A PHASE 4, OPEN-LABEL, SINGLE-ARM, MULTICENTER STUDY TO DESCRIBE THE SAFETY OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE IN CHILDREN 6 TO 17 YEARS OF AGE IN INDIA

Investigational Product Number:	PF-05208760
Investigational Product Name:	13-valent Pneumococcal Conjugate Vaccine
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Document History

Document	Version Date	Summary of Changes
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PROTOCOL SUMMARY

In India, the 13-valent pneumococcal conjugate vaccine (13vPnC) is licensed for infants and children aged 6 weeks to 5 years and adults aged ≥50 years. Based on data from a recent Phase 4/3 study (B1851140) in children and adolescents aged 6 to 17 years in India, where 13vPnC elicited robust immune responses for all 13 serotypes, the Drug Controller General of India (DCGI) granted approval for this age group. To generate additional safety data in individuals aged 6 to 17 years in India, a Phase 4 safety study was requested by the DCGI. In this study, electronic diaries will be given to the parent(s)/legal guardian(s)/caregiver(s) to collect local reactions and systemic events for 7 days after vaccination. Investigators will collect other adverse events (AEs) at the follow-up visit 1 month after vaccination.

STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s):	Primary Endpoint(s):
To describe the safety profile of 13vPnC in pediatric subjects 6 to 17 years of age.	• Local reactions within 7 days after vaccination. • Systemic events within 7 days after vaccination. • AEs within 1 month after vaccination.

STUDY DESIGN

This is a Phase 4, open-label, single-arm, multicenter study in which subjects 6 to 17 years of age will receive 1 dose of 13vPnC.

Approximate Duration of Subject Participation

Subjects will participate in the study for approximately 1 month.

Approximate Duration of the Study

Based on an estimated enrollment period of 3 months, the total study duration will be approximately 4 months.

Number of Subjects

Approximately 100 subjects will be enrolled.

SCHEDULE OF ACTIVITIES

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

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

Visit Number	**1**	**2**
Visit ID	**Vaccination**	**Follow-up Visit**
Visit Window (Days)	**Day 1**	**28 to 42 Days After Visit 1**
Informed consent (and assent if appropriate)	X	
Assign a subject identification number	X	
Demography	X	
Review inclusion criteria, exclusion criteria, and temporary delay criteria	X	
Medical history	X	
Physical examination	X	
Nonstudy vaccine data collection	X	X
Urine pregnancy test for female subjects of childbearing potential	X	
Confirm use of appropriate contraceptives throughout the study (if appropriate)	X	X
Prevaccination temperature	X	
13vPnC administration	X	
Assess acute reactions for at least 20 minutes after 13vPnC administration	X	
Provide 7-day e-diary, digital thermometer, and measuring device and provide instructions on their correct use	X	
Review e-diary data (Days 1 through 7; daily is optimal)	X----------X	
Collect e-diary		X
AE and SAE collection	X----------X	

Abbreviations: e-diary = electronic diary

1. INTRODUCTION

1.1. Indication in India

The 13-valent pneumococcal conjugate vaccine (13vPnC) is being investigated for the following:

- Active immunization for the prevention of disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F (including sepsis, meningitis, bacteremia, pneumonia, and acute otitis media) in infants and children from 2 months to 5 years of age.

- Active immunization for the prevention of pneumonia and invasive disease caused by *S pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F in children 6 to 17 years of age.

- Active immunization for the prevention of pneumonia and invasive disease caused by *S pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F in adults 50 years of age and older.

1.2. Background and Rationale

S pneumoniae infections are a significant cause of morbidity and mortality worldwide. In India, *S pneumoniae* is associated with high disease burden and mortality among young children.[1] Using modeling-based estimates, it is estimated that in 2010, about 3.6 million episodes of severe pneumonia and about 0.35 million all-cause pneumonia deaths occurred in children younger than 5 years of age in India.[2] Of these, it was estimated that about 0.56 million severe episodes of pneumococcal pneumonia and 105,000 pneumococcal deaths occurred in India. Older children are also affected, particularly those with certain underlying medical conditions, including diabetes mellitus, chronic cardiac or pulmonary disease, sickle cell disease, human immunodeficiency virus infection, other immunocompromising conditions, cochlear implants, or cerebrospinal fluid leaks.[3]

In India, 13vPnC is licensed for infants and children 6 weeks to 5 years of age and adults ≥50 years of age.[4] Following a recent Phase 4/3 study (B1851140), which assessed the immunogenicity and safety of 13vPnC in 200 healthy children and adolescents aged 6 to 17 years in India, the Drug Controller General of India (DCGI) granted approval for this age group. In this study, 13vPnC elicited robust immune responses for all 13 serotypes, with statistically significant increases in opsonophagocytic activity (OPA) titers to all 13 serotypes. No adverse events (AEs) were reported by the caregivers at the follow-up visit 1 month after vaccination. In this study, electronic diaries (e-diaries) were not used by the caregivers to collect local reactions and systemic events that were anticipated after vaccination. Such reactions have been collected in other pediatric and adult studies,[4] and from a US licensing study (6096A1-3011) in children and adolescents 15 months to 17 years of age.[5] The US clinical trial included 294 children 5 to <10 years of age previously vaccinated with at least 1 dose of 7-valent pneumococcal conjugate vaccine (7vPnC), and 298 children and adolescents 10 to 17 years of age not previously vaccinated with 7vPnC.

In this study, 13vPnC was demonstrated to be immunogenic and an acceptable safety profile was demonstrated in subjects 6 to 17 years of age.

To generate additional safety data in children and adolescents aged 6 to 17 years in India, a Phase 4 safety study was requested by the DCGI. In this study, e-diaries will be given to the parent(s)/legal guardian(s)/caregiver(s) to collect local reactions and systemic events for 7 days after vaccination. Investigators will collect other AEs at the follow-up visit 1 month after vaccination.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the local package insert.

This study is defined as a postauthorization safety study (PASS).

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s):	Primary Endpoint(s):
To describe the safety profile of 13vPnC in pediatric subjects 6 to 17 years of age.	• Local reactions within 7 days after vaccination. • Systemic events within 7 days after vaccination. • AEs within 1 month after vaccination.

3. STUDY DESIGN

This is a Phase 4, open-label, single-arm, multicenter study in which subjects 6 to 17 years of age will receive 1 dose of 13vPnC.

3.1. Approximate Duration of Subject Participation

Subjects will participate in the study for approximately 1 month.

3.2. Approximate Duration of the Study

Based on an estimated enrollment period of 3 months, the total study duration will be approximately 4 months.

3.3. Number of Subjects

Approximately 100 subjects will be enrolled.

4. SUBJECT ELIGIBILITY CRITERIA

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

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

4.1. Inclusion Criteria

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

1. Evidence of a personally signed and dated informed consent document (ICD) indicating that the subject's parent(s)/legal guardian(s) has/have been informed of all pertinent aspects of the study.

   Note: The subject's assent may also be required depending on local requirements.

2. Healthy male or female children 6 to 17 years of age at the time of vaccination.

3. Parent(s)/legal guardian(s)/child willing and able to comply with scheduled visits, treatment plan, and other study procedures.

4. Male subject not able to father children, male subject who is able to father children and willing to use a highly effective method of contraception, female subject not of childbearing potential, or female subject of childbearing potential and at risk for pregnancy who is willing to use a highly effective method of contraception.

   Note: Female subjects of childbearing potential are defined as female subjects ≥9 years old or have experienced menarche, whichever is earlier, and who are anatomically and functionally able to conceive.

4.2. Exclusion Criteria

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

1. Child who is a family member of:

   - Investigator site staff members directly involved in the conduct of the study;
   - Site staff members otherwise supervised by the investigator;
   - Pfizer employees directly involved in the conduct of the study.

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

3. History of severe adverse reaction, including hypersensitivity such as anaphylaxis, associated with a vaccine or vaccine component.

4. Contraindication to vaccination with pneumococcal conjugate vaccines (refer to local package insert).

5. Previous vaccination with licensed or investigational pneumococcal vaccine.

6. Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate intramuscular injection.

7. History of culture-proven invasive disease caused by *S pneumoniae*.

8. Major known congenital malformation or serious chronic disorder.

9. Known or suspected immune deficiency or suppression.

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

11. Pregnant females; breastfeeding females; fertile males and females of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study.

4.3. Criteria for Temporarily Delaying Vaccine Administration

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

1. Current febrile illness (temperature ≥100.4°F [38.0°C]) or other acute illness within 48 hours before 13vPnC administration.

4.4. Lifestyle Requirements

4.4.1. Contraception

All fertile male subjects and female subjects who are of childbearing potential who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the study.

The investigator or his or her designee will confirm that the subject has selected an appropriate method of contraception from the list of permitted contraception methods (see below). At time points indicated in the Schedule of Activities, the investigator or designee will instruct the subject of the need to use highly effective contraception consistently and correctly and document the conversation, and the subject's affirmation, in the subject's chart. In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner.

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

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

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

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

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

All sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, for the duration of the study.

4.5. Sponsor's Qualified Medical Personnel

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

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

5. INVESTIGATIONAL PRODUCTS

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

For this study, the investigational product is 13vPnC.

5.1. Allocation to Investigational Product

This is a Phase 4, single-arm, open-label study.

5.2. Subject Compliance

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

5.3. Investigational Product Supplies

Commercial 13vPnC will be provided by the sponsor to each study site. The vaccine will be labeled in accordance with local regulations.

5.3.1. Dosage Form and Packaging

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

13vPnC will be provided as a 0.5-mL dose in a prefilled syringe.

5.3.2. Preparation and Dispensing

Only appropriately qualified personnel should dispense the investigational product.

5.3.3. Administration

At Visit 1, all subjects will receive a single dose (0.5 mL) of 13vPnC intramuscularly in the left thigh or the left deltoid muscle as appropriate for the subject.

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

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

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

5.4. Investigational Product Storage and Accountability

5.4.1. Investigational Product Storage

13vPnC will be shipped at +2°C to +8°C to each study site upon request. Upon receipt at the study site, the vaccines should be immediately transferred to a +2°C to +8°C temperature-monitored refrigerator for storage.

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

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

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

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

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

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion.

Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

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

5.4.2. Investigational Product Accountability

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

5.4.3. Destruction of Investigational Product Supplies

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

5.5. Concomitant Medication(s)

5.5.1. Prohibited During the Study

The following are prohibited during the study:

- Vaccination with any licensed or investigational pneumococcal vaccine other than that specified by the protocol.
- Receipt of any other investigational product.

5.5.2. Permitted During the Study

The following are permitted during the study:

- Any other vaccine may be given according to local practice. If any vaccine other than 13vPnC is administered during the study, the name and date of administration will be documented in the CRF.
- Any medication, except those listed in Section 5.5.1, is permitted but will not be documented in the CRF.

6. STUDY PROCEDURES

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

6.1. Visit 1 - Vaccination (Day 1)

- Obtain written informed consent and, if applicable, assent (age dependent on local requirement) before performing any study-specific procedures.
- Assign a subject identification number.
- Obtain and record the subject demography (including date of birth, sex, race, and ethnicity).
- Obtain and record any nonstudy vaccinations received from 28 days prior to vaccination.
- Obtain and record the medical history, including the presence of chronic conditions and/or medical history of significance.
- Perform physical examination evaluating any clinically significant abnormalities, including worsening of medical history conditions, within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect and record any AEs and serious adverse events (SAEs) that occurred since the signing of the ICD.
- Perform a urine pregnancy test on female subjects of childbearing potential.
- Confirm use of appropriate contraceptives (if appropriate).
- On the day of vaccination, prior to vaccination, measure and record the subject's temperature using the preferred local method.
- Ensure that all of the inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met.
- Administer a single 0.5-mL injection of 13vPnC into the left thigh or the left deltoid muscle as appropriate for the subject.
- Observe the subject for at least 20 minutes after 13vPnC administration for any acute reactions. Record any AEs in the subject's source documents and on the AE section of the CRF.
- Issue an e-diary and provide instructions on its use for 7 days (Day 1 through Day 7, where Day 1 is the day of vaccination).
- Issue a measuring device and a digital thermometer and provide instructions on their use for 7 days (Day 1 through Day 7, where Day 1 is the day of vaccination).

- Ask the parent(s)/legal guardian(s)/caregiver(s) to contact the site staff or investigator immediately if the subject experiences redness or swelling at the injection site measuring greater than 7 cm (>14 measuring device units) from Day 1 to Day 7 after vaccination to determine if an unscheduled reactogenicity visit is required.

- Ask the parent(s)/legal guardian(s)/caregiver(s) to contact the investigator immediately if any significant illness or hospitalization occurs during the study period.

- Schedule an appointment for the next study visit.

- Remind the parent(s)/legal guardian(s)/caregiver(s) to bring the e-diary to the next study visit.

- The investigator or an authorized designee completes the source documents, completes the CRF, and updates the investigational product accountability records.

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

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

- Review the subject's e-diary data and collect the e-diary. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.

- Determine whether any AEs (including SAEs) have occurred since the last study visit and record them on the CRF (see Section 8).

- Collect and record any follow-up information on previously documented AEs and SAEs and record their end dates or confirm that they are still continuing.

- Record any nonstudy vaccinations.

- Confirm use of appropriate contraceptives (if appropriate).

- Complete the source documents and the CRFs.

6.3. Unscheduled Reactogenicity Visit

If the subject's parent(s)/legal guardian(s)/caregiver(s) report(s) redness or swelling at the injection site measuring >14 measuring device units (>7.0 cm), a contact **must** occur as soon as possible between the subject's parent(s)/legal guardian(s)/caregiver(s) and the investigator, or a medically qualified member of the study site staff, to assess if an unscheduled visit is required.

A site visit must be scheduled as soon as possible to assess the extent of the reaction unless:

- The subject is unable to attend the unscheduled visit, or
- The reaction is no longer present at the time of the contact, or
- An incorrect value was entered into the e-diary (confirmation of an e-diary data entry error).

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

If the subject is unable to attend the unscheduled visit, any ongoing reactions must be assessed at the next scheduled visit.

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

- Measure axillary temperature.
- Measure the minimum and maximum diameter of the redness or swelling in centimeters.
- Assess pain at the injection site (tenderness) in accordance with the criteria provided in Section 7.3.1.
- Complete the CRF.
- If applicable, remind the subject's parent(s)/legal guardian(s)/caregiver(s) to enter an end date of the reaction in the e-diary.

6.4. Subject Withdrawal

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

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

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

Subjects who withdraw from the study will not be replaced.

7. ASSESSMENTS

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

7.1. Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed immediately before administration of the vaccine dose. A negative pregnancy test result is required before the subject may receive the investigational product. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product.

7.2. Safety Assessments

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

A medical history and physical examination, including measurement of vital signs, will be performed on all subjects at Visit 1. Significant medical history and observations from the physical examination will be documented in the CRF.

The safety parameters include e-diary reports of local reactions at the 13vPnC injection site and systemic events that occur in the 7 days after investigational product administration. These prospectively collected occurrences of local reactions and systemic events are graded as described in Section 7.3.

Acute reactions within the first 20 minutes after investigational product administration will be assessed and documented in the AE CRF.

In addition, AEs and SAEs are collected, recorded, and reported as defined in Section 8.

7.3. Electronic Diary

The subject's parent(s)/legal guardian(s)/caregiver(s) will be issued an e-diary and will be asked to monitor and record the subject's local reactions and systemic events for 7 days after 13vPnC vaccination. The e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the subject's experience at that time. Local reactions and systemic events reported on the e-diary will be transferred electronically to the e-diary vendor (a trusted third party), where they will be available for review by investigators at all times via an internet-based portal. At intervals agreed upon between the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. The e-diary data do not need to be reported by the investigator in the CRF.

Investigators will be required to review the e-diary data online at frequent intervals to evaluate the subject's caregiver e-diary completion compliance and as part of the ongoing safety review.

7.3.1. Local Reactions

Local reactions (redness, swelling, and pain) at the 13vPnC injection site will be monitored daily for 7 days (Day 1 to Day 7) after each vaccination. An end date will be captured for all reactions either via the e-diary or CRF as applicable.

Redness and swelling will be measured and recorded in measuring device units and then categorized during analysis as mild, moderate, or severe based on the grading scale in Table 1 below. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm.

Pain at the vaccine injection site will be assessed by the subject's parent(s)/legal guardian(s)/caregiver(s) as mild, moderate, or severe according to the grading scale in Table 1 below.

If a subject experiences redness or swelling at the injection site measuring greater than 7 cm (>14 measuring device units), an unscheduled visit should take place to assess the reaction.

If a local reaction persists beyond the end of the e-diary period, the subject's parent(s)/legal guardian(s)/caregiver(s) will be requested to report that information and/or any new AEs that develop to the investigator. The investigator will enter this additional information in the subject's source notes and CRF.

Table 1. Grading Scale for Local Reactions

	Mild Grade 1	Moderate Grade 2	Severe Grade 3
Redness	1 to 4 measuring device units = 0.5 to 2.0 cm	5 to 14 measuring device units = 2.5 to 7.0 cm	>14 measuring device units = >7 cm
Swelling	1 to 4 measuring device units = 0.5 to 2.0 cm	5 to 14 measuring device units = 2.5 to 7.0 cm	>14 measuring device units = >7 cm
Pain at injection site (Tenderness)	Does not interfere with activity	Interferes with activity	Prevents daily activity

7.3.2. Systemic Events

Following vaccination at Visit 1 (Day 1 through Day 7, where Day 1 is the day of vaccination), the subject's parent(s)/legal guardian(s)/caregiver(s) will be asked to assess fatigue, headache, vomiting, diarrhea, muscle pain, and joint pain and to record the symptoms in the e-diary in the evening. The symptoms will be assessed as mild, moderate, or severe according to the grading scale in Table 2 below.

If a systemic event persists beyond the end of the e-diary period, the subject's parent(s)/legal guardian(s)/caregiver(s) will be requested to report that information and/or any new AEs that develop to the investigator. The investigator will enter this additional information in the CRF.

Table 2. Grading Scale for Systemic Events

	Mild Grade 1	Moderate Grade 2	Severe Grade 3
Fatigue (= tiredness in diaries)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Vomiting	1 to 2 times in 24 hours	More than 2 times in 24 hours	Requires intravenous hydration
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours
Muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity

7.3.3. Fever

A digital thermometer will be provided with instructions on how to measure the subject's temperature at home. Temperature will be collected in the evening daily for 7 days following vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination) and at any time during the 7 days after Visit 1 that fever is suspected. Fever is defined as a temperature of ≥100.4°F (≥38.0°C). The highest temperature for each day will be recorded in the e-diary.

In the event of a fever on Day 7, temperature will be measured daily until fever has resolved (1 day of temperature less than 100.4°F [38.0°C]) in order to collect a stop date in the CRF.

Temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis according to Table 3 below:

Table 3. Ranges for Fever (All Subjects)

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

8. ADVERSE EVENT REPORTING

8.1. Requirements

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

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

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

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

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

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

8.1.1. Additional Details on Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

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

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

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

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

8.1.4. Time Period for Collecting AE/SAE Information

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

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

8.1.4.1. Reporting SAEs to Pfizer Safety

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

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

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

8.1.4.2. Recording Nonserious AEs and SAEs on the CRF

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

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

8.1.5. Causality Assessment

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

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

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

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

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

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;

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

8.2.2. Abnormal Test Findings

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

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

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

8.2.3. Serious Adverse Events

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

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

- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

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

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

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

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

- A life-threatening illness, even if temporary in nature;
- A permanent impairment of a body function or permanent damage to a body structure;
- A condition necessitating medical or surgical intervention to prevent the above 2 bulleted items;
- Examples: clinically relevant increase in the duration of a surgical procedure; a condition that requires hospitalization or significant prolongation of existing hospitalization;
- Any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

8.2.4. Hospitalization

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

Hospitalization does not include the following:

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

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

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

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

8.3. Severity Assessment

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

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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

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

8.4.2. Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase, and acetaminophen drug and/or protein adduct levels.

Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

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

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

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

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

8.4.3.1. Exposure During Pregnancy

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

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

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

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

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

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

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

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

8.4.3.2. Exposure During Breastfeeding

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

8.4.3.3. Occupational Exposure

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

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

8.4.4. Medication Errors and Lack of Efficacy

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

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

8.4.4.1. Medication Errors

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

Medication errors include:

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

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

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

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

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

Other examples include, but are not limited to:

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

8.4.4.2. Lack of Efficacy

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

8.5. Medical Device Complaint Reporting Requirements

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

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

For medical device complaints not associated with an SAE, Pfizer Global Manufacturing is to be notified of all medical device complaints within 24 hours of the investigator's awareness of the event.

9. DATA ANALYSIS/STATISTICAL METHODS

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

9.1. Sample Size Determination

Sample size for this study is not based on statistical hypotheses testing or power calculations. The probabilities of observing at least 1 AE for a given true event rate of a particular AE at various sample sizes have been provided in the following table. For example, if a true AE event rate is 1.0%, the probability of observing at least 1 such AE is 63.4% with a sample size of 100 subjects.

Table 4. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True AE Event Rate	N = 90	N = 95	N = 100	N = 105	N = 110
0.1%	8.6%	9.1%	9.5%	10.0%	10.4%
0.5%	36.3%	37.9%	39.4%	40.9%	42.4%
1.0%	59.5%	61.5%	63.4%	65.2%	66.9%
2.5%	89.8%	91.0%	92.0%	93.0%	93.8%
5.0%	99.0%	99.2%	99.4%	99.5%	99.6%
10.0%	>99.9%	>99.9%	>99.9%	>99.9%	>99.9%

9.2. Safety Analysis

Safety endpoints are our primary endpoints in the study. All safety analyses will be performed on the safety population.

The safety population will include all subjects who receive 1 dose of an investigational product.

The proportion of subjects reporting local reactions at the injection site and systemic events on any day within the 7-day period after vaccination will be descriptively summarized. Local reactions and systemic events that persist beyond Day 7 will be listed in the clinical study report.

Severities of local reactions and systemic events reported after vaccination will also be descriptively summarized. Two-sided exact 95% confidence intervals (CIs) will be presented with the proportions.

AEs/SAEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized for all subjects. All summaries of AEs will show the number and percentage of subjects experiencing at least 1 event and the number of events.

Additional summaries by AE severity or by vaccine relationship may be produced.

9.3. Analysis Timing

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

9.4. Data Monitoring Committee

This study will not use a data monitoring committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

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

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

11.2. Record Retention

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

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

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

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

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

12.3. Subject Information and Consent

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

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

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

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

The investigator must ensure that each study subject, or parent(s) or legal guardian(s) if a minor, is fully informed about the nature and objectives of the study and possible risks associated with participation.

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

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

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

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

End of trial in all participating countries is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of 13vPnC at any time.

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

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

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

15.2. Publications by Investigators

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

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

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

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

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

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

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

16. REFERENCES

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3. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among children aged 6-18 years with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2013;62(25):521-524.

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5. Frenck R Jr, Thompson A, Senders S, et al. 13-valent pneumococcal conjugate vaccine in older children and adolescents either previously immunized with or naïve to 7-valent pneumococcal conjugate vaccine. *Pediatr Infect Dis J*. 2014;33(2):183-189.

Appendix 1. Abbreviations

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

Abbreviation	Term
7vPnC	7-valent pneumococcal conjugate vaccine
13vPnC	13-valent pneumococcal conjugate vaccine
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CI	confidence interval
CK	creatine kinase
CRF	case report form
CRM197	cross-reactive material 197
CSA	clinical study agreement
CT	clinical trial
DCGI	Drug Controller General of India
DILI	drug-induced liver injury
EC	ethics committee
e-diary	electronic diary
EDP	exposure during pregnancy
EU	European Union
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
ICD	informed consent document
ICH	International Council for Harmonisation
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
LFT	liver function test
LSLV	last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
OPA	opsonophagocytic activity
PASS	postauthorization safety study
PCD	primary completion date
PI	principal investigator
PT	prothrombin time
SAE	serious adverse event
SAP	statistical analysis plan
SRSD	single reference safety document
TBili	total bilirubin
ULN	upper limit of normal
US	United States

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