A PHASE 4, RANDOMIZED, OPEN-LABEL TRIAL TO DESCRIBE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE FORMULATED IN MULTIDOSE VIALS WHEN GIVEN WITH ROUTINE PEDIATRIC VACCINES IN HEALTHY INFANTS IN INDIA

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Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	10 January 2017	Not applicable (N/A)
Protocol Amendment 1	14 February 2017	Clarification added that this study is defined as a postauthorization safety study. Corrections made to the Secondary Objective and Data Analysis/Statistical Methods sections. Clarification added that OPA will be determined in all subjects for each blood sample collected 1 month after the infant series and 1 month after the toddler dose, where sufficient sera are available. References have been altered to match the AMA style of formatting.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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PROTOCOL SUMMARY

Background

Diseases caused by *Streptococcus pneumoniae* are a major public health problem affecting all age groups worldwide. Pfizer has entered into an agreement with Gavi, the Vaccine Alliance, to improve access to Prevenar ® (13-valent pneumococcal conjugate vaccine; 13vPnC) in countries that are supported by Gavi where individuals are at high risk of pneumococcal disease. To best supply 13vPnC for this program, Pfizer developed a multidose formulation of Prevenar 13 (4 doses per vial), which requires 2-phenoxyethanol (2-PE) as a preservative in order to prevent microbial growth. Currently, 2-PE is the preservative used in a number of commercially available vaccines. The multidose vial (MDV) occupies less cold-chain capacity than an equivalent number of doses presented in a single-dose prefilled syringe (PFS) that contains the 13vPnC formulation without preservative. In a study in the Gambia, the 13vPnC MDV formulation, with 2-PE as preservative, demonstrated immunogenicity and safety profiles comparable to those of the approved formulation of 13vPnC without 2-PE.

This study is being conducted to assess the safety, tolerability, and immunogenicity of the 13vPnC MDV formulation in infants and toddlers in India in response to a request from the Subject Expert Committee (SEC) and the Drugs Controller General of India (DCGI) following a no objection certificate (NOC) to the marketing authorization of the MDV 13vPnC+2-PE formulation in India.

Primary Objective and Endpoints

To describe the safety profile of 13vPnC with 2-PE in the MDV group and without 2-PE in the PFS group.

- Incidence of local reactions and systemic events at the following time periods in the MDV group and in the PFS group:
    - Within the 7 days after the first dose of the infant series.
    - Within the 7 days after the second dose of the infant series.
    - Within the 7 days after the third dose of the infant series.
    - Within the 7 days after the toddler dose.
- Incidence of adverse events (AEs) in the MDV group and in the PFS group from the first dose up to 1 month after the infant series.
- Incidence of AEs in the MDV group and in the PFS group from the toddler dose up to 1 month after the toddler dose.
- Incidence of serious adverse events (SAEs) in the MDV group and in the PFS group from the first dose up to 1 month after the toddler dose.

- Incidence of newly diagnosed chronic medical conditions in the MDV group and in the PFS group from 1 month after the infant series up to the toddler dose.

Study Design

- This is a randomized, open-label study in which subjects will receive either 13vPnC with 2-PE from an MDV or 13vPnC without 2-PE in a PFS.
- Subjects will be randomized in a 1:1 ratio to 1 of the 2 groups.
- Subjects will be vaccinated in a 3-dose infant series followed by a toddler dose.
- Subjects will have 2 blood draws of up to 5 mL at approximately 1 month after the infant series and 1 month after the toddler dose.

Approximate Duration of Subject Participation

Each subject is expected to participate from the first vaccination at 6 weeks of age to a post– toddler dose blood draw. The total duration of subject participation is therefore up to approximately 14 months.

Approximate Duration of the Study

This study is anticipated to last approximately 20 months, assuming a 6-month recruitment period. The total duration may differ depending on the actual enrollment rate. The end of the study is the last visit of the last subject, which is scheduled 1 month after the toddler dose.

Approximate Number of Subjects

Approximately 300 subjects (150 subjects per group) will be randomized in this study at approximately 8 sites. The number of subjects enrolled at each site may vary based on enrollment capabilities of each site and the final number of sites.

SCHEDULE OF ACTIVITIES

The schedule of activities table (Table 1) 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.

Table 1. Schedule of Activities

Visit Number	1	2	3	4	5	6
Visit ID	6-Week Visit	10-Week Visit	14-Week Visit	18-Week Visit	12-Month Visit	13-Month Visit
Visit Window[a]	42 to 72 Days of Age	28 to 42 Days After Visit 1	28 to 42 Days After Visit 2	28 to 42 Days After Visit 3	365 to 420 Days of Age	28 to 42 Days After Visit 5
Informed consent	**x**					
Review inclusion/exclusion criteria	**x**					
Demography	**x**					
Medical history, physical examination	**x**					
Weigh subject	**x**					
Axillary temperature	**x**	**x**	**x**		**x**	
Randomization	**x**					
13vPnC administration & 30-minute observation	**x**	**x**	**x**		**x**	
DTP-Hib-HBV administration	**x**	**x**	**x**			
Rotavirus vaccine administration	**x**	**x**	**x**			
Hepatitis A virus vaccine administration					**x**	
Provide parent with e-diary, caliper, thermometer, as appropriate for visit	**x**	**x**	**x**		**x**	
Review e-diary data		**x**	**x**	**x**		**x**
Confirm continued eligibility		**x**	**x**	**x**	**x**	
AE collection as appropriate for visit	**x**	**x**	**x**	**x**	**x**	**x**
Obtain blood sample				**x**		**x**

Abbreviations: DTP-Hib-HBV = diphtheria, tetanus, and pertussis; *Haemophilus influenzae* type b; and hepatitis B virus vaccine; e-diary = electronic diary.

a. Visit windows are included in this protocol so that subjects in this study all have their vaccinations and blood draws within a broadly uniform time frame. However, because of the population under study, it is recognized that it may not always be possible to adhere to these windows (for example, because of subject illness).

1. INTRODUCTION

Diseases caused by *Streptococcus pneumoniae* are a major public health problem affecting all age groups worldwide. Pfizer has entered into an agreement with Gavi, the Vaccine Alliance, to improve access to Prevenar 13® (13-valent pneumococcal conjugate vaccine; 13vPnC) in the countries that are supported by Gavi where individuals are at high risk of pneumococcal disease. Gavi is a global health partnership between the private and public sectors that aims to increase access to immunization in developing countries. To best supply 13vPnC for this program, Pfizer developed a multidose formulation of Prevenar 13 (4 doses per vial), which requires 2-phenoxyethanol (2-PE) as a preservative in order to prevent microbial growth. Currently, 2-PE is the preservative used in a number of commercially available vaccines, eg, diphtheria, tetanus, and acellular pertussis vaccine (DTaP; Daptacel); tetanus, low-dose diphtheria, and low-dose acellular pertussis vaccine (Tdap; Adacel); diphtheria, tetanus, and acellular pertussis; inactivated poliovirus; and *Haemophilus influenzae* type b vaccine (DTaP-IPV-Hib; Pentacel); and inactivated poliovirus vaccine (IPV; Ipol). The multidose vial (MDV) occupies less cold-chain capacity than an equivalent number of doses presented in a single-dose prefilled syringe (PFS) that contains the 13vPnC formulation without preservative.

1.1. Indication

Prevenar 13 is licensed in India for active immunization for the prevention of disease caused by *S 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 6 weeks to 5 years of age and for 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.

The MDV 13vPnC+2-PE formulation is also licensed in India for the above indication.

1.2. Background and Rationale

Infections caused by *S pneumoniae* are a major cause of morbidity and mortality all over the world. Pneumonia, febrile bacteremia, and meningitis are the most common manifestations of invasive pneumococcal disease (IPD). Pneumococcal meningitis is a severe disease with high mortality and high incidence of neurologic sequelae.[1] *S pneumoniae* also causes noninvasive pneumococcal disease, including otitis media, sinusitis, bronchitis, and nonbacteremic pneumonia. Of the estimated 8.8 million global annual deaths among children <5 years of age in 2008, the World Health Organization (WHO) estimated that 476,000 (333,000-529,000) were caused by pneumococcal infections. Disease rates and mortality are higher in developing than in industrialized settings, with the majority of deaths occurring in Africa and Asia. Development of pneumococcal resistance to commonly used antibiotics such as penicillins, macrolides, cephalosporins, and cotrimoxazole is a serious problem in some parts of the world. However, following the introduction of large-scale pneumococcal immunization, a reduction in the circulation of drug-resistant strains has been observed.[2]

Before the introduction of the 7-valent pneumococcal conjugate vaccine (7vPnC), marketed as Prevenar®/Prevnar®, the incidence of IPD in the United States was approximately 96/100,000 cases in children less than 5 years of age, with higher rates in children less than 2 years of age.[3] The ability of 7vPnC to prevent vaccine serotype–related pediatric IPD, pneumonia, and otitis media initially reported in controlled clinical trials[4,5,6] was subsequently established in clinical practice following the incorporation of 7vPnC into the routine childhood vaccination schedule in the United States and other countries.[7,8,9,10,11,12,13,14,15,16] Vaccination of children has also been shown to reduce IPD incidences among unimmunized adult populations in some countries.[17,18]

After the introduction of 7vPnC, the Active Bacterial Core surveillance (ABCs) data have shown a small but statistically significant increase in pneumococcal disease due to nonvaccine serogroups/serotypes in both infants and adults.[10,17,19] Serotypes 19A, 3, 15, 22F, 33F, and 35 have been isolated, with 19A being the most prevalent in children below 5 years of age.[19] To expand the serotype coverage, Pfizer developed 13vPnC. The efficacy of 13vPnC against vaccine-type IPD has been demonstrated in all ages in a number of national surveillances of pneumococcal disease in countries that have implemented widespread 13vPnC immunization.[20,21,22,23,24,25,26,27,28,29,30] The efficacy of 13vPnC against vaccine-type community-acquired pneumonia (including nonbacteremic) and IPD in adults aged ≥65 years is supported by the findings from the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA).[31]

13vPnC is licensed in the European Union and other European countries, the United States, and other countries globally, including India, as Prevenar 13/Prevnar 13®. It contains polysaccharides from the 7 serotypes included in 7vPnC and an additional 6 serotypes (1, 3, 5, 6A, 7F, and 19A), all conjugated to cross-reactive material 197 (CRM_{197}). It has been shown that the 6 additional serotypes in 13vPnC increase coverage for IPD prevention in children <5 years of age to 74% to 88% globally.[32] Importantly, the additional serotypes in 13vPnC are associated with a high percentage of pneumococcal disease in the developing world.[33,34] Vaccines are often presented as single-dose vials or PFSs; however, MDV formulations are commonly used in developing countries. In single-dose vaccine formulations, each dose remains sealed and protected until it is ready for administration, decreasing chances for wastage and contamination. Because each dose needs its own container, single-dose formulations occupy a greater volume per dose than MDVs with regard to supply-chain storage and medical waste disposal.[35,36] This issue is a significant problem when storage space and transport space are limited. The advantage of MDVs is that they allow the vaccine to occupy less cold-chain capacity than single-dose PFSs, therefore reducing cold-chain and storage costs. Unlike single-dose PFSs that are discarded immediately after single use, MDVs are used more than once. As the vaccine vial is punctured more than once, a preservative not present in the single-dose PFS is required to prevent microbial growth.

The preservative 2-PE is added to 13vPnC in MDVs. This preservative is a phenolic derivative used in vaccine production. It was studied at high concentrations in animal studies and did not result in adverse events (AEs).[37,38] Furthermore, a study published by Khandke et al[39] demonstrated that 2-PE at 5.0 mg per dose in the Prevenar 13 multidose formulation

met the antimicrobial effectiveness requirements of the European Pharmacopoeia. Currently, 2-PE is the preservative used in a number of commercially available vaccines, eg, diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (Daptacel; Infanrix) and hepatitis A inactivated and hepatitis B (recombinant) vaccine (Twinrix).[40]

In the open-label, randomized study in healthy infants in the Gambia (Study B4671001), the 13vPnC MDV formulation, with 2-PE as preservative, demonstrated immunogenicity and safety profiles comparable to those of the approved formulation of 13vPnC without 2-PE. In the Gambia study, the 13vPnC MDV formulation was given to healthy infants at 8, 12, and 16 weeks of age and compared to Prevenar 13 without added preservative. Pneumococcal immune responses were compared using noninferiority criteria, including the percentage of subjects with serum antipolysaccharide serotype-specific immunoglobulin G (IgG) concentration ≥0.35 μg/mL and the comparison of IgG geometric mean concentrations (GMCs) 1 month after the infant series. In addition, opsonophagocytic activity (OPA) geometric mean titers (GMTs) between groups receiving Prevenar 13 with or without 2-PE were compared. Noninferiority for the proportion of subjects achieving an IgG concentration ≥0.35 μg/mL was demonstrated for all 13 serotypes. Additionally, all 13 serotypes met the predefined noninferiority criterion for IgG GMCs. OPA GMTs were similar in both groups, except for serotype 3, for which the OPA GMT was lower, and serotype 18C, for which it was higher, in the group that received Prevenar 13 with 2-PE.

This study is being conducted in response to a request from the Subject Expert Committee (SEC) and the Drugs Controller General of India (DCGI) following a no objection certificate (NOC) to the marketing authorization of the MDV 13vPnC+2-PE formulation in India. This study will describe the safety, tolerability, and immunogenicity of 13vPnC with 2-PE presented in MDVs in infants and toddlers in India. This study is defined as a postauthorization safety study (PASS).

Additional information for 13vPnC with 2-PE (MDV) and 13vPnC without 2-PE (PFS) may be found in the single reference safety document (SRSD), which for this study is the local package label.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	Primary Endpoints
To describe the safety profile of 13vPnC with 2-PE in the MDV group and without 2-PE in the PFS group.	• Incidence of local reactions and systemic events at the following time periods in the MDV group and in the PFS group: o Within the 7 days after the first dose of the infant series. o Within the 7 days after the second dose of the infant series. o Within the 7 days after the third dose of the infant series. o Within the 7 days after the toddler dose. • Incidence of AEs in the MDV group and in the PFS group from the first dose up to 1 month after the infant series.

	• Incidence of AEs in the MDV group and in the PFS group from the toddler dose up to 1 month after the toddler dose. • Incidence of serious adverse events (SAEs) in the MDV group and in the PFS group from the first dose up to 1 month after the toddler dose. • Incidence of newly diagnosed chronic medical conditions in the MDV group and in the PFS group from 1 month after the infant series up to the toddler dose.
Secondary Objective	**Secondary Endpoints**
To describe the pneumococcal immune responses induced by 13vPnC with 2-PE in the MDV group and in the PFS group.	• The proportion of subjects with IgG concentrations equal to or above the defined threshold for each of the pneumococcal serotypes measured. o 1 month after the infant series in the MDV group and in the PFS group. o 1 month after the toddler dose in the MDV group and in the PFS group. • The serotype-specific IgG GMC for each of the pneumococcal serotypes measured o 1 month after the infant series in the MDV group and in the PFS group. o 1 month after the toddler dose in the MDV group and in the PFS group. • The serotype-specific OPA GMT for each of the pneumococcal serotypes measured o 1 month after the infant series in the MDV group and in the PFS group. o 1 month after the toddler dose in the MDV group and in the PFS group. • The proportion of subjects achieving a serotype-specific OPA titer ≥ the lower limit of quantitation (LLOQ) for each of the pneumococcal serotypes measured o 1 month after the infant series in the MDV group and in the PFS group. o 1 month after the toddler dose in the MDV group and in the PFS group.

3. STUDY DESIGN

- This is a randomized, open-label study in which subjects will receive either 13vPnC with 2-PE from an MDV or 13vPnC without 2-PE in a PFS (see Table 2).
- Subjects will be randomized in a 1:1 ratio to 1 of the 2 groups.
- Subjects will be vaccinated in a 3-dose infant series followed by a toddler dose.
- Subjects will have 2 blood draws of up to 5 mL at approximately 1 month after the infant series and approximately 1 month after the toddler dose.

Table 2. Study Vaccination Schedule

Randomization Group	Visit 1 6 Weeks	Visit 2 10 Weeks	Visit 3 14 Weeks	Visit 5 12 Months
Group 1: **MDV**	**MDV** DTP-Hib-HBV Rotavirus vaccine	**MDV** DTP-Hib-HBV Rotavirus vaccine	**MDV** DTP-Hib-HBV Rotavirus vaccine	**MDV** Hepatitis A virus vaccine
Group 2: **PFS**	**PFS** DTP-Hib-HBV Rotavirus vaccine	**PFS** DTP-Hib-HBV Rotavirus vaccine	**PFS** DTP-Hib-HBV Rotavirus vaccine	**PFS** Hepatitis A virus vaccine

Abbreviations: DTP-Hib-HBV = diphtheria, tetanus, and pertussis; *Haemophilus influenzae* type b; and hepatitis B virus vaccine; MDV = multidose vial; PFS = prefilled syringe.

3.1. Approximate Duration of Subject Participation

Each subject is expected to participate from the first vaccination at 6 weeks of age to a post–toddler dose blood draw. The total duration of subject participation is therefore up to approximately 14 months.

3.2. Approximate Duration of the Study

This study is anticipated to last approximately 20 months, assuming a 6-month recruitment period. The total duration may differ depending on the actual enrollment rate. The end of the study is the last visit of the last subject, which is scheduled 1 month after the toddler dose.

3.3. Approximate Number of Subjects

Approximately 300 subjects (150 subjects per group) will be randomized in this study at approximately 8 sites. The number of subjects enrolled at each site may vary based on enrollment capabilities of each site and the final number of sites.

4. SUBJECT ELIGIBILITY CRITERIA

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

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

4.1. Inclusion Criteria

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

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

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

3. Aged 6 weeks (42 to 72 days) at the time of vaccination. (The day of birth is considered Day 0.)

4. Available for the entire study period and whose parent(s)/legal guardian(s)/caregiver(s) can be reached by telephone.

5. Healthy infant as determined by medical history, physical examination, and judgment of the investigator.

6. Weight of 3.0 kg or greater at the time of vaccination.

4.2. Exclusion Criteria

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

1. Infant who is a direct descendant (child, grandchild) of

    - Investigator site staff members directly involved in the conduct of the study, or

    - Site staff members otherwise supervised by the investigator, or

    - 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 purely observational studies is acceptable.

3. Previous vaccination with licensed or investigational pneumococcal conjugate vaccine.

4. A previous anaphylactic reaction to any vaccine or vaccine-related component.

5. Contraindication to vaccination with pneumococcal conjugate vaccine, or any other vaccine or vaccine component. Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate intramuscular injection.

6. Known or suspected immune deficiency or suppression, including known human immunodeficiency virus infection.

7. Major known congenital malformation or serious chronic disorder.

8. Significant neurological disorder or history of seizure including febrile seizure, or significant stable or evolving disorders such as cerebral palsy, encephalopathy, hydrocephalus, or other significant disorders. Does not include resolving syndromes due to birth trauma such as Erb's palsy.

9. Other acute or chronic medical condition including recent 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.

10. Receipt of blood products or gamma globulin (including hepatitis B immunoglobulin and monoclonal antibodies, eg, Synagis).

4.3. Criteria for Temporarily Delaying Vaccine Administration

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

1. Current febrile illness (axillary temperature greater than or equal to 38.0°C [100.4°F]) or other acute illness within 48 hours before investigational product administration.

2. Subject is less than 5 days into a course of antibiotic therapy for other acute illness.

4.4. Subject Replacement

Subjects whose parent/legal guardian signed the informed consent document but are discontinued or withdrawn from the study before randomization will be replaced with additional subjects.

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 products are 13vPnC with 2-PE in MDVs and 13vPnC without 2-PE in PFSs.

5.1. Allocation to Investigational Product

The investigator's knowledge of the investigational product should not influence the decision to randomize a particular subject or affect the order in which subjects are randomized.

Allocation of subjects to vaccine groups will proceed through the use of an interactive response technology (IRT) system (interactive web-based response [IWR]). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the subject number. The site personnel will then be provided with a vaccine assignment, randomization number, and dispensable unit (DU) or container number when investigational product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the subject number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

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

5.2. Subject Compliance

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

5.3. Investigational Product Supplies

5.3.1. Dosage Form(s) and Packaging

13vPnC will be provided to the study site by the sponsor in MDVs and single-dose PFSs.

13vPnC contains saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to nontoxic diphtheria toxin CRM_{197}. The

vaccine is formulated to contain 2.2 μg of each saccharide, except for 4.4 μg of 6B, per 0.5-mL dose. The vaccine is formulated with 5 mM succinate buffer, 0.02% polysorbate 80, and 0.125 mg of aluminum as aluminum phosphate, per 0.5-mL dose.

13vPnC MDVs will also contain 4 mg of 2-PE per 0.5-mL dose. Four (4) doses of 13vPnC (2.0 mL) will be contained within each MDV. For the purposes of this study, only a single 0.5-mL dose will be administered from each of the MDVs.

5.3.2. Concomitant Study Vaccines

The following mandatory vaccines will be administered concomitantly with the investigational product as detailed in the schedule of activities:

- DTP-Hib-HBV
- Rotavirus vaccine
- Hepatitis A virus vaccine

DTP-Hib-HBV will be administered intramuscularly at 6, 10, and 14 weeks of age.

Rotavirus vaccine will be administered orally at 6, 10, and 14 weeks of age.

Hepatitis A virus vaccine will be administered intramuscularly at 12 months of age.

The SRSD for DTP-Hib-HBV, rotavirus vaccine, or hepatitis A virus vaccine is the local package insert.

5.4. Concomitant Medication(s)/Treatment(s)

5.4.1. Prior Treatment

Vaccines given at birth or before enrollment, including bacillus Calmette-Guerin (BCG) vaccine, hepatitis B virus (HBV) vaccine, or polio vaccine, may be given as per local recommendations.

All vaccinations received from birth until enrollment into the study will be recorded on the case report form (CRF).

5.4.2. Prohibited Vaccines and Medications

No pneumococcal vaccines (licensed or investigational) other than those described in this study may be given prior to or during the study.

Local anesthetic cream should not be used at the site of investigational product administration.

Prophylactic use of antipyretic and other pain medications to prevent symptoms that might occur as a result of study vaccine administration should be discouraged; however, it is

recognized that use of antipyretic medication is a matter of parental choice and local clinical practice.

5.4.3. Permitted Vaccines and Medications

In addition to the mandatory vaccines given concomitantly with the investigational product, other vaccines, including polio vaccine, may be administered as per local recommendations at any time. Vaccines concomitantly administered with the investigational product must be given in a different limb from that used to administer 13vPnC. All vaccinations received during the study will be recorded on the CRF.

Topical and inhaled corticosteroids are permitted during the course of the study.

Local anesthetic cream may be applied before the blood draws.

Antipyretic and other pain medications to treat symptoms are permitted.

Any medications, except those listed in Section 5.3.2, are permitted.

Details of any medication(s) given will not be collected in the CRF.

5.5. Preparation and Dispensing

Only qualified personnel should dispense the investigational products.

See the Investigational Product Manual (IP manual) or equivalent for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

5.6. Administration

Subjects will receive 1 dose of 13vPnC at each vaccination visit (Visits 1, 2, 3, and 5) in accordance with the study's schedule of activities.

13vPnC should be administered intramuscularly by injecting 0.5 mL into the anterolateral thigh muscle of the left leg at the vaccination visits.

For the purposes of this study, only a single 0.5-mL dose will be administered from each of the MDVs.

For DTP-Hib-HBV, rotavirus vaccine, and hepatitis A virus vaccine, dosage recommendations in the appropriate locally approved labeling should be followed. Concomitant vaccines must be given in a different limb from that used to administer 13vPnC.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute

hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

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

Investigational product administration details will be recorded on the CRF.

5.7. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products and other mandatory study vaccines, including DTP-Hib-HBV, rotavirus vaccine, and hepatitis A virus vaccine, 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.

5.8. 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.

5.8.1. Destruction of Investigational Product Supplies

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

6. STUDY PROCEDURES

6.1. Study Period

Visit windows are included in this protocol so that subjects in this study all have their vaccinations and blood draws within a broadly uniform time frame. However, because of the population under study, it is recognized that it may not always be possible to adhere to these windows (for example, because of subject illness).

6.1.1. Infant Series (6, 10, and 14 Weeks of Age)

6.1.1.1. Visit 1 (42 to 72 Days of Age)

- Obtain informed consent per local requirements from the subject's parent(s)/legal guardian(s) before performing study-specific procedures.
- Record the subject's demographic information (including date of birth, sex, and ethnicity).
- Obtain and record the subject's medical history including prior vaccinations.
- Perform a physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; extremities; neurological; musculoskeletal; and lymph nodes; including worsening of medical history conditions.
- Weigh the subject.
- Ensure that all inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met.

- On the day of vaccination, prior to vaccination, measure and record the subject's axillary temperature.

- After all entry criteria are confirmed, the subject will be randomized into 1 of the 2 vaccine groups using an IRT system (IWR), or equivalent system. An appropriate site staff member will use the IRT system to obtain the subject's investigational product DU or container number.

- Administer a single 0.5-mL intramuscular injection of 13vPnC from either an MDV or a PFS into the anterolateral thigh muscle of the left leg.

- Administer a single intramuscular dose of DTP-Hib-HBV into a different limb from that used to administer 13vPnC, according to local clinical practice.

- Administer a single dose of rotavirus vaccine according to local clinical practice.

- Observe the subject for at least 30 minutes after vaccination for any significant acute reactions. Any AEs noted during the observation period should be recorded in the subject's source documents and on the AE section of the CRF.

- Issue a caliper and a digital thermometer to the parent(s)/legal guardian(s)/caregiver(s) and provide instructions on their use.

- Issue a subject electronic diary (e-diary) to the parent(s)/legal guardian(s)/caregiver(s). Provide instruction on its completion 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 investigator immediately if any significant illness or hospitalization occurs during the study period, or if the subject experiences a large (>14 caliper units) local reaction.

- Schedule an appointment with the parent(s)/legal guardian(s)/caregiver(s) 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.

6.1.1.2. Visit 2 (28 to 42 Days After Visit 1)

- Review the subject's e-diary data and follow up on any ongoing local reactions or systemic events.

- Based on clinical evaluation, determine whether any AEs or SAEs have occurred since the last study visit and record them on the CRF.

- Review AEs that were ongoing from the previous visit and record their end dates or confirm that they are still ongoing.

- Ensure that the subject continues to be eligible for the study and meets none of the withdrawal criteria (Section 6.2).

- On the day of vaccination, prior to vaccination, measure and record the subject's axillary temperature.

- Ensure that the subject does not meet any of the temporary delay criteria (Section 4.3).

- An appropriate site staff member will use the IRT system to obtain the subject's investigational product DU or container number.

- Administer a single 0.5-mL intramuscular injection of 13vPnC from an MDV or a PFS into the anterolateral thigh muscle of the left leg.

- Administer a single intramuscular dose of DTP-Hib-HBV into a different limb from that used to administer 13vPnC, according to local clinical practice.

- Administer a single dose of rotavirus vaccine according to local clinical practice.

- Observe the subject for at least 30 minutes after vaccination for any significant acute reactions. Any AE noted during the observation period should be recorded on the source documents and on the AE section of the CRF.

- Issue a caliper and a digital thermometer (if necessary) to the parent(s)/legal guardian(s)/caregiver(s) and provide instructions on their use.

- Issue a subject e-diary (if necessary) to the parent(s)/legal guardian(s)/caregiver(s). Provide instruction on its completion 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 investigator immediately if any significant illness or hospitalization occurs during the study period, or if the subject experiences a large (>14 caliper units) local reaction.

- Schedule an appointment with the parent(s)/legal guardian(s)/caregiver(s) 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.

6.1.1.3. Visit 3 (28 to 42 Days After Visit 2)

- Review the subject's e-diary and follow up on any ongoing local reactions or systemic events.
- Based on clinical evaluation, determine whether any AEs or SAEs have occurred since the last study visit and record them on the CRF.
- Review AEs that were ongoing from the previous visit and record their end dates or confirm that they are still ongoing.
- Ensure that the subject continues to be eligible for the study and meets none of the withdrawal criteria (Section 6.2).
- On the day of vaccination, prior to vaccination, measure and record the subject's axillary temperature.
- Ensure that the subject does not meet any of the temporary delay criteria (Section 4.3).
- An appropriate site staff member will use the IRT system to obtain the subject's investigational product DU or container number.
- Administer a single 0.5-mL intramuscular injection of 13vPnC from an MDV or a PFS into the anterolateral thigh muscle of the left leg.
- Administer a single intramuscular dose of DTP-Hib-HBV into a different limb from that used to administer 13vPnC, according to local clinical practice.
- Administer a single dose of rotavirus vaccine according to local clinical practice.
- Observe the subject for at least 30 minutes after vaccination for any significant acute reactions. Any AE noted during the observation period should be recorded on the source documents and on the AE section of the CRF.
- Issue a caliper and a digital thermometer (if necessary) to the parent(s)/legal guardian(s)/caregiver(s) and provide instructions on their use.
- Issue a subject e-diary (if necessary) to the parent(s)/legal guardian(s)/caregiver(s). Provide instruction on its completion 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 investigator immediately if any significant illness or hospitalization occurs during the study period, or if the subject experiences a large (>14 caliper units) local reaction.
- Schedule an appointment with the parent(s)/legal guardian(s)/caregiver(s) 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.

6.1.2. Post–Infant Series Visit (18 Weeks of Age)

6.1.2.1. Visit 4 (28 to 42 Days After Visit 3)

- Collect the subject's e-diary.

- Review the subject's e-diary data and follow up on any ongoing local reactions or systemic events.

- Based on clinical evaluation, determine whether any AEs or SAEs have occurred since the last study visit and record them on the CRF.

- Review AEs that were ongoing from the previous visit and record their end dates or confirm that they are still ongoing.

- Ensure that the subject continues to be eligible for the study and meets none of the withdrawal criteria (Section 6.2).

- Collect an approximately 5-mL blood sample.

- Schedule an appointment with the parent(s)/legal guardian(s)/caregiver(s) for the next study visit.

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

6.1.3. Toddler Dose (12 Months of Age)

6.1.3.1. Visit 5 (365 to 420 Days of Age)

- Based on clinical evaluation, determine whether SAEs or newly diagnosed chronic medical conditions have occurred since the last study visit and record them on the CRF.

- Review AEs that were ongoing from the previous visit and record their end dates or confirm that they are still ongoing.

- On the day of vaccination, prior to vaccination, measure and record the subject's axillary temperature.

- Ensure that the subject continues to be eligible for the study and meets none of the withdrawal criteria (Section 6.2).

- Ensure that the subject does not meet any of the temporary delay criteria (Section 4.3).

- An appropriate site staff member will use the IRT system to obtain the subject's investigational product DU or container number.

- Administer a single 0.5-mL intramuscular injection of 13vPnC from an MDV or a PFS into the anterolateral thigh muscle of the left leg.

- Administer a single dose of hepatitis A virus vaccine into a different limb from that used to administer 13vPnC, according to local clinical practice.

- Observe the subject for at least 30 minutes after vaccination for any significant acute reactions. Any AE noted during the observation period should be recorded on the source documents and on the AE section of the CRF.

- Issue a caliper and a digital thermometer to the parent(s)/legal guardian(s)/caregiver(s) and provide instructions on their use.

- Issue a subject e-diary to the parent(s)/legal guardian(s)/caregiver(s). Provide instruction on its completion 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 investigator immediately if any significant illness or hospitalization occurs during the study period, or if the subject experiences a large (>14 caliper units) local reaction.

- Schedule an appointment with the parent(s)/legal guardian(s)/caregiver(s) 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.

6.1.4. Post–Toddler Dose Visit (13 Months of Age)

6.1.4.1. Visit 6 (28 to 42 Days After Visit 5)

- Collect the subject's e-diary.

- Review the subject's e-diary data and follow up on any ongoing local reactions or systemic events.

- Based on clinical evaluation, determine whether any AEs or SAEs have occurred since the last study visit and record them on the CRF.

- Review AEs that were ongoing from the previous visit and record their end dates or confirm that they are still ongoing.

- Collect a blood sample (approximately 5 mL).

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

6.1.5. Unscheduled Visits

If a local reaction at the pneumococcal injection site is greater than 14 caliper units (7.0 cm), a study site visit will be required to assess the extent of the reaction. The subject's parent(s)/legal guardian(s)/caregiver(s) should contact the study personnel to arrange for an additional visit to the study site for assessment by the investigator or a medically qualified member of the investigator's staff, 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 7.1.2.

- 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.

For the purpose of assessments performed during unscheduled visits, a medically qualified member of study staff is a study physician or a study nurse, as applicable to the investigator's local practice.

6.2. Subject Withdrawal

An investigator and/or sponsor can withdraw a subject from the study if deemed appropriate. In addition, if a subject fails to continue to meet the inclusion criteria, new information becomes available that would exclude the subject, or the subject develops a condition or situation that would meet exclusion criteria, the subject may be considered for withdrawal.

Reasons why a subject may discontinue or be withdrawn from the study include, but are not limited to, failure to meet entrance criteria (screening failure), AE, death, protocol violation, lost to follow-up, no longer willing to participate in the study, study terminated by sponsor, investigator declined further study participation, or any other reason. Subjects who have received the investigational product will not be replaced regardless of the reason for withdrawal.

Lost to follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. Lost to follow-up is defined by the inability to reach the subject's parent(s)/legal guardian(s)/caregiver(s) after a minimum of 2 documented phone calls, faxes, or emails as

well as lack of response by the subject's parent(s)/legal guardian(s)/caregiver(s) to 1 registered mail letter. All attempts should be documented in the subject's medical records.

If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

The subject's parent(s)/legal guardian(s) may withdraw the subject from the study at any time at their own request, or the subject 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's parent(s)/legal guardian(s)/caregiver(s). All attempts to contact the subject's parent(s)/legal guardian(s)/caregiver(s) and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow up with the subject's parent(s)/legal guardian(s)/caregiver(s) regarding any unresolved AEs.

If the subject's parent(s)/legal guardian(s) withdraw(s) the child from the study, and also withdraw(s) consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Withdrawal of consent:

Subjects whose parent(s)/legal guardian(s) request(s) to discontinue receipt of investigational product will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a subject's parent(s)/legal guardian(s) specifically withdraw(s) consent for any further contact with him or her or persons previously authorized by the subject's parent(s)/legal guardian(s) to provide this information. Subject's parent(s)/legal guardian(s) should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or posttreatment study follow-up. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7. ASSESSMENTS

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

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

7.1. 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 7.1.

Acute reactions within the first 30 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.

7.1.1. Electronic Diary

Subject's parent(s)/legal guardian(s)/caregiver(s) will be required to use an e-diary, based on appropriate technology, and will be asked to monitor and record local reactions and systemic events for 7 days following vaccination (Day 1 through Day 7, where Day 1 is the day of 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 will be collected in the e-diary in the evening daily during the e-diary reporting period.

Data on local reactions and systemic events reported on the e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or appropriately qualified designee) are required to review the e-diary data online at frequent intervals as part of the ongoing safety review. The investigator or designee must contact the subject's parent(s)/legal guardian(s)/caregiver(s) in order to obtain stop dates for any ongoing local reactions or systemic events on the last day that the e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

7.1.2. Local Reactions

Redness and swelling will be measured and recorded in caliper units (range: 1 to 14) for the first 7 days following vaccination (Days 1 to 7), and then categorized using the scale shown in Table 3. The measurements will then be recorded in the e-diary.

A caliper will be given to the subject's parent(s)/legal guardian(s)/caregiver(s) with instructions for measuring both redness and swelling at the injection site. Each caliper unit is equivalent to 0.5 cm. The parent(s)/legal guardian(s)/caregiver(s) will be asked to measure the largest diameters of the local reaction. Where a caliper measurement is between 2 values, the higher value should be reported. At the time of entry into the e-diary, the parent(s)/legal guardian(s)/caregiver(s) should record the maximum severity of the reaction since the previous entry into the e-diary.

Table 3. Local Reaction Grading Scale

	GRADE 1 mild	GRADE 2 moderate	GRADE 3[a] severe
Redness	1 to 4 caliper units (or measuring device units) = 0.5 to 2.0 cm	5 to 14 caliper units (or measuring device units) = 2.5 to 7.0 cm	>14 caliper units (or measuring device units) = >7.0 cm
Swelling	1 to 4 caliper units (or measuring device units) = 0.5 to 2.0 cm	5 to 14 caliper units (or measuring device units) = 2.5 to 7.0 cm	>14 caliper units (or measuring device units) = >7.0 cm
Pain at injection site (tenderness)	Hurts if gently touched (eg, whimpers, winces, protests, or withdraws)	Hurts if gently touched (with crying)	Causes limitation of limb movement

a. Local reactions >14 caliper units (>7.0 cm) should be assessed by the study site.

7.1.3. Systemic Events and Fever

The e-diary will be used to record the presence of systemic events (loss of or decreased appetite, drowsiness, and irritability) daily for 7 days (Day 1 to Day 7) after each vaccination, using the grading scale in Table 4.

A digital thermometer will be given to the subject's parent(s)/legal guardian(s) with instructions on how to measure the child's axillary temperature at home. Axillary temperature will be collected at evening bedtime daily for 7 days (Day 1 to Day 7) after each vaccination, and at any time during the 7 days when fever is suspected. The highest temperature for each day will be recorded in the e-diary.

Fever is defined as a temperature of ≥38.0°C (100.4°F).

Temperature will be measured and recorded to 1 decimal place and then categorized according to the scale for fever (see Table 4).

Table 4. Grading Scale for Fever and Systemic Events

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

Systemic Events	GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe
Decreased appetite (loss of appetite)	Decreased interest in eating	Decreased oral intake	Refusal to feed
Drowsiness (increased sleep)	Increased or prolonged sleeping bouts	Slightly subdued; interfering with daily activity	Disabling; not interested in usual daily activity
Irritability (fussiness) (synonymous with restless sleep; decreased sleep)	Easily consolable	Requiring increased attention	Inconsolable; crying cannot be comforted

7.2. Biological Samples

Serum samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the subject's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the informed consent document, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the subject's genetic material will be performed.

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

7.3. Immunogenicity

Serotype-specific IgG concentrations to the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) will be determined in all subjects from the blood sample taken 1 month after the infant series and 1 month after the toddler dose of 13vPnC.

To support the clinical development of Pfizer's pneumococcal conjugate vaccines, a high-throughput, multiplex direct Luminex-based immunoassay (dLIA) platform has been developed to replace the WHO standardized enzyme-linked immunosorbent assay (ELISA) platform. Pfizer's 13-plex dLIA was validated using immunized human serum that contains IgG antibodies against the Prevnar 13 serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. There are several advantages to using a multiplex assay approach over the WHO reference ELISA for testing clinical samples. While both measure pneumococcal serotype-specific IgG antibodies, the Luminex-based assay is performed in a multiplex format, which generates more results in a shorter period of time, requires less serum, and generates less laboratory waste compared to ELISA. In addition, in part because of its multiplex format, Pfizer's 13-plex pneumococcal dLIA platform accommodates 143 tests on a single assay plate, while the ELISA platform would require 36 assay plates to achieve the same number of tests.

An examination of the percentage of vaccine responders reaching IgG concentrations ≥0.35 μg/mL is historically based on the WHO reference ELISA, and the WHO Expert Committee has provided guidance on acceptable bridging strategies for manufacturers that use an alternative assay platform for clinical evaluations. To bridge the validated 13-plex dLIA to the WHO ELISA platform, a comprehensive bridging study was performed using residual serum from pivotal Prevnar 13 studies. On the basis of the bridging data submitted to, and approved by, the US Food and Drug Administration (FDA), an IgG threshold level of 0.35 μg/mL using the 13-plex dLIA platform is appropriate for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19F, and 23F, while lower threshold values for the 13-plex dLIA platform are justified for serotypes 5 (0.23 μg/mL), 6B (0.10 μg/mL), and 19A (0.12 μg/mL) in order to maintain the same proportion of vaccine responders reported using the ELISA platform.

Serotype-specific OPA assays for the 13 pneumococcal serotypes will be performed in all subjects from the blood samples taken 1 month after the infant series and 1 month after the toddler dose of 13vPnC, where sufficient sera are available. Results will be reported as antibody titers.

8. ADVERSE EVENT REPORTING

8.1. Requirements

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

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

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

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

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

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

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

8.1.1. Additional Details on Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject's parent(s)/legal guardian(s)/caregiver(s). In addition, each study subject's 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's parent(s)/legal guardian(s)/caregiver(s) provide(s) 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 4 and from Visit 5 to Visit 6.

Between Visit 4 and Visit 5, only newly diagnosed chronic medical conditions and SAEs will be reported. In addition, end dates will be reported for any events ongoing from the previous visit.

8.1.4.1. Reporting SAEs to Pfizer Safety

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

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the

investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

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

8.1.4.2. Recording Nonserious AEs and SAEs on the CRF

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

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

8.1.5. Causality Assessment

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

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

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

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

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

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

Additionally, AEs may include signs and symptoms resulting from:

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

8.2.2. Abnormal Test Findings

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

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

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

8.2.3. Serious Adverse Events

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

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

Or that is considered to be:

- An important medical event.

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

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

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

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

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

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

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

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

8.2.4. Hospitalization

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

Hospitalization does not include the following:

- Rehabilitation facilities;

- Hospice facilities;

- Respite care (eg, caregiver relief);

- Skilled nursing facilities;

- Nursing homes;

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

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

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

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

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

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

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

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

8.3. Severity Assessment

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, 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, 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 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.

Medication errors include:

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

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

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

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

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

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

8.4.4.2. Lack of Efficacy

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

8.5. Medical Device Complaint Reporting Requirements

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

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

9. DATA ANALYSIS/STATISTICAL METHODS

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

9.1. Sample Size Determination

Sample size is justified by the probability of detection of AEs and the precision of estimates of GMCs. The sample size of 150 per group offers reasonable detection probability of AEs commonly seen in other studies, and provides reasonable width of the confidence interval (CI) around the GMC.

The primary endpoints include the incidence of AEs in the MDV group. AE incidences were obtained from infant series data from a related Pfizer study, B4671001. The incidences from the 2 vaccine groups, MDV and PFS, were combined. The combined sample size was 500. The probability of detecting at least 1 indicated event is presented in Table 5. Incidences are sorted in descending order.

Table 5. Probability of Detection of at Least 1 Adverse Event in the Infant Series

	Incidence After Combining MDV and PFS (n=500 in Study B4671001)	Proposed Sample Size for MDV in Study B4671004	Probability of at Least 1 Indicated AE
Any AE	50.0%	150	100.0%
Any related AE	0.6%	150	59.5%
Any SAE	0.2%	150	25.9%

Abbreviations: MDV = multidose vial; PFS = prefilled syringe.

For the immunogenicity comparison of the MDV and PFS groups, 2-sided 95% CIs comparing the groups will be compiled, but no formal noninferiority criteria are specified.

Precision for GMCs is quantified by dividing the upper limit of the 95% CI by the GMC. Standard deviations (SDs) of each serotype's assays, in log scale, were derived from Table 21 in the B4671001 clinical study report (CSR). Assay SDs were obtained for both MDV and PFS intervals. CCI [redacted]

CCI [redacted]

CCI

[redacted]

9.2. Efficacy Analysis

9.2.1. Analysis of the Primary Endpoints

Not applicable.

9.2.2. Analysis of the Secondary Endpoints

The proportions of subjects with IgG ≥ the defined threshold will be accompanied by 2-sided 95% CIs. The Clopper-Pearson method will be used.

GMCs will be obtained by log transformation of concentrations, averaging the transformed values, then exponentiating the results. 95% confidence will also be obtained for CIs. The CIs will be calculated in the log scale with reference to the appropriate t-distribution. Then the lower and upper limits will be exponentiated.

Empirical reverse cumulative distribution curves (RCDCs) will be compiled for each serotype at each blood sampling time point.

Two (2)-sided 95% CIs comparing the 2 vaccine groups will also be compiled in order to quantify the differences between the 2 vaccine groups. For the proportions of subjects with IgG ≥ the defined threshold for each of the pneumococcal serotypes measured, the 2-sided 95% CI on MDV minus PFS will be compiled using the method of Chan and Zhang.[42] For the GMC, the 2-sided 95% CI on MDV minus PFS will be compiled, using the log concentrations, as a 2-sample CI on the difference between means. The t-distribution will be used. The lower and upper limits will be exponentiated, so the results will describe the ratio of MDV to PFS.

Assay results below the limit of quantification will be set to the limit of detection before analysis. Missing data will not be replaced or imputed.

Two (2) analysis populations will be defined for the infant immunogenicity analyses: infant evaluable and infant all-available immunogenicity. To be included in the infant evaluable immunogenicity population, the subject must

1. have been eligible,

2. have received 3 doses of vaccine,

3. have post–Dose 3 blood drawn within the prespecified time frame,

4. have at least 1 valid and determinate post–Dose 3 assay result, and

5. have no other major protocol violations.

To be included in the infant all-available immunogenicity population, a subject must have at least 1 valid and determinate assay result after Dose 3.

Two (2) analysis populations will be defined for the toddler immunogenicity analyses: toddler evaluable and toddler all-available immunogenicity. To be included in the toddler evaluable immunogenicity population, the subject must

1. have been eligible,

2. have received 3 doses of vaccine in the infant series and 1 toddler dose,

3. have post–Dose 4 blood drawn within the prespecified time frame,

4. have at least 1 valid and determinate post–Dose 4 assay result, and

5. have no other major protocol violations.

To be included in the toddler all-available immunogenicity population, a subject must have at least 1 valid and determinate assay result after Dose 4.

A subject could be evaluable (or all-available) in the infant series and all-available (or evaluable) for the toddler dose.

The primary immunogenicity populations for the infant and toddler analyses will be their respective evaluable populations.

Subjects in these populations will be assigned to their randomized vaccination regimen.

9.3. Analysis of Demographic Characteristics

The demographic characteristics that will be summarized using descriptive statistics include sex, ethnicity, and age at each vaccination.

9.4. Safety Analysis

Local injection site reactions, systemic events, and AEs will be summarized by vaccine group and by vaccination.

The proportions of subjects with local reactions at the injection site and systemic events reported on any day within the 7-day period after each vaccination will be estimated for each vaccine group. Local reactions will not be compiled for concurrent vaccinations.

Local reactions and systemic events that persist beyond Day 7 will be listed in the CSR.

AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA). AEs within 1 month after vaccination will be summarized by vaccine group for each vaccination separately. AEs will also be summarized from the first dose up to 1 month after the infant series.

SAEs will be summarized from the first dose up to 1 month after the toddler dose.

Newly diagnosed chronic medical conditions will be summarized from 1 month after the infant series up to the toddler dose.

All safety analyses will be performed on the safety population, which will include any subject with at least 1 vaccination. Subjects will be assigned to the vaccine actually received. If a subject receives different vaccines at different time points, then local reactions, systemic events, and AEs immediately following the vaccination will be assigned to the vaccine most recently received. Compilation of AEs or SAEs from the first infant dose up to the toddler dose will be assigned to the vaccine received. If a subject receives both vaccines during the infant series, then the subject will be assigned to the randomized vaccine group.

9.5. Interim Analysis

No formal interim analysis will be conducted for this study. However, as this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment or to support clinical development. This includes compilation of results of the infant series before completion of the toddler dose.

9.6. Data Monitoring Committee

This study will not use a data monitoring committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

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

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

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should

be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

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

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

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

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

12.3. Subject Information and Consent

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

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

maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

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

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

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

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

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

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

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Appendix 1. Abbreviations

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

Abbreviation	Term
2-PE	2-phenoxyethanol
7vPnC	7-valent pneumococcal conjugate vaccine
13vPnC	13-valent pneumococcal conjugate vaccine
ABCs	Active Bacterial Core surveillance
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCG	bacillus Calmette-Guerin
CAPiTA	Community-Acquired Pneumonia Immunization Trial in Adults
CI	confidence interval
CK	creatine kinase
CRF	case report form
CRM_{197}	cross-reactive material 197
CSA	clinical study agreement
CSR	clinical study report
CT	clinical trial
DCGI	Drugs Controller General of India
DILI	drug-induced liver injury
dLIA	direct Luminex-based immunoassay
DTaP	diphtheria, tetanus, and acellular pertussis vaccine
DTaP-IPV-Hib	diphtheria, tetanus, and acellular pertussis; inactivated poliovirus; and *Haemophilus influenzae* type b vaccine
DTP-Hib-HBV	diphtheria, tetanus, and pertussis; *Haemophilus influenzae* type b; and hepatitis B virus vaccine
DU	dispensable unit
EC	ethics committee
e-diary	electronic diary
EDP	exposure during pregnancy
ELISA	enzyme-linked immunosorbent assay
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMT	geometric mean titer
HBV	hepatitis B virus
ICH	International Council for Harmonisation

Abbreviation	Term
ID	identification
IgG	immunoglobulin G
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IPD	invasive pneumococcal disease
IPV	inactivated poliovirus vaccine
IRB	institutional review board
IRT	interactive response technology
IWR	interactive web-based response
LFT	liver function test
LLOQ	lower limit of quantitation
LSLV	last subject last visit
MDV	multidose vial
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
NOC	no objection certificate
OPA	opsonophagocytic activity
PASS	postauthorization safety study
PCD	primary completion date
PFS	prefilled syringe
PI	principal investigator
PT	prothrombin time
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SEC	subject expert committee
SRSD	single reference safety document
TBili	total bilirubin
Tdap	tetanus, low-dose diphtheria, and low-dose acellular pertussis vaccine
ULN	upper limit of normal
US	United States
WHO	World Health Organization

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