# A PHASE 1, RANDOMIZED, OPEN-LABEL TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF PNEUMOCOCCAL CONJUGATE FORMULATIONS IN HEALTHY ADULTS 18 THROUGH 49 YEARS OF AGE

| | |
|---|---|
| **Study Intervention Number:** | [redacted] |
| **Study Intervention Name:** | N/A |
| **US IND Number:** | TBD |
| **EudraCT/CTIS Number:** | N/A |
| **ClinicalTrials.gov ID:** | TBD |
| **Pediatric Investigational Plan Number:** | N/A |
| **Protocol Number:** | C4801001 |
| **Phase:** | Phase 1 |

**Brief Title:** A Phase 1 Study to Evaluate the Safety and Immunogenicity of Pneumococcal Conjugate Formulations in Healthy Adults 18 Through 49 Years of Age

[redacted]

## Document History

| Document | Version Date |
|---|---|
| Original protocol | 26 May 2022 |

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# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

**Protocol Title:** A Phase 1, Randomized, Open-Label Trial to Evaluate the Safety and Immunogenicity of Pneumococcal Conjugate Formulations in Healthy Adults 18 Through 49 Years of Age

**Brief Title:** A Phase 1 Study to Evaluate the Safety and Immunogenicity of Pneumococcal Conjugate Formulations in Healthy Adults 18 Through 49 Years of Age

### Regulatory Agency Identification Number(s):

| | |
|---|---|
| **US IND Number:** | TBD |
| **[EudraCT/CTIS] Number:** | N/A |
| **ClinicalTrials.gov ID:** | TBD |
| **Pediatric Investigational Plan Number:** | N/A |
| **Protocol Number:** | C4801001 |
| **Phase:** | Phase 1 |

### Rationale:

*Streptococcus pneumoniae* causes invasive (eg, meningitis, sepsis, bacteremic pneumonia) and noninvasive (eg, OM, nonbacteremic pneumonia, sinusitis) disease associated with significant healthcare burden, morbidity, and mortality. 13vPnC (Prevnar 13®) was licensed by the FDA and other countries for use in infants and young children for the prevention of pneumococcal disease more than a decade ago. It was subsequently indicated for prevention of pneumonia in adults ≥18 years of age. 13vPnC has been introduced into national immunization programs for pediatric and adult populations around the world. 20vPnC was developed to expand protection against pneumococcal invasive disease and pneumonia and has been approved by the FDA and EMA for adults ≥18 years of age. 20vPnC contains the identical polysaccharide conjugates and excipients as 13vPnC but with additional conjugate polysaccharides for 7 additional serotypes.

[redacted]

[redacted]

This randomized, open-label Phase 1 study is designed to evaluate the safety and immunogenicity of [redacted]

**Objectives, Endpoints, and Estimands:**

| Objectives | Endpoints | Estimands |
|---|---|---|
| **Primary:** | **Primary:** | **Primary:** |
| To describe the safety profile of [redacted] candidates in adults 18 through 49 years of age | • Prompted local reactions (redness, swelling, and pain at the injection site)<br>• Prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain)<br>• AEs<br>• SAEs | In participants receiving the study intervention from each group, the percentage of participants reporting:<br>• Prompted local reactions within 7 days after administration<br>• Prompted systemic events within 7 days after administration<br>• AEs within 1 month after administration<br>• SAEs within 1 month after administration |
| **Secondary:** | **Secondary:** | **Secondary:** |
| To describe the immune responses elicited by the [redacted] candidates | • OPA titers [redacted] | In participants complying with the key protocol criteria (evaluable participants) from each group:<br>• [redacted] OPA GMTs 1 month after administration |

**Overall Design:**

This is a Phase 1, multicenter, randomized, open-label study to evaluate alternative [redacted] This study will be conducted at investigator sites in the US. Approximately 405 adults 18 through 49 years of age with no history of pneumococcal vaccination will be enrolled. Participants will be enrolled and randomized equally to 1 of 9 groups (45 participants per group): 6 groups will receive 1 of 6 different [redacted] candidates and 3 groups will receive either [redacted], 13vPnC, or PCV15 (see Study Intervention Groups table below).

There are 3 preformulated products that will be administered at 2 different volumes to create the 6 different [redacted] candidates [redacted]

- [redacted]
  - [redacted]
  - [redacted]
- [redacted]
  - [redacted]
  - [redacted]
- [redacted]
  - [redacted]
  - [redacted]

All formulations include $AlPO_4$.

The key control group will receive polysaccharide conjugate [redacted] contained in 13vPnC (Prevnar 13) and 20vPnC (Prevnar 20™). In addition, PCV15 (Vaxneuvance [Merck]) and 13vPnC are both licensed in the US for use in adults and will be included as supplemental controls.

**Study Intervention Groups**

| Group | Carrier Protein | Chemistry | Polysaccharide Dose | Dose Volume | n |
|---|---|---|---|---|---|
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 45 |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 45 |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 45 |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 45 |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 45 |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 45 |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 45 |

**Study Intervention Groups**

| Group | Carrier Protein | Chemistry | Polysaccharide Dose | Dose Volume | n |
|---|---|---|---|---|---|
| PCV15 (control) | N/A | N/A | [redacted] | 0.5 mL | 45 |
| 13vPnC (control) | $CRM_{197}$ | RAC | [redacted] | 0.5 mL | 45 |

Abbreviations: N/A = not applicable; RAC = reductive amination chemistry; [redacted]

On Day 1 (Visit 1), participants will be assessed for eligibility, have blood drawn for immunogenicity assessments, receive a dose of 1 of the [redacted] candidates or controls, be observed for 30 minutes after administration, and receive safety follow-up and e-diary instructions. The study interventions will be prepared and administered by designated staff.

Local reactions (pain, redness, and swelling) occurring at the injection site and systemic events (fever, fatigue, headache, muscle pain, and joint pain) will be prompted for and collected daily in an e-diary from Day 1 through Day 7 after administration of study intervention, where Day 1 is the day of administration. AEs (including nonserious AEs and SAEs) will be assessed for approximately 1 month after study intervention administration (through Visit 2).

At Visit 2 (28-42 days after Visit 1), participants will return for follow-up. Information will be collected from the participants on AEs and e-diary follow-up (as needed), and blood will be drawn for immunogenicity assessments.

Approximately 15 participants from each group will be enrolled at specialty sites that will collect [redacted] and approximately 20 mL for sera for OPA and IgG measurements. The remaining participants enrolled at other sites will have 60 mL of blood drawn for sera for OPA and IgG measurements.

**Number of Participants:**

Approximately 405 participants (approximately 45 per group) will be randomized to study intervention.

**Study Population:**

Key inclusion and exclusion criteria are listed below (for the full set of criteria, see Section 5.1 and Section 5.2 of this protocol):

**Inclusion Criteria**

Participants must meet the following key inclusion criteria to be eligible for enrollment into the study:

1. Male or female participants ≥18 and ≤49 years of age at the time of consent.

2. Adults determined by clinical assessment (including medical history and clinical judgment) to be eligible for the study, including adults with preexisting stable disease (defined as disease not requiring significant change in therapy or hospitalization for worsening disease) within 12 weeks before receipt of study intervention.

3. Female participants of childbearing potential or male participants who are able to father children and are willing to use acceptable methods of contraception for at least 28 days after the dose of study intervention; or female participants not of childbearing potential; or male participants not able to father children.

   Note: Female participants of nonchildbearing potential must meet the criteria described in the WOCBP section of the protocol.

4. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

**Exclusion Criteria**

Participants with any of the following characteristics/conditions will be excluded:

1. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component in pneumococcal conjugate vaccines and any other diphtheria toxoid–containing vaccine.

2. Serious chronic disorder, including metastatic malignancy, severe COPD requiring supplemental oxygen, end-stage renal disease with or without dialysis, cirrhosis of the liver, clinically unstable cardiac disease, or any other disorder that in the investigator's opinion would make the participant inappropriate for entry into the study.

3. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

4. Known or suspected immunodeficiency or other conditions associated with immunosuppression, including, but not limited to, immunoglobulin class/subclass deficiencies, generalized malignancy, HIV infection, leukemia, lymphoma, or organ or bone marrow transplant.

5. Congenital, functional, or surgical asplenia.

6. Current febrile illness (body temperature ≥100.4°F [≥38.0°C]) or other acute illness within 48 hours before study intervention administration.

7. Previous vaccination with any licensed or investigational pneumococcal vaccine, or planned receipt of any licensed or investigational pneumococcal vaccine through study participation.

8. Currently receives treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, or planned receipt through the last blood draw (Visit 2). Participants may not be enrolled if corticosteroids were administered within 28 days before study intervention administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, or ears) corticosteroids are permitted.

9. Receipt of blood/plasma products or immunoglobulin within the 60 days before study intervention administration, or planned receipt during study participation.

10. Receipt of any inactivated or otherwise nonlive vaccine within 14 days or any live vaccine within 28 days before administration of study intervention.

11. Participation in other studies involving investigational drugs, investigational vaccines (except for investigational pandemic vaccines recommended and authorized in this population for emergency use), or investigational devices within 28 days prior to study entry and/or during study participation. Participation in purely observational studies is acceptable.

**Study Arms and Duration:**

Each participant will participate in the study for approximately 1 month (Visit 1 through Visit 2). The study duration is estimated to be approximately 2 months.

[redacted] of the controls [redacted], 13vPnC and PCV15) will be administered intramuscularly in the deltoid muscle of the preferably nondominant arm by a site staff member or designee. The preformulated products and controls will be provided to the site by the sponsor.

| Study Intervention(s) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Intervention Name (Formulations)** | [redacted] | | [redacted] | | [redacted] | | [redacted] | 13vPnC (Prevnar 13) 0.5 mL suspension for injection | Vaxneuvance (pneumococcal 15-valent conjugate vaccine) suspension for injection |
| **Arm name (group of participants receiving a specific intervention or no intervention)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 13vPnC control group | PCV15 control group |
| **Dose volume** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 0.5 mL administered | 0.5 mL administered |
| **Route of administration** | Intramuscular injection | Intramuscular injection | Intramuscular injection | Intramuscular injection | Intramuscular injection | Intramuscular injection | Intramuscular injection | Intramuscular injection | Intramuscular injection |
| **Use** | Experimental | Experimental | Experimental | Experimental | Experimental | Experimental | Control | Control | Control |
| **IMP or NIMP/AxMP** | IMP | IMP | IMP | IMP | IMP | IMP | IMP | NIMP | NIMP |

**Statistical Methods:**

The study size of this Phase 1 study is not based on any formal hypothesis test for safety or immunogenicity results. All statistical analyses will be descriptive.

The primary objective is to describe the safety profile of the [redacted] candidates; this will be done by summary statistics (including counts and percentages of participants and the associated 2-sided 95% CIs) for local reactions, systemic events, AEs, and SAEs for each study intervention group. With 45 participants per study group, the study will provide a greater than 90% chance of observing at least 1 AE in each group if the true rate is at least 5%.

The secondary objective will be to describe the pneumococcal immunogenicity of the [redacted] candidates by summarizing OPA GMTs approximately 1 month after study intervention administration for each group. The corresponding 95% CI for the GMTs will also be provided.

**Ethical Considerations:**

Participants enrolled in this study are in an age group that is not currently covered by the indication for vaccines containing [redacted] conjugate. These participants are relatively healthy and therefore are not recommended for pneumococcal conjugate vaccines. Receiving the [redacted] candidates or controls will not interfere with the standard of care for these participants. For those with risk factors for pneumococcal vaccination, the investigator site and ICD will inform participants to seek advice from their healthcare provider regarding the need for immunization after the study.

The study will provide the immune impact of [redacted] that could potentially benefit adults and children.

The investigational [redacted] candidates have not yet been evaluated in clinical studies; therefore, the initial safety data will be generated in this [redacted] Phase 1 study. [redacted] The most common AEs noted in adults after vaccination with 20vPnC are primarily related to local reactions (injection site pain, redness, and swelling) and systemic events (fever, headache, fatigue, joint pain, and muscle pain). Safety reviews of data from the 3 completed Phase 3 adult trials has not revealed any unexpected safety concerns.

[redacted]

### 1.3. Schedule of Activities

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

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

| Visit Identifier<br><br>Visit Description | Visit 1<br>Study Intervention Administration | Visit 2<br>Follow-Up After Study Intervention Administration | Notes |
|---|---|---|---|
| **Visit Window (Days)** | **Day 1** | **28 to 42 Days After IP Administration** | • See Section 8.4.3 for follow-up AE and SAE assessments. |
| Obtain informed consent | X | | • Informed consent should be obtained prior to undergoing any study-specific procedures.<br>• See Section 10.1.3 for additional information. |
| Assign participant number via the IRT | X | | |
| Record demography | X | | |
| Perform clinical assessment, including medical history | X | | |
| Record nonstudy vaccinations | X | X | |
| Record concomitant medication use for treatment of SAEs | X | X | |
| Obtain oral temperature prior to study intervention administration | X | | |
| Contraception check, if applicable | X | X | • See Section 10.4 for additional information. |

| Visit Identifier<br><br>Visit Description | Visit 1<br>Study Intervention Administration | Visit 2<br>Follow-Up After Study Intervention Administration | Notes |
|---|---|---|---|
| **Visit Window (Days)** | **Day 1** | **28 to 42 Days After IP Administration** | • See Section 8.4.3 for follow-up AE and SAE assessments. |
| Perform urine pregnancy test for female participants of childbearing potential | X | | • See Section 8.3.6 for additional information. |
| Review inclusion and exclusion criteria | X | | • The investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly until 28 days after the last dose of the study intervention and document the conversation and the participant's affirmation in the participant's chart. |
| Review continued eligibility | | X | |
| Assign randomization number via the IRT | X | | |
| Specialty sites: Obtain blood sample for immunogenicity assessment [redacted] | ~20 mL (for immunogenicity) [redacted] | ~20 mL (for immunogenicity) [redacted] | • Blood samples from participants enrolled at specialty sites (n=15/group).<br>• [redacted] |
| Other sites: Obtain blood sample for immunogenicity assessment | ~60 mL | ~60 mL | • Blood sample for Visit 1 will be collected prior to administration. |
| Administer study intervention | X | | • See Section 6.1 for additional information. |
| Observe and record acute reactions for 30 minutes after study intervention administration | X | | |
| Provide a participant contact card | X | | |

| Visit Identifier<br><br>Visit Description | Visit 1<br>Study Intervention Administration | Visit 2<br>Follow-Up After Study Intervention Administration | Notes |
|---|---|---|---|
| **Visit Window (Days)** | **Day 1** | **28 to 42 Days After IP Administration** | • See Section 8.4.3 for follow-up AE and SAE assessments. |
| Provide participant with an e-diary (device or application), thermometer, and measuring device, and instruct to collect prompted local reactions and systemic events | X | | • Participants will record in an e-diary prompted local reactions and systemic events occurring within 7 days after administration. Instruct the participant to complete the e-diary from Day 1 through Day 7, with Day 1 being the day of study intervention administration. Participants will be instructed to contact the study staff or investigator if they experience redness or swelling measuring >20 measuring device units, severe pain at the injection site, or any Grade 4 prompted systemic event. |
| Review e-diary | | X | • Designated site staff will review e-diary data online at frequent intervals (daily is optimal) for the 7 days following administration to evaluate participant compliance and reported events as part of the ongoing safety review. |
| Collect e-diary or assist the participant to delete the application | | X | • Any e-diary devices given to participants are to be collected at Visit 2. |
| Record and report AEs and SAEs | X----------X | | • AEs include nonserious AEs and SAEs.<br>• See Section 8.4 for additional information. |

## 2. INTRODUCTION

*S pneumoniae* causes invasive disease (eg, meningitis, sepsis, bacteremic pneumonia) and noninvasive disease (eg, OM, nonbacteremic pneumonia, sinusitis) associated with a significant healthcare burden, morbidity, and mortality.[1] The 13-valent pneumococcal conjugate vaccine (Prevnar 13, 13vPnC) was licensed more than a decade ago by the FDA and in other countries for use in infants and young children for the prevention of pneumococcal disease. It was subsequently indicated for prevention of pneumonia in adults ≥18 years of age. 13vPnC has been introduced into national immunization programs for pediatric and adult populations worldwide.

Despite significant reductions in pneumococcal disease following use of 13vPnC, a significant burden of pneumococcal disease remains. The pneumococcal 20-valent conjugate vaccine (20vPnC, Prevnar 20) was developed to expand protection against IPD and pneumonia and has been approved by the FDA and EMA for adults ≥18 years of age. It is also being developed for pediatric patients. 20vPnC contains the identical polysaccharide conjugates and excipients as 13vPnC, but with additional conjugate polysaccharides for 7 additional serotypes.

[redacted]

### 2.1. Study Rationale

The purpose of the study is to evaluate the safety and immunogenicity of [redacted] candidates [redacted]

The study is open-label, so as to allow maximum flexibility for testing and generating the [redacted]. The risk of this approach is low as this is a 1-dose Phase 1 exploratory study, there is no clinical endpoint in this study, and immunogenicity endpoints are not easily biased. The risk of bias in terms of safety assessments is also low as the participants and investigators will have little preconceived ideas about these candidates. [redacted].

### 2.2. Background

Since the [redacted]

[redacted]

Literature suggests that increased levels of vaccine-elicited antibodies may decrease nasal carriage.[5,6] [redacted]

Potential mechanisms for enhancing the immunogenicity of [redacted]

- Increases in the polysaccharide dose level may increase the immune response. Early in the development of Prevnar (7vPnC), the impact of the polysaccharide dose level was assessed in an infant study using a 5-valent pneumococcal conjugate vaccine showing higher dose levels of some conjugates resulted in higher immunogenicity in infants for certain serotypes. Subsequently, in a mixing study with 2 and 4 times the standard dose of 7vPnC, higher immunogenicity was observed with 4 times the standard dose for serotypes in older adults.[7] In a study conducted by Jackson et al, older adults previously vaccinated with PPSV23 were given either a single dose of 13vPnC or 2 concurrent doses of 13vPnC. There were no safety issues identified in the study, and the response to a double dose of 13vPnC was higher than that of a single dose for a majority of the 13vPnC serotypes evaluated [redacted][8] In contrast, in an infant study by Rupp et al evaluating an investigational 15-valent pneumococcal conjugate vaccine prepared with double the standard dose of polysaccharide and $CRM_{197}$ conjugate, an increase in immunogenicity was not observed for most serotypes.[9] [redacted]
- [redacted]
- [redacted]

[redacted]

## 2.3. Benefit/Risk Assessment

The investigational [redacted] candidates have not yet been evaluated in clinical studies; therefore, safety data are not available. [redacted]. The most common AEs noted in adults after vaccination with 20vPnC are primarily related to local reactions (injection site pain, redness, and swelling) and systemic events (fever, headache, fatigue, joint pain, and muscle pain). Safety review of data from the 3 completed Phase 3 adult trials

has not revealed any unexpected safety concerns. See the 13vPnC and 20vPnC package inserts for additional details.

In a dose-ranging study to assess the safety and immunogenicity of 1-fold, 2-fold, and 4-fold higher doses of 7vPnC or 9vPnC compared to a standard dose of PPSV23 conducted in adults ≥70 years of age with no history of pneumococcal vaccination, local reactions occurred at higher frequencies for the 4-fold higher dose level than with any other dose of 7vPnC, 9vPnC, or PPSV23.[7] However, at the 2-fold higher dose, local reactions were not statistically significantly higher than the standard dose and there were no significant differences between groups for systemic events.[7] [redacted] this study gives dose-ranging safety information for serotypes with $CRM_{197}$. In a study by Jackson et al, older adults previously vaccinated with PPSV23 were given either a single dose of 13vPnC or 2 concurrent doses of 13vPnC. The response to a double dose of 13vPnC in previously vaccinated adults was higher than that of a single dose for a majority of the 13vPnC serotypes that were evaluated, [redacted]. While double dose of 13vPnC was associated with a higher frequency of solicited local and systemic AEs than the single dose among those previously vaccinated with PPSV23, the AEs tended to be mild or moderate and were self-limited.[8]

[redacted]

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

Additional potential risks of clinical significance are presented in the table in Section 2.3.1.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of the [redacted] candidates may be found in the IB, which is the SRSD, for this study. For 13vPnC and PCV15, the SRSD will be the individual USPI respectively.

### 2.3.1. Risk Assessment

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Study Intervention(s): Administration with [redacted]** | | |
| The safety profile of the [redacted] candidates [redacted] is not yet fully characterized. Local and systemic reactions to the [redacted] candidates may occur (injection site redness, injection site swelling, and injection site pain; fever, fatigue, headache, muscle pain, and joint pain) following study intervention. | [redacted] | • Eligibility criteria have been selected to ensure that only appropriate participants are included in the study (see Section 5).<br>• All study participants will be observed for 30 minutes after study intervention administration.<br>• E-diary and AE data will be monitored by the investigator (or designee) and sponsor. |
| **Study Intervention: Administration with [redacted]** | | |
| The relevant key risks associated with [redacted] include: local reactions (injection site pain, redness, and swelling) and systemic events (fever, headache, fatigue, joint pain, and muscle pain). Uncommon events can include allergic reactions, which may be associated with skin rash, face or lip swelling, wheezing, shortness of breath, or rare severe allergic reactions (eg, anaphylactic shock). | The risks are derived from the related 13vPnC clinical trials and postmarketing data and the 13vPnC USPI. | • Eligibility criteria have been selected to ensure that only appropriate participants are included in the study (see Section 5).<br>• All study participants will be observed for 30 minutes after study intervention administration.<br>• E-diary and AE data will be monitored by the investigator (or designee) and sponsor. |
| **Study Intervention: Vaccination with 13vPnC** | | |
| The relevant key risks associated with 13vPnC include: local reactions (injection site pain, redness, and swelling) and systemic events (fever, headache, fatigue, joint pain, and muscle pain). Uncommon events can include allergic reactions, which may be associated with skin rash, face or lip swelling, wheezing, shortness of breath, or rare severe allergic reactions (eg, anaphylactic shock). | The risks are derived from the related 13vPnC clinical trials and postmarketing data and the clinical data described in the 13vPnC USPI. | • Eligibility criteria have been selected to ensure that only appropriate participants are included in the study (see Section 5).<br>• All study participants will be observed for 30 minutes after vaccination.<br>• E-diary and AE data will be monitored by the investigator (or designee) and sponsor. |

| | | |
|---|---|---|
| **Study Intervention: Vaccination with PCV15** | | |
| The relevant key risks associated with PCV15 include: local reactions (injection site pain, redness, and swelling) and systemic events (fever, headache, fatigue, joint pain, and muscle pain). | The risks are derived from the USPI for Vaxneuvance under the Prescribing Information section. | • Eligibility criteria have been selected to ensure that only appropriate participants are included in the study (see Section 5).<br>• All study participants will be observed for 30 minutes after vaccination.<br>• E-diary and AE data will be monitored by the investigator (or designee) and sponsor. |
| **Study Procedures: Venipuncture** | | |
| Venipuncture is required to collect immunogenicity data from participants. | There is the risk of fainting, and pain, swelling, bruising, and infection at the venipuncture site. | • Only qualified nurses, physicians, nurse practitioners, physician assistants, phlebotomists, or medical assistants certified or otherwise authorized to draw blood per the standards and procedures of the investigative site, as allowed by institutional, local, and country guidance, will be allowed to draw blood, to minimize local complications. |
| **Other** | | |
| Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic. | Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2. | • Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. |

### 2.3.2. Benefit Assessment

Joining this study will be contributing to research to help others. [redacted] A safe and immunogenic pneumococcal conjugate vaccine with expanded pneumococcal serotype coverage would fulfill an unmet need for expanded protection against pneumococcal disease.

### 2.3.3. Overall Benefit/Risk Conclusion

Participants enrolled in this study are in an age group that is not currently covered by the indication for vaccines containing [redacted]. These participants are relatively healthy and therefore are not recommended for pneumococcal conjugate vaccines. Receiving the [redacted] candidates or controls will not interfere with standard of care for these participants. For those with risk factors for pneumococcal vaccination, the investigator site and ICD will inform participants to seek advice from their healthcare provider regarding the need for immunization after the study.

The study will provide the immune impact of [redacted] that could potentially benefit adults and children.

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with [redacted] candidates are justified by the anticipated benefits that may be afforded to healthy participants and those at high risk of pneumococcal disease.

## 3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

| Objectives | Endpoints | Estimands |
|---|---|---|
| **Primary:** | **Primary:** | **Primary:** |
| To describe the safety profile of [redacted] candidates in adults 18 through 49 years of age | • Prompted local reactions (redness, swelling, and pain at the injection site)<br>• Prompted systemic events (fever, headache, fatigue, muscle pain, and joint pain)<br>• AEs<br>• SAEs | In participants receiving the study intervention from each group, the percentage of participants reporting:<br>• Prompted local reactions within 7 days after administration<br>• Prompted systemic events within 7 days after administration<br>• AEs within 1 month after administration<br>• SAEs within 1 month after administration |

| Objectives | Endpoints | Estimands |
|---|---|---|
| **Secondary:** | **Secondary:** | **Secondary:** |
| To describe the immune responses elicited by the [redacted] candidates | • OPA titers [redacted] | In participants complying with the key protocol criteria (evaluable participants) from each group:<br>• [redacted] OPA GMTs 1 month after administration |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | | |

## 4. STUDY DESIGN

### 4.1. Overall Design

This is a Phase 1, multicenter, randomized, open-label, active-control study designed to evaluate the safety and immunogenicity of different [redacted] candidates [redacted] This study will be conducted at investigator sites in the US. Approximately 405 adults 18 through 49 years of age with no history of pneumococcal vaccination will be enrolled. Participants will be enrolled and randomized equally to 1 of 9 groups (45 participants per group): 6 groups will receive 1 of 6 different [redacted] candidates and 3 groups will receive [redacted], 13vPnC, or PCV15 (see Table 1) by site-based randomization [redacted].

[redacted]

The following preformulated products have been manufactured and will comprise the following [redacted] candidates:

All formulations include $AlPO_4$.

The key control group will receive polysaccharide conjugate for [redacted] as contained in 13vPnC (Prevnar 13) and 20vPnC (Prevnar 20). In addition, PCV15 (Vaxneuvance [Merck]), which is also licensed in the US for use in adults, and 13vPnC will be included as controls.

**Table 1. Study Intervention Groups**

| Group | Carrier Protein | Chemistry | Polysaccharide Dose | Dose Volume | n |
|---|---|---|---|---|---|
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 45 |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 45 |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] L | 45 |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 45 |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 45 |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 45 |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 45 |

**Table 1. Study Intervention Groups**

| Group | Carrier Protein | Chemistry | Polysaccharide Dose | Dose Volume | n |
|---|---|---|---|---|---|
| PCV15 (control) | N/A | N/A | [redacted] | 0.5 mL | 45 |
| 13vPnC (control) | $CRM_{197}$ | RAC | [redacted] | 0.5 mL | 45 |

Abbreviations: N/A = not applicable; [redacted].

On Day 1 (Visit 1), participants will be assessed for eligibility, have blood drawn for immunogenicity assessments, receive 1 dose of 1 of the [redacted] candidates or controls, be observed for 30 minutes after administration, and receive safety follow-up and e-diary instructions.

Local reactions (pain, redness, and swelling) occurring at the injection site and systemic events (fever, fatigue, headache, muscle pain, and joint pain) will be prompted for and collected daily in an e-diary from Day 1 through Day 7 after study intervention administration, where Day 1 is the day of administration. AEs (including nonserious AEs and SAEs) will be assessed for approximately 1 month after study intervention administration (through Visit 2).

At Visit 2 (28-42 days after Visit 1), participants will return for follow-up. Information will be collected from the participants on AEs and e-diary follow-up (as needed), and blood will be drawn for immunogenicity assessments.

[redacted].

The study duration is estimated to be approximately 2 months.

### 4.2. Scientific Rationale for Study Design

Pfizer is investigating [redacted]

[redacted] Clinical dosage is [redacted]

managed by volume administered (0.5 or 0.25 mL). [redacted]

[redacted]

The primary control study intervention for the study, [redacted]

The inclusion of 13vPnC as a control will be informative about differences between the responses to the current formulation [redacted]

The inclusion of PCV15 will be informative about the response to the [redacted] in PCV15, as determined by the Pfizer assays. PCV15 contains capsular polysaccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F individually conjugated to $CRM_{197}$. The vaccine formulation contains 2.0 µg of each saccharide, except for 4.0 µg of 6B, per 0.5-mL dose.

In adults, administration of a single dose of pneumococcal conjugate vaccine induces immune responses, so the candidates in this study will be evaluated after a single dose. [redacted]

### 4.2.1. Diversity of Study Population

This study will be conducted in the US and the diversity strategy will include high performing sites with the potential to support the recruitment of diverse populations. The diversity strategy for this study will include the following:

- Selecting sites that have access to diverse participants within their locale.
- Educating sites about the importance of increasing diversity on clinical trials and Pfizer commitment.

- Investigator site recruitment plans that are cocreated with and include diverse recruitment tools and information to support enrollment.
- Real-world data is used to target outreach and potential referring physicians.
- Continual monitoring of diverse enrollment to identify additional opportunities to include diverse populations.

### 4.2.2. Choice of Contraception/Barrier Requirements

Human reproductive safety data are not available for the candidate formulations, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

## 4.3. Justification for Dose

[redacted] The polysaccharide conjugates and $CRM_{197}$ have been tested at up to 4 times the standard dose in adults and up to 2 times the standard dose in infants. In dose-ranging studies with investigational vaccines and with 13vPnC, immune responses were at times higher, but not consistently, leaving dose-response to remain in question. The safety profile was acceptable even at the highest doses in these studies.[7,8,9]

[redacted].

[redacted] No significant adverse effects were seen with animal data in rats at the highest dose range.

## 4.4. End of Study Definition

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

A participant is considered to have completed the study if they have completed all periods of the study, including the last visit.

# 5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a

prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

### 5.1. Inclusion Criteria

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

**Age and Sex:**

1. Male or female participants ≥18 and ≤49 years of age at the time of consent.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

**Disease Characteristics:**

2. Participants who are willing and able to comply with all scheduled visits, the investigational plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Adults determined by clinical assessment, including medical history and clinical judgment, to be eligible for the study, including adults with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease, within 12 weeks before receipt of study intervention.

4. Participants who can be expected to be available for the duration of the study and can be contacted by telephone during study participation.

5. Female participants of childbearing potential or male participants who are able to father children and are willing to use acceptable methods of contraception for at least 28 days after the dose of study intervention; or female participants not of childbearing potential; or male participants not able to father children.

    Note: Female participants of nonchildbearing potential must meet the criteria described in the WOCBP (Section 10.4.3) section of the protocol.

**Other Inclusion Criteria:**

6. Participants capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

## 5.2. Exclusion Criteria

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

**Medical Conditions:**

1. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component in pneumococcal conjugate vaccines and any other diphtheria toxoid–containing vaccine.

2. Serious chronic disorder, including metastatic malignancy, severe COPD requiring supplemental oxygen, end-stage renal disease with or without dialysis, cirrhosis of the liver, clinically unstable cardiac disease, or any other disorder that in the investigator's opinion would make the participant inappropriate for entry into the study.

3. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

4. History of microbiologically proven invasive disease caused by *S pneumoniae*.

5. Known or suspected immunodeficiency or other conditions associated with immunosuppression, including, but not limited to, immunoglobulin class/subclass deficiencies, generalized malignancy, HIV infection, leukemia, lymphoma, or organ or bone marrow transplant.

6. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

7. Congenital, functional, or surgical asplenia.

8. Current febrile illness (body temperature ≥100.4°F [≥38.0°C]) or other acute illness within 48 hours before study intervention administration.

9. Pregnant female participants or breastfeeding female participants (known or suspected).

**Prior/Concomitant Therapy:**

10. Previous vaccination with any licensed or investigational pneumococcal vaccine, or planned receipt of any licensed or investigational pneumococcal vaccine through study participation.

11. Currently receives treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, or planned receipt through the last blood draw

(Visit 2). Participants may not be enrolled if corticosteroids were administered within 28 days of study intervention administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, or ears) corticosteroids are permitted.

12. Receipt of blood/plasma products or immunoglobulin within the 60 days before study intervention administration, or planned receipt during study participation.

13. Receipt of any inactivated or otherwise nonlive vaccine within 14 days or any live vaccine within 28 days before administration of study intervention.

**Prior/Concurrent Clinical Study Experience:**

14. Participation in other studies involving investigational drugs, investigational vaccines (except for investigational pandemic vaccines recommended and authorized in this population for emergency use), or investigational devices within 28 days prior to study entry and/or during study participation. Participation in purely observational studies is acceptable.

**Diagnostic Assessments:**

Not applicable.

**Other Exclusion Criteria:**

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

### 5.3. Lifestyle Considerations

#### 5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use acceptable effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence

as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

### 5.4. Screen Failures

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

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

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

Not applicable.

## 6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and noninvestigational medicinal products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to investigational products [redacted] and noninvestigational products (13vPnC and PCV15).

Study interventions will be provided as 4 preformulated products in vials and 2 products in PFSs, as outlined below:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- 13vPnC (Prevnar 13) (PFS)
- PCV15 (Vaxneuvance) (PFS)

The study interventions [redacted] will be prepared by adjusting the volume extracted from the preformulated products in vials to a dose of either 0.25 mL or 0.5 mL. The study intervention [redacted] will be prepared by adjusting the volume extracted from the preformulated product in the vial to a dose of 0.5 mL. The PFSs will be administered as 0.5-mL doses for 13vPnC and PCV15.

## 6.1. Study Intervention(s) Administered

| Study Intervention(s) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Intervention name** | [redacted] | | | | | | | 13vPnC (Prevnar 13) 0.5-mL suspension for injection | PCV15 (Vaxneuvance) (pneumococcal 15-valent conjugate vaccine) suspension for injection |
| **Arm name (group of participants receiving a specific intervention or no intervention)** | [redacted] group, n=45 | [redacted] group, n=45 | [redacted] group, n= 45 | [redacted] group, n=45 | [redacted] group, n=45 | [redacted] group, n=45 | [redacted] monovalent control group, n=45 | 13vPnC control group, n=45 | PCV15 control group, n=45 |
| **Dosage level(s)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 2.2 µg for all serotypes except 6B; 4.4 µg for serotype 6B per 0.5-mL dose | 2.0 µg for all serotypes except 6B; 4.0 µg for serotype 6B per 0.5-mL dose |
| **Dose volume** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 0.5 mL | 0.5 mL |
| **Type** | Biologic | Biologic | Biologic | Biologic | Biologic | Biologic | Biologic | Biologic | Biologic |

| Study Intervention(s) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Dose formulation** | Suspension for injection in a single-use vial | Suspension for injection in a single-use vial | Suspension for injection in a single-use vial | Suspension for injection in a single-use vial | Suspension for injection in a single-use vial | Suspension for injection in a single-use vial | Suspension for injection in a single-use vial | Sterile liquid suspension formulation in a PFS containing saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to $CRM_{197}$ | Sterile liquid suspension formulation in a PFS containing saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F individually conjugated to $CRM_{197}$ |
| **Route of administration** | Intramuscular injection | Intramuscular injection | Intramuscular injection | Intramuscular injection | Intramuscular injection | Intramuscular injection | Intramuscular injection | Intramuscular injection | Intramuscular injection |
| **Use** | Experimental | Experimental | Experimental | Experimental | Experimental | Experimental | Control | Control | Control |
| **IMP or NIMP/AxMP** | IMP | IMP | IMP | IMP | IMP | IMP | IMP | NIMP | NIMP |
| **Sourcing** | Provided centrally by the sponsor | Provided centrally by the sponsor | Provided centrally by the sponsor | Provided centrally by the sponsor | Provided centrally by the sponsor | Provided centrally by the sponsor | Provided centrally by the sponsor | Provided centrally by the sponsor | Provided centrally by the sponsor |
| **Packaging and labeling** | Study intervention will be provided in vials. Each vial will be labeled as required per country requirement. | Study intervention will be provided in vials. Each vial will be labeled as required per country requirement. | Study intervention will be provided in vials. Each vial will be labeled as required per country requirement. | Study intervention will be provided in vials. Each vial will be labeled as required per country requirement. | Study intervention will be provided in vials. Each vial will be labeled as required per country requirement. | Study intervention will be provided in vials. Each vial will be labeled as required per country requirement. | Study intervention will be provided in vials. Each vial will be labeled as required per country requirement. | Study intervention will be provided in a PFS. Each PFS will be labeled as required per country requirement. | Study intervention will be provided in a PFS. Each PFS will be labeled as required per country requirement. |

Study intervention will be supplied by Pfizer as PFSs or vials as open-label supply. Each vial will be packaged in a carton, with a label and tamper-evident seal, and will be labeled as required per country requirement. Each syringe will be packaged in a commercial carton and will be labeled as required per country requirement. Refer to the IPM for additional details.

### 6.1.1. Administration

All participants will be administered 1 of the [redacted] candidates [redacted] or a control [redacted] PCV15, or 13vPnC).

Study intervention will be provided by the sponsor to the study sites. A 0.25-mL or 0.5-mL dose of 1 of the preformulated products or a 0.5-mL dose of 1 of the controls will be administered intramuscularly in the deltoid muscle of the nondominant arm by a site staff member or designee. The description of the [redacted] candidates and controls can be found in the IPM.

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

Study intervention administration details will be recorded on the CRF.

### 6.1.2. Medical Devices

1. In this study, medical devices being deployed are the PFSs containing 13vPnC and PCV15.

2. Instructions for medical device use are provided in the IPM or in the package insert.

3. All medical device deficiencies (including malfunctions of the device, use error and inadequate labelling) must be detected, documented, and reported by the study personnel throughout the study. Please refer to Section 8.4.9 for details.

## 6.2. Preparation, Handling, Storage, and Accountability

The investigator or an approved representative, eg, pharmacist, will ensure that all study interventions are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Study interventions should be stored in their original containers and in accordance with the labels.

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

3. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to labeled storage conditions, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the IPM.

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

6. Study interventions should be stored in their original containers.

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IPM. All destruction must be adequately documented. 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.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IPM.

### 6.2.1. Preparation and Dispensing

See the IPM for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the preparation and dispensing.

The study intervention will be prepared by qualified site personnel according to the IPM.

## 6.3. Assignment to Study Intervention

Allocation (randomization) of participants to intervention groups will proceed through the use of an IRT system (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 ID and password, the protocol number, and the participant number.

The site personnel will then be provided with a randomization number corresponding to the assigned intervention group, and DU or container number(s) when study intervention and proper dose is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

The site will record the study intervention assignment on the applicable CRF, if required.

Study intervention will be dispensed at the study visits summarized in the SoA.

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

This is an open-label study. The investigator's knowledge of the intervention assignment must not influence the decision to enroll a particular participant or affect the order in which participants are enrolled. Potential bias will be reduced by the following steps: central IRT system for randomization

## 6.4. Blinding

This is an open-label study.

### 6.4.1. Blinding of Participants

Participants will be unblinded to their assigned study intervention.

### 6.4.2. Blinding of Site Personnel

Investigators and other site staff will be unblinded to participants' assigned study intervention.

### 6.4.3. Blinding of the Sponsor

Sponsor staff will be unblinded to participants' assigned study intervention. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study.

## 6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

The site will complete the required dosage preparation record located in the IPM. The use of the preparation record is required. The use of alternative preparation records must be approved by the Sponsor's clinical research pharmacist prior to its use.

## 6.6. Dose Modification

Not applicable.

## 6.7. Continued Access to Study Intervention After the End of the Study

This exploratory study is describing the tolerability and immunogenicity of 6 [redacted] candidates. There will be no further intervention provided to participants at the end of their study participation. It is expected that participants will be treated as required with standard-of-care treatments, as advised by their usual care physician.

## 6.8. Treatment of Overdose

For this study, any dose of study intervention greater than 0.5 mL of study intervention within a 24-hour time period will be considered an overdose. If the participant assigned to 0.25 mL has inadvertently been administered a 0.5-mL dose, this will not be considered an overdose but will be a dosing error and a protocol deviation requiring communication to the sponsor (Section 8.4.10).

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs as medically appropriate and at least until the next scheduled follow-up.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**

### 6.9. Prior and Concomitant Therapy

The name and date of administration for all nonstudy vaccinations received from the time of signing of the ICD to Visit 2 will be collected and recorded in the CRF.

Medications taken to treat SAEs from the time of signing of the ICD through Visit 2 will be recorded in the CRF.

#### 6.9.1. Prohibited During the Study

- Receipt of any investigational vaccines, drugs, or medical devices is prohibited during study participation.
- Receipt of nonstudy pneumococcal vaccine is prohibited during study participation.
- Receipt of any other licensed nonstudy vaccine is prohibited during study participation, except as noted in Section 6.9.2.
- Receipt of blood/plasma products, immunoglobulins, and/or immunosuppressive therapy (including a ≥14-day course of systemic corticosteroids) is prohibited during study participation.

#### 6.9.2. Permitted During the Study

- Prescription and nonprescription medications, vitamins, minerals, and herbal remedies are permitted during participation in the study.
- Inhaled/nebulized, topical (eg, skin, eyes, ears), or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted during study participation.
- Licensed inactivated influenza vaccine may be given >14 days after study intervention administration (Visit 1).
- If medically necessary (eg, during a pandemic), a COVID-19 vaccine, or tetanus vaccine required following wound care, may be given during the study, with preference for >7 days after study intervention administration (Visit 1), if feasible.

## 7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

### 7.1. Discontinuation of Study Intervention

Since this is a single-dose study, this section is not applicable.

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

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study include the following:

- Refused further study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AE;
- Physician decision;
- Pregnancy;
- Protocol deviation;
- Screen failure;
- Participant request;
- Vaccination error without associated AE;
- No longer meets eligibility criteria;
- Other.

If a participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

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

#### 7.2.1. Withdrawal of Consent

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

whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

### 7.3. Lost to Follow-Up

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

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

## 8. STUDY ASSESSMENTS AND PROCEDURES

### 8.1. Administrative Procedures

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

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

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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

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

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

### 8.2. Efficacy and/or Immunogenicity Assessments

Blood will be collected before study intervention administration (Visit 1) and approximately 1 month after administration (Visit 2) to assess immunogenicity.

Approximately 135 participants (approximately n=15/group) will be enrolled at specific investigator sites, [redacted] and approximately 20 mL of blood will be collected for sera measurements of immunogenicity (OPA titers and IgG concentrations) at each time point (Visit 1 and Visit 2). The remaining approximately 270 participants enrolled at other sites (approximately n=30/group) will have approximately 60 mL of blood collected for measurement of immunogenicity (OPA titers and IgG concentrations) at each time point (Visit 1 and Visit 2).

[redacted]

**Immune Responses**

OPA titers and IgG concentrations [redacted] will be measured in sera collected at Visits 1 and 2.

[redacted]

[redacted]

### 8.2.1. Biological Samples

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

No testing of the participant's genetic material will be performed, [redacted]

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

## 8.3. Safety Assessments

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

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

Prompted e-diary events, including local reactions (redness, swelling, and pain at the injection site) and systemic events (fever, headache, fatigue, muscle pain, and joint pain) that occur from Days 1 through 7, where Day 1 is the day of study intervention administration, are graded as noted in Table 2 and Table 3. AEs and SAEs will be collected from the signing of the ICD through Visit 2.

Planned time points for all safety assessments are provided in the SoA. Unscheduled safety measurements may be obtained at any time during the study to assess any perceived safety issues.

### 8.3.1. Participant Electronic Diary

Participants will be asked to monitor and record local reactions and systemic events after vaccination (Day 1 through Day 7, where Day 1 is the day of study intervention administration) using an e-diary through an application installed on a provisioned device or on the participant's own personal device. This allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience. Data reported in the e-diary will be transferred electronically to the e-diary vendor, where they will be available for review by investigators, their appropriately qualified designees, and sponsor staff at all times via an internet-based portal. At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically to Pfizer for analysis and reporting.

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

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

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

### 8.3.2. Grading Scale for Prompted Events

The grading scales used in this study to assess prompted events as described below are based on concepts outlined in the FDA CBER guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[26]

#### 8.3.2.1. Local Reactions

From Day 1 through Day 7 following study intervention administration at Visit 1, where Day 1 is the day of study intervention administration, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the e-diary in the evening. Redness and swelling will be measured and recorded in measuring device (caliper) units (range: 1 to 21+) and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 2. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. Pain at the study intervention injection site will be assessed by the participant as mild, moderate, or severe according to the grading scale in Table 2. The participant will be prompted to contact the investigator if he/she experiences a severe (Grade 3 or above) local reaction to assess the reaction and perform an unscheduled assessment or visit as appropriate. Only an investigator is able to classify a participant's local reaction as Grade 4, after physical examination of the participant or documentation from another medically qualified source (eg, emergency room

or hospital record). If a participant experiences a Grade 4 local reaction, the investigator must immediately notify the sponsor. Site staff will educate the participants regarding signs and symptoms that would prompt site contact. Grade 4 reactions will be collected as AEs on the CRF. The event will be graded using the AE intensity grading scale (Section 10.3.3).

The procedure for notification of the sponsor is provided in the investigator site file or equivalent.

**Table 2. Grading Scales for Local Reactions**

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

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

a. Participants experiencing Grade 3 local reactions are required to contact the investigator site. In the event that the participant does not call, the investigator will call the participant.
b. Grade 4 assessment should be made by the investigator; Grade 4 local reactions will not be collected in the e-diary but will be collected as AEs on the CRF. The intensity of the local reaction should be graded using the AE intensity grading scale in Section 10.3.3.
c. Prevents daily activity, eg, results in missed days of school or work or is otherwise incapacitating.

### 8.3.2.2. Systemic Events

From Day 1 through Day 7 following study intervention administration at Visit 1, where Day 1 is the day of study intervention administration, participants will be asked to assess headache, fatigue, muscle pain, and joint pain and to record the symptoms in the e-diary in the evening. The symptoms will be assessed by the participant as mild, moderate, or severe according to the grading scale in Table 3 below. Participants will also be instructed to contact site staff or the investigator if they experience any severe (Grade 3 or above) prompted systemic event within 7 days after administration. Study staff may also contact the participant to obtain additional information on Grade 3 events entered into the e-diary.

Only an investigator is able to classify a participant's systemic event as Grade 4, after physical examination of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant. If a participant experiences a Grade 4 systemic event, the investigator must immediately notify the sponsor. Grade 4 events will be collected as an AE on the CRF. The event will be graded using the AE intensity grading scale (See Section 10.3.3).

The procedure for notification of the sponsor is provided in the investigator site file or equivalent.

**Table 3. Grading Scales for Systemic Events**

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

a. Prevents daily routine activity, eg, results in missed days of school or work or is otherwise incapacitating; includes use of narcotics for analgesia.
b. Grade 4 assessment should be made by the investigator; Grade 4 systemic events will not be collected in the e-diary but will be collected as AEs on the CRF. The intensity of the systemic event should be graded using the AE intensity grading scale in Section 10.3.3.

#### 8.3.2.2.1. Fever

In order to record information on fever, a digital thermometer will be given to the participant with instructions on how to measure oral temperature at home. Temperature will be collected in the evening daily for 7 days following each study intervention administration (Days 1 through 7, where Day 1 is the day of study intervention administration) and at any time during the 7 days that fever is suspected. The highest temperature for each day will be recorded in the e-diary. In the event of a fever on Day 7, temperature will be collected daily until the fever has resolved (1 day of temperature <100.4°F [<38.0°C]) in order to collect a

stop date in the CRF. Participants reporting a fever >102.0°F (>38.9°C) will be prompted to contact the study site. Study staff may also contact the participant to obtain additional information if a temperature of >102.0°F (>38.9°C) is entered into an e-diary. Temperature will be measured and recorded to 1 decimal place.

Temperatures obtained in degrees Fahrenheit will be programmatically converted to degrees Celsius for reporting. Fever will be grouped into ranges for the analysis according to Table 4.

**Table 4. Ranges for Fever**

| |
|---|
| ≥38.0°C to 38.4°C |
| >38.4°C to 38.9°C |
| >38.9°C to 40.0°C[a] |
| >40.0°C[a] |

Note: Fever is defined as a temperature of ≥38.0°C.

a. Participants reporting a fever >102.0°F (>38.9°C) will be prompted to contact the study site.

### 8.3.3. Physical Examinations

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

### 8.3.4. Vital Signs

The participant's oral temperature will be measured prior to study intervention administration.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

### 8.3.5. Clinical Safety Laboratory Assessments

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

### 8.3.6. Pregnancy Testing

Following screening, pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention and from the study.

## 8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in Appendix 3.

The definitions of device-related safety events (ADEs and SADEs) ca.n be found in Appendix 8. Device deficiencies are covered in Section 8.4.9.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

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

During the active collection period as described in Section 8.4.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

### 8.4.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each participant begins from the time the participant provides informed consent, which is obtained before the participant’s participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 2.

Follow-up by the investigator continues throughout the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

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

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

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

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

#### 8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the Vaccine SAE Reporting Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

#### 8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded on the AE section of the CRF.

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

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.

### 8.4.2. Method of Detecting AEs and SAEs

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

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

### 8.4.3. Follow-Up of AEs and SAEs

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

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

Further information on follow-up procedures is provided in Appendix 3.

### 8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

### 8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

#### 8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.

- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:

    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by injection, inhalation, or skin contact.

    - A male family member or healthcare provider who has been exposed to the study intervention by injection, inhalation, or skin contact then inseminates his female partner prior to or around the time of conception.

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

- If EDP occurs in a participant or participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Reporting Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until Visit 2.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting Form is maintained in the investigator site file.

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

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly 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 including miscarriage and missed abortion should be reported as an SAE;

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

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

#### 8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

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

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

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

#### 8.4.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the Vaccine SAE Reporting Form, regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a

CRF; however, a copy of the completed Vaccine SAE Reporting Form must be maintained in the investigator site file.

### 8.4.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

### 8.4.8. Adverse Events of Special Interest

Not applicable.

#### 8.4.8.1. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

### 8.4.9. Medical Device Deficiencies

Medical devices being provided for use in this study are those listed in Section 6.1.2. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 8.

Note: AEs and/or SAEs that are associated with a medical device deficiency will follow the same processes as other AEs or SAEs, as outlined in Sections 8.4.1 through 8.4.4 and Appendix 3 of the protocol.

#### 8.4.9.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

Importantly, reportable device deficiencies are not limited to problems with the device itself but also include incorrect or improper use of the device and even intentional misuse, etc.

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

The method of documenting medical device deficiencies is provided in Appendix 8.

#### 8.4.9.2. Follow-Up of Medical Device Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention.

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

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

#### 8.4.9.3. Prompt Reporting of Device Deficiencies to the Sponsor

When a device deficiency occurs:

1. The investigator notifies the sponsor by telephone or email within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency.

2. The device deficiency must be recorded on the Medical Device Complaint form.

3. If an AE (either serious or nonserious) associated with the device deficiency occurs, then the AE must be entered into the AE section of the CRF.

4. If an SAE associated with the device deficiency is brought to the attention of the investigator, the investigator must immediately notify Pfizer Safety of the SAE (see Section 8.4.1.1). All relevant details related to the role of the device in the event must be included in the Vaccine SAE Reporting Form as outlined in Sections 8.4.1.1 and 8.4.1.2.

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

#### 8.4.9.4. Regulatory Reporting Requirements for Device Deficiencies

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

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

### 8.4.10. Vaccination Errors

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

Vaccination errors are recorded and reported as follows:

| Recorded on the Vaccination Error Page of the CRF | Recorded on the Adverse Event Page of the CRF | Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness |
|---|---|---|
| All (regardless of whether associated with an AE) | Any AE or SAE associated with the vaccination error | Only if associated with an SAE |

Vaccination errors include:

- Vaccination errors involving participant exposure to the study intervention;
- Potential vaccination errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Other examples include, but are not limited to:

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

Such vaccination 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.

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

In the event of a vaccination dosing error, the sponsor should be notified within 24 hours.

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

### 8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

## 8.6. Genetics

### 8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study. [redacted]

See Section 10.5 for information regarding genetic research. Details on processes for collection and shipment of these samples will be provided separately.

### 8.6.2. Retained Research Samples for Genetics

Not applicable.

## 8.7. Biomarkers

Biomarkers are not evaluated in this study.

## 8.8. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.2.

## 8.9. Health Economics

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

## 8.10. Study Procedures

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

The timing of visit procedures (ie, prior to randomization and after randomization) must be maintained; however, there is flexibility in the order in which the procedures can be conducted at each visit. The ICD must be signed prior to the start of any study procedure.

### 8.10.1. Visit 1 – Study Intervention Administration – Day 1

Prior to randomization:

- Obtain a personally signed and dated ICD indicating that the participant has been informed of all pertinent aspects of the study before performing any study-specific procedures.
- Assign a participant number via the IRT.

- Obtain and record the participant's demographic information (including date of birth, sex, race, and ethnicity). The complete date of birth (ie, DD-MMM-YYYY) will be collected to critically evaluate the immune response and safety profile by age.

- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if significant, record such findings on the medical history CRF.

- Measure and record the participant's oral temperature (°F/°C)

- Record nonstudy vaccinations given up to 28 days prior to study intervention administration, in source documents, if applicable (see Section 6.9).

- If applicable, instruct the participant to use appropriate contraceptives until 28 days after administration of the last dose of study intervention and document the conversation and the participant's affirmation in the participant's source document (see Section 10.4).

- Perform urine pregnancy test for female participants of childbearing potential (see Section 8.3.6).

- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.

- Assign a randomization number and a study intervention container number via the IRT. This must be the last step before proceeding. A site staff member will prepare the study intervention according to the IPM.

After randomization:

[redacted]

- Collect approximately 60 mL of blood prior to study intervention administration.

- Administer a single 0.25-mL or 0.5-mL injection of the assigned study intervention into the deltoid muscle of the preferably nondominant arm (see Section 6.1).

After study intervention administration:

- Site staff will observe the participant for 30 minutes after administration of study intervention for any reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on the Vaccine SAE Reporting Form, as applicable. Record concomitant medications used to treat SAEs.
- Record concomitant medications used to treat SAEs, if applicable.
- Record AEs and SAEs as described in Section 8.4.
- Explain the e-diary technologies available for this study (Section 8.3.1) and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device, if required. Provide instructions on the e-diary's use and completion and ask the participant to complete the e-diary from Day 1 through Day 7, with Day 1 being the day of study intervention administration.
- Issue the participant a measuring device to measure injection site reactions and a digital thermometer and provide instructions on their use.
- Ask the participant to contact the investigator site staff or investigator as soon as possible during the 7-day postadministration period if the participant has redness and/or swelling at the injection site measuring >20 measuring device units (>10 cm) or severe injection site pain (prevents daily activity) to determine if an unscheduled visit is required (refer to Section 8.10.3).
- Ask the participant to contact the investigator site staff or investigator as soon as possible if he or she experiences a fever ≥104°F (≥40.0°C) or any severe systemic event from Day 1 through Day 7 after study intervention administration (where Day 1 is the day of administration) to determine if an unscheduled visit is required (see Section 8.10.3).
- Ask the participant to contact the site staff or investigator immediately if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs.
- Provide the participant with the participant contact card containing the study and investigator information (see Section 10.1.11).
- Remind the participant to use appropriate contraceptives until 28 days after study intervention administration, if applicable.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- The investigator or an authorized designee completes the CRF and the source documents and updates the study intervention accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online at frequent intervals (daily is optimal) for the 7 days (Day 1 is the day of study intervention administration) following administration to evaluate participant compliance and as part of the ongoing safety review.

### 8.10.2. Visit 2 – Follow-Up After Study Intervention Administration – 28 to 42 Days After Study Intervention Administration

- Ensure and document that the participant continues to be eligible for the study (see Section 7 for participant discontinuation/withdrawal).
- Record nonstudy vaccinations, if applicable, as described in Section 6.9.
- Discuss contraceptive use since Visit 1 (see Section 10.4), if applicable, and record any contraceptive use in the source documents.
- Review the participant's e-diary data. Collect stop dates of any e-diary events (local reactions or systemic events) ongoing on the last day that the e-diary was completed and record stop dates in the CRF.
- Collect the participant's e-diary or assist the participant in removing the study application from his or her own personal device.
- Determine if any AEs (including nonserious AEs and SAEs) have occurred since the previous visit, follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing), record such AEs as described in Section 8.4, and record concomitant medications used to treat SAEs.

[redacted]

- The investigator or an authorized designee completes the CRF and the source documents.

### 8.10.3. Unscheduled Visit for a Grade 3 Systemic Event or Suspected Grade 4 Reaction

If the participant reports redness or swelling at the injection site measuring >20 measuring device units (>10.0 cm) or severe injection site pain (Section 8.3.2.1), a temperature >40°C

during the 7 days following study intervention administration at Visit 1, or a severe systemic event (Section 8.3.2.2) during the 7 days following study intervention administration at Visit 1, a telephone contact must occur as soon as possible between the investigator or medically qualified designee and the participant to assess if an unscheduled investigator site visit is required. A site visit should be scheduled as soon as possible to assess the extent of the injection site reaction unless any of the following is true:

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

This telephone contact will be recorded in the participant's source documentation and the CRF. If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing reactions must be assessed at the next study visit. During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff, such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure oral temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in Section 8.3.2.1.
- Assess systemic events (if present) in accordance with the grades provided in Section 8.3.2.2.
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

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

## 9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in the 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. Statistical Hypothesis

There is no formal statistical hypothesis testing planned for this study.

#### 9.1.1. Estimands

The estimands corresponding to the primary and secondary objectives are described in the table in Section 3. The estimands to evaluate the immunogenicity objectives will be based on the evaluable immunogenicity population (see Section 9.2 for definition). The estimands estimate the study intervention effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing serology results will not be imputed. Immunogenicity results that are below the LLOQ will be set to 0.5 × LLOQ in the analysis.

In the primary safety objective evaluations, missing e-diary data will not be imputed. A partial AE start date (eg, missing day, missing both month and day) will be imputed by assigning the earliest possible start date using all available information (eg, stop date of AE, vaccination date from the same participant) following the Pfizer standards for handling incomplete AE start date. An AE with a completely missing start date is not allowed in the data collection. No other missing information will be imputed in the safety analysis..

### 9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

| Participant Analysis Set | Description |
|---|---|
| Enrolled | All participants who sign the ICD. |
| Randomized | All participants who are assigned a randomization number in the IRT system. |
| Evaluable immunogenicity | All eligible randomized participants who receive the study intervention to which they are randomly assigned, have at least 1 valid immunogenicity result from the blood sample collected within an appropriate window 1 month after administration, and have no other major protocol deviations as determined by the clinician. |
| [redacted] | [redacted] |
| Safety | All participants who receive the study intervention. |

### 9.3. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in Section 9.4. It will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary [redacted]

#### 9.3.1. General Considerations

In general, the study data will be summarized by study intervention groups. CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level.

[redacted] Participants will be summarized according to the study intervention group to which they were randomized. Missing laboratory results will not be imputed.

The safety analyses are based on the safety population. Participants will be summarized according to the study interventions they received.

##### 9.3.1.1. Analyses for Binary Data

Descriptive statistics for categorical variables (eg, proportions) are the percentage (%), the numerator (n) and denominator (N) used in the percentage calculation, and the 2-sided 95% CIs, where applicable.

The exact 95% CI for binary endpoints for each group will be computed using the F distribution (Clopper-Pearson).

##### 9.3.1.2. Analyses for Continuous Data

Unless otherwise stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum.

###### 9.3.1.2.1. Geometric Means

The geometric mean for each group will be calculated as the mean of the logarithmically transformed assay results and then exponentiating the mean. The 2-sided 95% CI will be obtained by exponentiating the CI for the mean of the logarithmically transformed assay results based on Student's t distribution.

[redacted]

[redacted]

### 9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

| Endpoints and Estimands | Statistics |
|---|---|
| • Percentage of participants with local reactions (redness, swelling, and pain at the injection site) within 7 days after study intervention administration in each group<br>• Percentage of participants with systemic events (fever, fatigue, headache, muscle pain, and joint pain) within 7 days after study intervention administration in each group | • Descriptive summary statistics for participants with each local reaction/systemic event within 7 days after study intervention administration, by severity level |
| • Percentage of participants with AEs from study intervention administration through 1 month after administration in each group | • Descriptive summary statistics |
| • Percentage of participants with SAEs from study intervention administration through 1 month after administration in each group | • Descriptive summary statistics |

### 9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

| Endpoints and Estimands | Statistics |
|---|---|
| • [redacted] OPA GMT 1 month after study intervention administration | • GMT and 2-sided 95% CI |

[redacted]

| | |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

[redacted].

### 9.4. Interim Analyses

No interim analysis will be conducted for this study. 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 for supporting clinical development.

#### 9.4.1. Analysis Timing

Statistical analyses will be carried out as specified below:

- An analysis will be conducted when safety data through approximately 1 month after study intervention administration are available.
- Immunogenicity data of OPA and IgG results through Visit 2 (1 month after study intervention administration) may be analyzed, when available, for 1 or more immunogenicity endpoints [redacted].
- A final analysis of safety, including complete OPA and IgG results available after the completion of the study, will be performed. [redacted]

This is an open-label Phase 1 exploratory study. Immunogenicity data reviews by the sponsor may be conducted at any time the data are available to aid in decision-making for the sponsor programs.

Certain analyses may be combined if the data become available around the same time. Additional analyses may be conducted or combined if required for regulatory purposes or for further clinical evaluation of the study intervention.

### 9.5. Sample Size Determination

The sample size of this study is not driven by any formal hypothesis test. It is determined primarily based on the consideration of providing pioneer information on the immune responses induced by the [redacted] candidates and the corresponding safety profiles in order to support a decision for further clinical development.

The primary safety objective includes the endpoints for AEs, local reactions, and systemic events. Table 5 shows the binomial probability of detecting at least 1 AE. The number of participants in each study group is 45, which provides a >90% chance of observing at least 1 event in a group, assuming a true event rate of at least 5%.

**Table 5. Probability of Detecting at Least 1 Adverse Event in a Study Group**

| True Rate of AEs | Probability of Observing at Least 1 AE |
|---|---|
| 2.0% | 59.7% |
| 3.0% | 74.6% |
| 4.0% | 84.1% |
| 5.0% | 90.1% |
| 6.0% | 93.8% |

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

### 10.1.1. Regulatory and Ethical Considerations

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

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

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

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

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

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

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

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

### 10.1.2. Financial Disclosure

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

### 10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

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

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

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

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

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

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

Participants must be reconsented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

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

### 10.1.4. Data Protection

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

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

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

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

### 10.1.5. Committees Structure

#### 10.1.5.1. Data Monitoring Committee

This study will not use an EDMC.

### 10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

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

EudraCT/CTIS

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

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

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

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

### 10.1.7. Data Quality Assurance

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

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

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

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

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

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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

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

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow

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

### 10.1.8. Source Documents

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

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

In this study, the CRF will serve as the source document. A document must be available at the investigative site that identifies those data that will be recorded on the CRF and for which the CRF will be the source document.

Definition of what constitutes source data and its origin can be found in the Source Document Locator, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the data management plan, which is maintained by the sponsor

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

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

### 10.1.9. Study and Site Start and Closure

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

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

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk

assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

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

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

### 10.1.10. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. 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

upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

### 10.1.11. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the supporting study documentation/study portal or other electronic system.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from nonstudy healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number is to be used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the participant directly; if a participant calls that number directly, they will be directed back to the investigator site.

## 10.2. Appendix 2: Clinical Laboratory Tests

Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

Pregnancy test (β-hCG): Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC for participants who are WOCBP.

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

### 10.3.1. Definition of AE

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

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

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

### 10.3.2. Definition of an SAE

| **An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:** |
|---|
| **a. Results in death** |
| **b. Is life-threatening**<br><br>The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe. |
| **c. Requires inpatient hospitalization or prolongation of existing hospitalization**<br><br>In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.<br><br>Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE. |

**d. Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

**e. Is a congenital anomaly/birth defect**

**f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic**

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

**g. Other situations:**

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

### 10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

**AE and SAE Recording/Reporting**

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the Vaccine SAE Reporting Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Reporting Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Reporting Form for reporting of SAE information.

| **Safety Event** | **Recorded on the CRF** | **Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness** |
|---|---|---|
| SAE | All | All |
| Nonserious AE | All | None |
| Exposure to the study intervention under study during pregnancy or breastfeeding | All AEs or SAEs associated with EDP or EDB<br><br>Note: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF | All instances of EDP are reported (whether or not there is an associated SAE)*<br>All instances of EDB are reported (whether or not there is an associated SAE)** |
| Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB) | None. Exposure to a study nonparticipant is not collected on the CRF | The exposure (whether or not there is an associated AE or SAE) must be reported*** |

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the Vaccine SAE Reporting Form.
** **EDB** is reported to Pfizer Safety using the Vaccine SAE Reporting Form, which would also include details of any SAE that might be associated with the EDB.
*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the Vaccine SAE Reporting Form.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Reporting Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

**Assessment of Intensity**

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

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

| GRADE | If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows: | |
|---|---|---|
| 1 | MILD | Does not interfere with participant's usual function. |
| 2 | MODERATE | Interferes to some extent with participant's usual function. |

| | | |
|---|---|---|
| 3 | SEVERE | Interferes significantly with participant's usual function. |

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

**Assessment of Causality**

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

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

### 10.3.4. Reporting of SAEs

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

| SAE Reporting to Pfizer Safety via the Vaccine SAE Reporting Form |
|---|
| • Facsimile transmission of the Vaccine SAE Reporting Form is the preferred method to transmit this information to Pfizer Safety.<br><br>• In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the Vaccine SAE Reporting Form sent by overnight mail or courier service.<br><br>• Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Reporting Form pages within the designated reporting time frames. |

## 10.4. Appendix 4: Contraceptive and Barrier Guidance

### 10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s)

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use contraception/barrier as detailed below:
  - Agree to use a male condom when having sexual intercourse with a WOCBP who is not currently pregnant.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

### 10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of inclusion criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

A female participant is eligible to participate if she is not pregnant or breastfeeding and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).
  - OR
- Is a WOCBP and agrees to use an acceptable contraceptive method during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

### 10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;

    - Documented bilateral salpingectomy;

    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to a medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:

        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

        - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

### 10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.

Sexual Abstinence

8. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated

in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Other Effective Methods

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom, with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

## 10.5. Appendix 5: Genetics

Use/Analysis of DNA

[redacted]

- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA and/or RNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
  - Samples for specified genetic analysis (see Section 8.6.1) will be stored for up to 15 years or other period as per local requirements.
- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

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

### Potential Cases of Drug-Induced Liver Injury

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

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

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili 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 T bili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

- Participants with AST/ALT and T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** T bili 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 T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

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

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or 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, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

## 10.7. Appendix 7: Kidney Safety Monitoring Guidelines

### 10.7.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline serum creatinine (Scr measurement to eGFR [Scr-based eGFR] or [eCrCl]). Baseline and postbaseline Scys makes it feasible to distinguish AKI from other causes of Scr increase. If Scr increase is confirmed after baseline, then reflex measurement of Scys is indicated to estimate the combined Scr-Scys eGFR calculation (for adults only).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

### 10.7.2. Age-Specific Kidney Function Calculation Recommendations

#### 10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations

| 2021 CKD-EPI Scr Only | Scr (mg/dL) | Scys (mg/L) | Recommended eGFR Equation |
|---|---|---|---|
| Female | if ≤0.7 | N/A | $eGFR = 143 \times (Scr/0.7)^{-0.241} \times (0.9938)^{Age}$ |
| Female | if >0.7 | N/A | $eGFR = 143 \times (Scr/0.7)^{-1.200} \times (0.9938)^{Age}$ |
| Male | if ≤0.9 | N/A | $eGFR = 142 \times (Scr/0.9)^{-0.302} \times (0.9938)^{Age}$ |
| Male | if >0.9 | N/A | $eGFR = 142 \times (Scr/0.9)^{-1.200} \times (0.9938)^{Age}$ |
| **2021 CKD-EPI Scr-Scys Combined** | **Scr (mg/dL)** | **Scys (mg/L)** | **Recommended eGFR Equation** |
| Female | if ≤0.7 | if ≤0.8 | $eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$ |
| Female | if ≤0.7 | if >0.8 | $eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$ |
| Female | if >0.7 | if ≤0.8 | $eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$ |
| Female | if >0.7 | if >0.8 | $eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$ |
| Male | if ≤0.9 | if ≤0.8 | $eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$ |
| Male | if ≤0.9 | if >0.8 | $eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$ |
| Male | if >0.9 | if ≤0.8 | $eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$ |
| Male | if >0.9 | if >0.8 | $eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$ |

Note: The table source is Inker LA, et al. N Engl J Med. 2021;385(18):1737-49.

### 10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to KDIGO criteria.

## 10.8. Appendix 8: AEs, ADEs, SAEs, SADEs, USADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting in Medical Device Studies

**Definitions of a Medical Device Deficiency**

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European MDR 2017/745 for clinical device research (if applicable).

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

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1.2 for the list of sponsor medical devices).

### 10.8.1. Definition of AE and ADE

| **AE and ADE Definition** |
|---|
| • An AE is defined in Appendix 3 (Section 10.3.1).<br><br>• An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device. |

### 10.8.2. Definition of SAE, SADE, and USADE

| **SAE Definition** |
|---|
| • An SAE is defined in Appendix 3 (Section 10.3.2). |
| **SADE Definition** |
| • An SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE.<br><br>• Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate. |

| USADE Definition |
| --- |
| • A USADE (also identified as UADE in US Regulations 21 CFR 813.3) is a SADE that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file. |

### 10.8.3. Definition of Device Deficiency

| Device Deficiency Definition |
| --- |
| • A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate information supplied by the manufacturer. |

### 10.8.4. Recording/Reporting and Follow-Up of Medical Device Deficiencies

| Device Deficiency Recording |
| --- |
| • When a device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.<br><br>• The investigator will then record all relevant device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice, and will also capture the required information on the Medical Device Complaint form.<br><br>• It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the Medical Device Complaint form.<br><br>• There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.<br><br>• If the investigator determines that the medical device deficiency may have injured the participant (ie, the medical device deficiency is associated with an AE or SAE), then the investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis will be documented in the participant's medical record and recorded as the |

AE or SAE rather than the individual signs/symptoms. Requirements for recording and reporting an AE or SAE are provided in Appendix 3 (Section 10.3.3).

- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

**Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency**

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

| Follow-Up of Medical Device Deficiency |
|---|
| • The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.<br><br>• New or updated information regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint form.<br><br>• New or updated information regarding any SAE that was potentially associated with the medical device deficiency will be submitted to Pfizer Safety on the Vaccine SAE Reporting Form within 24 hours of receipt of the information, according to the requirements provided in Appendix 3. |

### 10.8.5. Reporting of SAEs

Reporting of an SAE to Pfizer Safety must be performed according to the processes described in Appendix 3 (Section 10.3.4).

### 10.8.6. Reporting of SADEs

| SADE Reporting to Pfizer Safety |
|---|
| Note: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs (ie, an SADE) that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.<br><br>• Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.<br><br>• The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations. |

## 10.9. Appendix 9: Abbreviations

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

| Abbreviation | Term |
|---|---|
| 7vPnC | 7-valent pneumococcal conjugate vaccine |
| 9vPnC | 9-valent pneumococcal conjugate vaccine |
| 13vPnC | 13-valent pneumococcal conjugate vaccine |
| 20vPnC | 20-valent pneumococcal conjugate vaccine |
| ADE | adverse device effect |
| ADL | activity/activities of daily living |
| AE | adverse event |
| AKI | acute kidney injury |
| $AlPO_4$ | aluminum phosphate |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AxMP | auxiliary medicinal product |
| BCR | B-cell receptor |
| b-hCG | b-human chorionic gonadotropin |
| [redacted] | [redacted] |
| CBER | Center for Biologics Evaluation and Research |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| CK | creatine kinase |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| CONSORT | Consolidated Standards of Reporting Trials |
| COPD | chronic obstructive pulmonary disease |
| COVID-19 | coronavirus disease 2019 |
| CRF | case report form |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| CRO | contract research organization |
| CSR | clinical study report |
| CTIS | Clinical Trial Information System |
| DCT | data collection tool |
| DILI | drug-induced liver injury |
| DNA | deoxyribonucleic acid |
| DU | dispensable unit |
| EC | ethics committee |
| ECC | emergency contact card |
| ECG | electrocardiogram |
| eCrCl | estimated creatinine clearance |
| eCRF | electronic case report form |

| Abbreviation | Term |
|---|---|
| EDB | exposure during breastfeeding |
| e-diary | electronic diary |
| EDMC | External Data Monitoring Committee |
| EDP | exposure during pregnancy |
| eGFR | estimated glomerular filtration rate |
| EMA | European Medicines Agency |
| eSAE | electronic serious adverse event |
| EU | European Union |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database) |
| FDA | (United States) Food and Drug Administration |
| 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 |
| HIV | human immunodeficiency virus |
| HRT | hormone replacement therapy |
| IB | investigator's brochure |
| ICD | informed consent document |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ID | identification |
| IgG | immunoglobulin G |
| IMP | investigational medicinal product |
| IND | investigational new drug |
| INR | international normalized ratio |
| IPAL | Investigational Product Accountability Log |
| IPD | invasive pneumococcal disease |
| IPM | investigational product manual |
| IRB | institutional review board |
| IRT | interactive response technology |
| ISO | International Organization for Standardization |
| IWR | interactive Web-based response |
| KDIGO | Kidney Disease: Improving Global Outcomes |
| LFT | liver function test |
| LLOQ | lower limit of quantitation |
| MDR | medical device regulation |
| MHCII | major histocompatibility complex class II |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

| Abbreviation | Term |
|---|---|
| [redacted] | [redacted] |
| MQI | medically qualified individual |
| N/A | not applicable |
| NIMP | noninvestigational medicinal product |
| NIP | national immunization program |
| OM | otitis media |
| OPA | opsonophagocytic activity |
| [redacted] | [redacted] |
| PCV15 | 15-valent pneumococcal conjugate vaccine |
| PFS | prefilled syringe |
| PI | principal investigator |
| [redacted] | [redacted] |
| PPE | personal protective equipment |
| PPSV23 | 23-valent pneumococcal polysaccharide vaccine |
| PSSA | Pfizer's Serious Adverse Event Submission Assistant |
| PT | prothrombin time |
| QTL | quality tolerance limit |
| RAC | reductive amination chemistry |
| RNA | ribonucleic acid |
| SADE | serious adverse device effect |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| [redacted] | [redacted] |
| Scr | serum creatinine |
| Scys | serum cystatin C |
| SoA | schedule of activities |
| SOP | standard operating procedure |
| SRSD | single reference safety document |
| SUSAR | suspected unexpected serious adverse reaction |
| TBD | to be determined |
| T bili | total bilirubin |
| TCR | T-cell receptor |
| UADE | unanticipated adverse device effect |
| ULN | upper limit of normal |
| US | United States |
| USADE | unanticipated serious adverse device effect |
| USPI | United States prescribing information |
| VE | vaccine efficacy |
| WOCBP | woman/women of childbearing potential |

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# Document Approval Record

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|---|---|
| **Document Name:** | C4801001 Clinical Protocol, 26 May 2022 |
| **Document Title:** | A PHASE 1, RANDOMIZED, OPEN-LABEL TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF PNEUMOCOCCAL CONJUGATE FORMULATIONS IN HEALTHY ADULTS 18 THROUGH 49 YEARS OF AGE |

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