be graded as described in Section 7.2.1.3 and Section 7.2.1.4.

Reactions occurring within 30 minutes after investigational product administration will be documented and recorded in the AE CRF.

AEs and SAEs will be collected and reported as described in Section 8.

7.2.1. Local Reactions and Systemic Events

7.2.1.1. Electronic Diary

The subject will be issued an e-diary, based on a smartphone or equivalent technology. Starting on the day of vaccination, local reactions, systemic events, and any antipyretics or pain medication used to treat symptoms will be monitored by the subject's legally acceptable representative/parent/legal guardian for 7 days for subjects aged 6 to <18 years or by the subject for 14 days for subjects aged 18 to <65 years. The e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the subject's experience at that time. Data on local reactions, systemic events, and antipyretics/pain medication used to treat symptoms reported in the e-diary will be transferred electronically to the e-diary vendor, where they will be available for review by investigators via an internet-based portal. At intervals agreed to by the vendor and Pfizer, the data will be transferred electronically into Pfizer's event database for analysis and reporting.

Investigators (or appropriately qualified designee) are required to review the e-diary data online at frequent intervals during e-diary periods, as part of the ongoing safety review.

The investigator or designee will obtain from the subject stop dates for any symptoms ongoing on the last day that the e-diary was completed. The stop dates will be documented in the source documents and the information entered in the CRF.

7.2.1.2. Grading Scales for Local Reactions and Systemic Events

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[32]

7.2.1.3. Local Reactions

For subjects aged 6 to <18 years, the subject's legally acceptable representative/parent/legal guardian will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the e-diary for 7 consecutive days starting on the day of vaccination.

For subjects aged 18 to <65 years, subjects will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the e-diary for 14 consecutive days starting on the day of vaccination.

Redness and swelling will be measured and recorded in caliper units (range: 1 to 14+) by the subject's legally acceptable representative/parent/legal guardian, and then categorized as mild, moderate, or severe based on the grading scale in Table 2 for subjects aged 6 to <12 years.

Redness and swelling will be measured and recorded in caliper units (range: 1 to 21+) by the subject's legally acceptable representative/parent/legal guardian, and then categorized as mild, moderate, or severe based on the grading scale in Table 3 for subjects aged 12 to <18 years.

Redness and swelling will be measured and recorded in caliper units (range: 1 to 21+) by the subject, and then categorized as mild, moderate, or severe based on the grading scale in Table 3 for subjects aged 18 to <65 years.

Caliper units can be converted to centimeters according to the following formula:
1 caliper unit = 0.5 cm.

Pain at the injection site will be assessed by the subject or the subject's legally acceptable representative/parent/legal guardian as mild, moderate, or severe according to the grading scales in Table 2 and Table 3.

When a severe/Grade 3 local reaction is recorded, the subject/legally acceptable representative/parent/legal guardian will contact the investigator, who will assess the reaction and perform a severe local reaction or fever assessment visit as appropriate. In the event that the subject/legally acceptable representative/parent/legal guardian does not call, the investigator will call the subject/legally acceptable representative/parent/legal guardian.

7.2.1.3.1. Management of Grade 4 Local Reactions

Only an investigator is able to classify a subject's local reaction as Grade 4, after physical examination of the subject or telephone contact with the subject/legally acceptable representative/parent/legal guardian. Confirmed Grade 4 local reactions require immediate notification to the sponsor and include:

- Skin necrosis or exfoliative dermatitis (for redness) or skin necrosis (for swelling):

Consider whether the reaction is an important medical event (Section 8.2.3). If yes, report the reaction as an SAE; if no, report it as an AE. Grade the severity of the necrosis or exfoliative dermatitis using the AE severity grading scale in Section 8.3.

- An emergency room visit for management of pain at the injection site:

  Consider whether the reaction is an important medical event (Section 8.2.3). If yes, report the reaction as an SAE; if no, report it as an AE. Grade the severity of the injection site pain using the AE severity grading scale in Section 8.3.

- Hospitalization for management of pain at the injection site:

  Report the hospitalization for injection site pain management as an SAE and grade the severity of the injection site pain using the AE severity grading scale in Section 8.3.

Table 2. Local Reaction Grading Scale (for Subjects Aged 6 to <12 Years)

	GRADE 1 mild	GRADE 2 moderate	GRADE 3[a] severe	GRADE 4[b]
Redness	1 to 4 caliper units (or measuring device units) 0.5 to 2.0 cm	>4 to 14 caliper units (or measuring device units) >2.0 to 7.0 cm	>14 caliper units (or measuring device units) >7.0 cm	Necrosis or exfoliative dermatitis[b]
Swelling	1 to 4 caliper units (or measuring device units) 0.5 to 2.0 cm	>4 to 14 caliper units (or measuring device units) >2.0 to 7.0 cm	>14 caliper units (or measuring device units) >7.0 cm	Necrosis[b]
Pain (tenderness) at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain (tenderness) at the injection site

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

a. When subjects experience local reactions >14 caliper units (>7.0 cm) or severe pain (tenderness) at the injection site, the subject/legally acceptable representative/parent/legal guardian will telephone the study site. In the event that the subject/legally acceptable representative/parent/legal guardian does not call, the investigator will call the subject/legally acceptable representative/parent/legal guardian.
b. Grade 4 assessment should be made by the investigator and recorded as an AE on the CRF. Manage as shown in Section 7.2.1.3.1 and Section 8.3.

Table 3. Local Reaction Grading Scale (for Subjects Aged 12 to <18 Years and 18 to <65 Years)

	GRADE 1 mild	GRADE 2 moderate	GRADE 3[a] severe	GRADE 4[b]
Redness	5 to 10 caliper units (or measuring device units) 2.5 to 5.0 cm	>10 to 20 caliper units (or measuring device units) >5.0 to 10.0 cm	>20 caliper units (or measuring device units) >10.0 cm	Necrosis or exfoliative dermatitis[b]
Swelling	5 to 10 caliper units (or measuring device units) 2.5 to 5.0 cm	>10 to 20 caliper units (or measuring device units) >5.0 to 10.0 cm	>20 caliper units (or measuring device units) >10.0 cm	Necrosis[b]
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain at the injection site

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

a. When subjects experience local reactions >20 caliper units (>10.0 cm) or severe pain at the injection site, the subject/legally acceptable representative/parent/legal guardian will telephone the study site. In the event that the subject/legally acceptable representative/parent/legal guardian does not call, the investigator will call the subject/legally acceptable representative/parent/legal guardian.
b. Grade 4 assessment for local reactions should be made by the investigator and recorded as an AE on the CRF. Manage as shown in Section 7.2.1.3.1 and Section 8.3.

7.2.1.4. Systemic Events

Starting on the day of vaccination, and for 7 consecutive days, postvaccination systemic events will be assessed by the subject's legally acceptable representative/parent/legal guardian each day for subjects aged 6 to <18 years, and if present, they will be graded as mild, moderate, or severe and recorded in the e-diary, using the grading scale in Table 4.

Starting on the day of vaccination, and for 14 consecutive days, postvaccination systemic events will be assessed by the subject each day for subjects aged 18 to <65 years, and if present, they will be graded as mild, moderate, or severe and recorded in the e-diary, using the grading scale in Table 4.

When a severe/Grade 3 systemic event is recorded, the subject/legally acceptable representative/parent/legal guardian will contact the investigator, who will assess the reaction. In the event that the subject/legally acceptable representative/parent/legal guardian does not call, the investigator will call the subject/legally acceptable representative/parent/legal guardian.

7.2.1.4.1. Management of Grade 4 Systemic Events

Only an investigator is able to classify a subject's systemic event as Grade 4, after physical examination of the subject or telephone contact with the subject/legally acceptable

representative/parent/legal guardian. Confirmed Grade 4 systemic events require immediate notification to the sponsor and include:

- An emergency room visit for management of a systemic event:

  Consider whether the systemic event is an important medical event (Section 8.2.3). If yes, report the event as an SAE; if no, report it as an AE. Grade the severity of the systemic event using the AE severity grading scale in Section 8.3.

- Hospitalization for management of a systemic event:

  Report hospitalization for management of a systemic event as an SAE and grade the severity of the systemic event according to the AE severity grading scale in Section 8.3.

Table 4. Systemic Event Grading Scale (for All Age Groups and Categories)

	GRADE 1 mild	GRADE 2 moderate	GRADE 3[a] severe	GRADE 4[b]
Fatigue (tiredness)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization
Vomiting	1 to 2 times in 24 hours	>2 times in 24 hours	Requires intravenous hydration	Emergency room visit or hospitalization
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization
Muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization

Abbreviation: CRF = case report form.

a. When subjects experience severe systemic events, the subject/legally acceptable representative/parent/legal guardian will telephone the study site. In the event that the subject/legally acceptable representative/parent/legal guardian does not call, the investigator will call the subject/legally acceptable representative/parent/legal guardian.

b. Grade 4 assessment for systemic events should be made by the investigator and recorded as an AE on the CRF. Manage as shown in Section 7.2.1.4.1 and Section 8.3.

7.2.1.5. Fever

Starting on the day of vaccination, temperature will be measured by the subject's legally acceptable representative/parent/legal guardian each evening for 7 consecutive days and at any time during these periods that fever is suspected for subjects aged 6 to <18 years. A digital thermometer will be given to the subject's legally acceptable representative/parent/legal guardian with instructions on how to measure the subject's axillary temperature.

Starting on the day of vaccination, temperature will be measured by the subject each evening for 14 consecutive days and at any time during these periods that fever is suspected for subjects aged 18 to <65 years. A digital thermometer will be given to the subject with instructions on how to measure his/her axillary temperature.

Fever is defined as an axillary temperature of ≥37.5°C. The highest temperature for each day will be recorded in the e-diary. In the event of a fever, temperature will be collected daily until fever has resolved (1 day with a temperature less than 37.5°C). Temperature will be measured and recorded to 1 decimal place by the subject/legally acceptable representative/parent/legal guardian and then categorized during analysis according to the scale shown in Table 5.

Where a fever ≥39.0°C is recorded, the subject/legally acceptable representative/parent/legal guardian will contact the investigator by telephone and the investigator will assess whether a severe local reaction or fever assessment visit is required (refer to Section 6.3). If the subject/legally acceptable representative/parent/legal guardian does not call the investigator, the investigator will contact the subject/legally acceptable representative/parent/legal guardian.

Table 5. Scale for Fever

37.5 to 38.4°C
38.5 to 38.9°C
39.0 to 40.0°C
>40.0°C

7.2.1.6. Use of Antipyretic Medication and Pain Medication

Starting on the day of vaccination and for 7 consecutive days for subjects aged 6 to <18 years or for 14 consecutive days for subjects aged 18 to <65 years, the use of antipyretic medication and pain medication for treatment of symptoms will be recorded in the e-diary.

7.3. Immunogenicity

In total, 2 blood samples will be collected for assessment of the immune responses. Approximately 10 mL of blood will be collected at Day 1 prior to receipt of investigational product and 1 month later (28 to 42 days after Visit 1). A total volume of approximately 20 mL of blood will collected during the study to allow adequate volume required for repeat testing or additional antigen-specific immunogenicity testing to be performed.

In case of difficulty in obtaining a blood sample, it is possible to reschedule the sampling provided that the date remains within the authorized protocol window. Refer to the Schedule of Activities for the time points.

Serum samples will be obtained at the study site and be shipped for analysis. Sample collection, storage, and shipping instructions will be provided in the SRM.

Antibody-mediated serum OPA against each of the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) will be measured centrally using a quantitative functional OPA assay. Results will be expressed as titers for each serotype.

Serum concentrations of anticapsular IgG antibodies for each of the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) will be determined in all subjects for each blood sample and expressed as micrograms per milliliter (μg/mL). The Luminex-based assay will employ 2 pneumococcal cell wall polysaccharide-containing extracts, as absorbents in the serum dilution buffer.

7.4. 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 subject's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the informed consent document, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the subject's genetic material will be performed.

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

8. ADVERSE EVENT REPORTING

8.1. Requirements

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

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

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

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

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

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

investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

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

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

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

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

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject/legally acceptable representative/parent/legal guardian provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including Visit 2.

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

8.1.4.1. Reporting SAEs to Pfizer Safety

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

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

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

8.1.4.2. Recording Nonserious AEs and SAEs on the CRF

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

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

8.1.5. Causality Assessment

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

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

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

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

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;

- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

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

8.2.2. Abnormal Test Findings

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

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

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

8.2.3. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

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

Or that is considered to be:

- An important medical event.

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

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

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

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

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

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

- Any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;

- Fetal distress, fetal death, or any congenital abnormality or birth defects.

8.2.4. Hospitalization

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

Hospitalization does not include the following:

- Rehabilitation facilities;

- Hospice facilities;

- Respite care (eg, caregiver relief);

- Skilled nursing facilities;

- Nursing homes;

- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

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

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);

- Social admission (eg, subject has no place to sleep);

- Administrative admission (eg, for yearly physical examination);

- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);

- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, 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 subject's usual function.
2	MODERATE	Interferes to some extent with subject's usual function.
3	SEVERE	Interferes significantly with subject's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

The severity grading scale shown above should be used when assessing the severity of any AE/SAE, and Grade 4 postvaccination local reactions and systemic events as described in Section 7.2.1.3 and Section 7.2.1.4.

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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

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

8.4.2. Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8.4.3.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

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

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

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

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

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as

SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

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

8.4.3.2. Exposure During Breastfeeding

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

8.4.3.3. Occupational Exposure

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

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

8.4.4. Medication Errors and Lack of Efficacy

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

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

8.4.4.1. Medication Errors

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

Medication errors include:

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

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

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

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

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

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.

8.4.4.2. Lack of Efficacy

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

8.5. Medical Device Complaint Reporting Requirements

All medical device complaints, regardless of whether the medical device complaint is associated with an AE, will be recorded on the applicable pages within the CRF. This includes potential incidents or malfunctions associated with the use of a medical device product. An incident or malfunction is an event that might have led to death or serious

deterioration in health, or if it occurred again might lead to death or serious deterioration in health.

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

9. DATA ANALYSIS/STATISTICAL METHODS

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

9.1. Sample Size Determination

The study size is not based on any formal statistical hypothesis test. All statistical analysis will be descriptive. The number of subjects for each age group is defined to enroll a wide range of subjects within 6 to 64 years of age. The sample size for each age group and the total are described in Section 3.3.

The probabilities of observing at least 1 occurrence of any local reaction or systemic event with a true incidence rate when 13vPnC is administered to 50 subjects in the 6- to <18-year age group and 150 subjects in the 18- to <65-year age group, and the probabilities of observing at least 1 occurrence of any AE with a true incidence rate when 13vPnC is administered to the total of 200 subjects are displayed in Table 6.

Table 6. Probability of Observing at Least 1 Event by Assumed True Incidence Rates With Different Sample Sizes

Assumed True Incidence Rate	N=50	N=150	N=200
1.0%	0.39	0.78	0.87
1.5%	0.53	0.90	0.95
2.0%	0.64	0.95	0.98
3.2%	0.80	0.99	>0.99
5.0%	0.92	>0.99	>0.99

9.2. Analysis Populations

The safety population will include all subjects who receive 1 dose of study vaccine. The safety population will be the only analysis population for the primary endpoints.

For immunogenicity analyses, 2 analysis populations will be defined: the evaluable immunogenicity population and the all-available immunogenicity population. The evaluable immunogenicity population will include any subject who was eligible, received study vaccine, had blood drawn within the specified time frame 1 month after vaccination, had at least 1 valid and determinate assay result (OPA titer or IgG concentration) for at least 1 serotype

1 month after vaccination, and had no major protocol violations as determined by the sponsor's clinician.

Additional criteria may be described in the SAP. The evaluable immunogenicity population will be the primary analysis population for immunogenicity results.

The all-available immunogenicity population will include all subjects who received study vaccine and had at least 1 valid and determinate OPA titer or IgG concentrations for at least 1 serotype 1 month after vaccination. The all-available immunogenicity population will be the secondary analysis population for immunogenicity results.

9.3. Immunogenicity Analysis

Secondary endpoints include OPA GMTs and IgG GMCs 1 month after vaccination, and OPA and IgG GMFRs measured from before vaccination to 1 month after vaccination. Each serotype will be analyzed separately.

OPA GMTs, IgG GMCs, and their associated 95% confidence intervals (CIs) will be provided before vaccination and 1 month after vaccination. The OPA GMTs and IgG GMCs will be calculated as the mean of the assay results after making the logarithm transformation and then back transformation to its original scale. Two (2)-sided 95% CIs will be constructed by back transformation of the CI for the mean of the logarithmically transformed assay results computed based on the Student t distribution.

OPA GMFRs and IgG GMFRs will be calculated along with corresponding 2-sided 95% CIs. The CIs for GMFRs will be back transformations of a CI based on the Student t distribution for the mean difference of the log-transformed assay results before vaccination and 1 month after vaccination.

Reverse cumulative distribution curves (RCDCs) of OPA titers and IgG concentrations will be compiled for each serotype before vaccination and 1 month after vaccination.

Immunogenicity analysis will be summarized for subjects of all ages, and for each age group (6 to <18 years old and 18 to <65 years old), if needed.

9.4. Safety Analysis

Safety is the primary objective. The safety endpoints are local reactions, systemic events, and unsolicited AEs and SAEs. The proportion of subjects with local reactions and systemic events reported on any day within the 7 days following vaccination for the 6- to <18-year age group, or within the 14-day period for the 18- to <65-year age group, will be compiled. These proportions, with the associated 2-sided 95% Clopper-Pearson CIs, will be summarized for each age group (6 to <18 years old and 18 to <65 years old). Severities of local reactions and systemic events will also be descriptively summarized.

AEs will be categorized according to MedDRA and will be summarized for subjects of all ages. All summaries will show the number and percentage of subjects experiencing at least

1 event and the number of events. Additional summaries by AE severity or by vaccine relationship may be produced. In addition, AEs and SAEs will be summarized for each age group (6 to <18 years old and 18 to <65 years old).

9.5. Interim Analysis

No formal interim analysis will be conducted for this study. However, as this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and/or to support clinical development.

9.6. Data Monitoring Committee

This study will not use a data monitoring committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

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

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

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

11.2. Record Retention

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

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

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

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

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

12.3. Subject Information and Consent

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

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

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

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

The investigator must ensure that each study subject, or his or her legally acceptable representative/his or her parent/legal guardian if a minor, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative/parent/legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must reconsent as adults to remain in the study. If the enrollment of emancipated minors is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a legally acceptable representative, parent, or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative/parent/legal guardian and the subject's assent, when applicable, before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent/assent document.

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

End of trial in all participating countries is defined as LSLV.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the

discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of 13vPnC at any time.

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

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

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

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

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

EudraCT

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

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

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

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

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

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

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

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

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

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Appendix 1. Abbreviations

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

Abbreviation	Term
7vPnC	7-valent pneumococcal conjugate vaccine
13vPnC	13-valent pneumococcal conjugate vaccine
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
CK	creatine kinase
COPD	chronic obstructive pulmonary disease
CRF	case report form
CRM_{197}	cross-reactive material 197 (nontoxic variant of diphtheria toxin)
CSA	clinical study agreement
CSF	cerebrospinal fluid
CT	clinical trial
DILI	drug-induced liver injury
DMARD	disease-modifying antirheumatic drug
EC	ethics committee
e-diary	electronic diary
EDP	exposure during pregnancy
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FSFV	first subject first visit
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMT	geometric mean titer
GVHD	graft-versus-host disease
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplant
ICH	International Council for Harmonisation
ID	identification
IgG	immunoglobulin G
IND	investigational new drug application
INR	international normalized ratio
IPD	invasive pneumococcal disease
IRB	institutional review board

Abbreviation	Term
IUD	intrauterine device
IWR	interactive web response
LFT	liver function test
LSLV	last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
NSAID	nonsteroidal anti-inflammatory drug
OPA	opsonophagocytic activity
PCD	primary completion date
PD	pneumococcal disease
PI	principal investigator
PPSV23	23-valent pneumococcal polysaccharide vaccine
PT	prothrombin time
RCDC	reverse cumulative distribution curves
SAE	serious adverse event
SAP	statistical analysis plan
SCD	sickle-cell disease
SRM	study reference manual
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
UI	uncertainty interval
ULN	upper limit of normal
US	United States