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Protocol B4671004

# 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

Statistical Analysis Plan
(SAP)

**Version:** 1.0

**Date:** 02 Jul 2017

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## TABLE OF CONTENTS



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## LIST OF TABLES



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# 1. VERSION HISTORY

This statistical analysis plan (SAP) for Study B4671004 is based on the final protocol amendment 1 dated 14 Feb 2017.

**Table 1. Summary of Major Changes in SAP Amendments**

| SAP Version | Change | Rationale |
|---|---|---|
| 1.0 | Not Applicable | Not Applicable |

# 2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B4671004. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

## 2.1. Study Objectives

### 2.1.1. Primary Objective

To describe the safety profile of 13-valent pneumococcal conjugate vaccine (13vPnC) with 2-phenoxyethanol (2-PE) in the multidose vial (MDV) group and without 2-PE in the prefilled syringe (PFS) group.

### 2.1.2. Secondary Objective

To describe the pneumococcal immune responses induced by 13vPnC with 2-PE in the MDV group and in the PFS group.

## 2.2. 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. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

### 3.1. Primary Endpoints

- 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.

Each day of vaccination will be considered Day 1.

### 3.2. Secondary Endpoints

- The proportion of subjects with immunoglobulin G (IgG) concentrations equal to or above the defined threshold for each of the pneumococcal serotypes measured:
  - 1 month after the infant series in the MDV group and in the PFS group.
  - 1 month after the toddler dose in the MDV group and in the PFS group.

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- The serotype-specific IgG geometric mean concentration (GMC) for each of the pneumococcal serotypes measured:
  - 1 month after the infant series in the MDV group and in the PFS group.
  - 1 month after the toddler dose in the MDV group and in the PFS group.
- The serotype-specific opsonophagocytic activity (OPA) geometric mean titer (GMT) for each of the pneumococcal serotypes measured:
  - 1 month after the infant series in the MDV group and in the PFS group.
  - 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:
  - 1 month after the infant series in the MDV group and in the PFS group.
  - 1 month after the toddler dose in the MDV group and in the PFS group.

The defined thresholds for IgG are listed below:

- ≥0.35 μg/mL will be used for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19F, and 23F.
- ≥0.23 μg/mL will be used for serotype 5.
- ≥0.10 μg/mL will be used for serotype 6B.
- ≥0.12 μg/mL will be used for serotype 19A.

### 3.3. Other Endpoints

Not applicable.

### 3.4. Baseline Variables and Study Conduct

#### 3.4.1. Demographic, Medical History, and Baseline Characteristic Variables

The demographic variables are age at randomization/first vaccination visit (in days), sex, race, ethnicity, and baseline weight. Age, in days, will be calculated as (randomization/first vaccination date – date of birth + 1). Weight at the time of the first vaccination (enrollment) is the baseline weight measured on the day of the first vaccination. Ages at the other vaccinations will also be compiled.

Medical history will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA).

### 3.4.2. E-Diary Completion

An electronic diary (e-diary) will be considered transmitted if any data for the local reactions or the systemic events are present on any day. If all data are missing for all items on the e-diary for every day following vaccination, then the e-diary will be considered not transmitted.

For transmitted e-diaries, the following variables will be defined: "Day 1," "Day 2," "Day 3," "Day 4," "Day 5," "Day 6," "Day 7," and "Day 1 to Day 7."

An e-diary will be considered complete if all expected data for all 7 days are available (ie, not missing) and data are valid. Otherwise, the e-diary will be considered incomplete.

For any given day, an e-diary will be considered complete if all expected data are available.

For completed e-diaries, the following variables will be defined: "Day 1," "Day 2," "Day 3," "Day 4," "Day 5," "Day 6," "Day 7," and "Day 1 to Day 7."

For e-diaries that are incomplete, an indicator variable for the percentage of days without data will be derived as follows:

=1, if data have been transmitted and are complete for 7 days (100%).

=2, if data have been transmitted and are complete for 6 days (≥75% to <100%).

=3, if data have been transmitted and are complete for 4 or 5 days (≥50% to <75%).

=4, if data have been transmitted and are complete for 2 or 3 days (≥25% to <50%).

=5, if data have been transmitted and are complete for 0 or 1 day (<25%).

### 3.4.3. Concomitant Vaccine(s)

Nonstudy vaccines will be categorized according to the World Health Organization (WHO) Drug Dictionary (WHODD).

## 3.5. Safety Endpoints

### 3.5.1. Adverse Events

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (see Section 6.4.1).

Tier 1 events: These are prespecified events of clinical importance and are maintained in a list in the product's safety review plan.

Tier 2 events: These are events that are not tier 1 but are "common." A MedDRA preferred term is defined as a tier 2 event if there are at least 4 subjects with the given preferred term in any vaccine group.

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Tier 3 events: These are events that are neither tier 1 nor tier 2 events.

### 3.5.2. Reactogenicity Endpoints

Reactogenicity data captured in the e-diary consist of local reactions (redness, swelling, and pain at the injection site [tenderness]) and systemic events (fever, decreased appetite [loss of appetite], drowsiness [increased sleep], and irritability [fussiness]).

#### 3.5.2.1. Local Reactions

Local reactions reported in the e-diary are redness, swelling, and pain at the injection site (tenderness).

Redness and swelling will be measured and recorded in caliper units (range: 1 to 14 and >14) for the first 7 days following vaccination (Days 1 to 7), and then categorized using the scale shown in Table 3 below. 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. When 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<br>Mild | GRADE 2<br>Moderate | GRADE 3[a]<br>Severe |
|---|---|---|---|
| Redness | 1 to 4 caliper units (or measuring device units)<br>=<br>0.5 to 2.0 cm | 5 to 14 caliper units (or measuring device units)<br>=<br>2.5 to 7.0 cm | >14 caliper units (or measuring device units)<br>=<br>>7.0 cm |
| Swelling | 1 to 4 caliper units (or measuring device units)<br>=<br>0.5 to 2.0 cm | 5 to 14 caliper units (or measuring device units)<br>=<br>2.5 to 7.0 cm | >14 caliper units (or measuring device units)<br>=<br>>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.

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Although the e-diary was designed in such a way that the parent could not skip a question without answering it, the possibility of conflicting responses still exists. For redness and swelling, caliper units could be recorded as no or the root question could be missing an answer; or redness/swelling could be recorded as yes with a caliper unit of zero (if defaulted by the database). The combination of no with a caliper unit recorded will result in the answer to the root question being considered yes. The combination of yes with a caliper unit equal to 0 will result in the caliper unit being considered ">0." A missing value for the root question with a positive value for caliper units will result in the answer to the root question being considered yes. These rules are summarized in Table 4 below.

**Table 4. Data Conventions for Redness and Swelling in the Presence of Inconsistent or Missing Responses**

| Reported Response | | Recoded Response | |
|---|---|---|---|
| **Present** | **Caliper Units** | **Present** | **Caliper Units** |
| Missing | Missing | Missing | Missing |
| Missing | 0 | Missing | Missing |
| Missing | 1-14 | Yes | 1-14 |
| Missing | >14 | Yes | >14 |
| | | | |
| Yes | Missing | Yes | Missing |
| Yes | 0 | Yes | >0 |
| Yes | 1-14 | Yes | 1-14 |
| Yes | >14 | Yes | >14 |
| | | | |
| No | Missing | No | Missing |
| No | 0 | No | Missing |
| No | 1-14 | Yes | 1-14 |
| No | >14 | Yes | >14 |

Redness and swelling will be further categorized according to the following scale based on the recoded responses:

= missing, if both variables (presence/absence and caliper units) are missing or otherwise unavailable, or if present (ie, yes) and caliper units are missing.

=0 (absent), if not present (ie, no) and caliper units are missing.

=1 (mild), if present and the area is 0.5 to 2.0 cm (1 to 4 caliper units), or if present and caliper units are >0.

=2 (moderate), if present and the area is 2.5 to 7.0 cm (5 to 14 caliper units).

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=3 (severe), if present and the area is >7.0 cm (>14 caliper units).

In addition, the maximum diameter of the affected area for redness and swelling will be determined. The maximum diameter will be derived as follows:

= xx (maximum actual value), if present on at least 1 day in the required interval and caliper units are >0.

= missing, if values are a mixture of absent and missing for the required days in the interval.

=0, if all values are absent for all required days in the interval.

For the purpose of creating an indicator variable for tenderness on each day, the following algorithm will be used:

=1 (present), if tenderness is recorded as present or as interferes with limb movement.

=0 (absent), if tenderness is recorded as none discernible.

= missing, if tenderness is missing.

For the local reactions, 3 more derivations are required: whether or not a specific reaction occurred on "any day," whether or not the subject experienced "any local reaction" on a given day, and whether or not the subject experienced "any local reaction" on "any day."

For the occurrence of a specific reaction on "any day," the following algorithm is used and is summarized in Table 5:

=1 (yes), if the subject reports the specified reaction as yes (or present) on any day in the required interval.

=0 (no), if the subject reports the specified reaction as no (or absent) for all days in the required interval.

= missing, if the subject reports the specified reaction as a combination of no and missing for all days in the required interval.

**Table 5. Derivation of "Each Day" and "Any Day" for Local Reactions in the Presence of Missing Values**

| Subject | Day | Response | Each Day | Any Day |
|---|---|---|---|---|
| **1** | 1 | Missing | Missing | |
| | 2 | No | No | |
| | 3 | Yes | Yes | |
| | 4 | No | No | Yes |
| | | | | |

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**Table 5. Derivation of "Each Day" and "Any Day" for Local Reactions in the Presence of Missing Values**

| Subject | Day | Response | Each Day | Any Day |
|---|---|---|---|---|
| **2** | 1 | No | No | |
| | 2 | Yes | Yes | |
| | 3 | Missing | Missing | |
| | 4 | No | No | Yes |
| | | | | |
| **3** | 1 | No | No | |
| | 2 | Missing | Missing | |
| | 3 | No | No | |
| | 4 | No | No | Missing |
| | | | | |
| **4** | 1 | No | No | |
| | 2 | No | No | |
| | 3 | No | No | |
| | 4 | No | No | No |

Note: These are examples of derivations. The electronic diary will contain data for 7 days.

For "any local reaction" on a given day, a similar rule applies:

=1 (yes), if the subject reports any reaction as yes (or present) on the given day in the required interval.

=0 (no), if the subject reports all reactions as no (or absent) on the given day in the required interval.

= missing, if the subject reports all reactions as a combination of no and missing on the given day in the required interval.

For "any local reaction on any day," a similar rule applies:

=1 (yes), if the subject reports any reaction as yes (or present) on any day in the required interval.

=0 (no), if the subject reports all reactions as no (or absent) for all days in the required interval.

= missing, if the subject reports all reactions as a combination of no and missing.

In summarizing local reactions (over all expected days), the derivation of "any reaction" in the presence of missing values is depicted in Table 6.

**Table 6. Derivation of Any Reaction for Local Reactions in the Presence of Missing Values**

| Number of Reactions Reported | Number of Missing Values | Summary Value |
|---|---|---|
| One or more | None | Reaction |
| One or more | One or more | Reaction |
| None | None | No reaction |
| None | One or more | Missing |

The duration of each reaction will be calculated in days from the start of the first reported reaction to resolution of the last reported reaction, inclusive, ie, end date – start date + 1. Resolution information is the last day on which the report was recorded in the e-diary, or the date the reaction ended if it continued beyond Day 7 (or the last record in the e-diary if before Day 7). If there is no known date on which the reaction ended, then duration will be missing. Subjects with no reported reaction have no duration because it is not applicable.

### 3.5.2.2. Systemic Events and Fever

The systemic events reported in the e-diary after each vaccination are loss of or decreased appetite, drowsiness, and irritability. These will be recorded as present or absent.

#### 3.5.2.2.1. Systemic Events

The presence of systemic events will be recorded in the e-diary daily for 7 days (Day 1 to Day 7) after each vaccination, using the grading scale in Table 7.

**Table 7. Systemic Event Grading Scale**

| Systemic Events | GRADE 1<br>Mild | GRADE 2<br>Moderate | GRADE 3<br>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 |

For decreased appetite or loss of appetite on each day, an indicator variable will be created for decreased appetite on each day, using the following algorithm:

= missing, if decreased appetite is missing.

=0 (none), if no loss of appetite.

=1 (mild), if decreased interest in eating.

=2 (moderate), if decreased oral intake.

=3 (severe), if refusal to feed.

For drowsiness (synonymous with increased sleep) on each day, an indicator variable will be created for drowsiness on each day, using the following algorithm:

= missing, if increased sleep is missing.

=0 (none), if no synonym with increased sleep.

=1 (mild), if increased or prolonged sleeping bouts.

=2 (moderate), if slightly subdued; interfering with daily activity.

=3 (severe), if disabling; not interested in usual daily activity.

For irritability (fussiness, synonymous with restless sleep; decreased sleep) on each day, an indicator variable will be created for irritability on each day, using the following algorithm:

= missing, if irritability is missing.

=0 (none), if no fussiness.

=1 (mild), if easily consolable.

=2 (moderate), if requiring increased attention.

=3 (severe), if inconsolable; crying that cannot be comforted.

For the systemic events, 3 more derivations are required: whether or not a specific reaction occurs on “any day”, whether or not the subject experiences “any systemic event” on a given day, and whether or not the subject experiences “any systemic event” on any day. Algorithms similar to those described in Section 3.5.2.1 will be used.

#### 3.5.2.2.2. Fever

The subject's axillary temperature will be recorded in the e-diary for 7 days (Day 1 to Day 7) after each vaccination. The protocol defines fever as a temperature ≥38.0°C (or ≥100.4°F). If more than 1 temperature was taken for a subject on the same day, the highest temperature will be recorded in the e-diary.

Fever will be classified for a given day based on the following scale:

=., if temperature is missing, or otherwise unavailable.

=0 (absent), if temperature is not missing and <38.0°C (100.4°F).

=1, if temperature is ≥38.0°C (100.4°F) and ≤38.4°C (101.1°F).

=2, if temperature is ≥38.5°C (101.2°F) and ≤38.9°C (102.0°F).

=3, if temperature is ≥39.0°C (102.1°F) and ≤40.0°C (104.0°F).

=4, if temperature is >40.0°C (104.0°F).

Each category of fever will be included as a separate event in summaries of systemic events.

Similar to the derivations specified for local reactions (Section 3.5.2.1), fever each day and duration of fever will be derived. However, "each day" and "duration" will be limited to temperature ≥38.0°C [≥100.4°F]) only.

## 4. ANALYSIS POPULATIONS

Each subject will be assessed to determine if he or she meets the criteria for inclusion in each analysis population. Classifications will be documented per standard operating procedures. Assessment of subject inclusion in the infant populations may be completed before all toddler-dose procedures are completed.

### 4.1. Evaluable Analysis Populations

The evaluable immunogenicity population will be defined for the 3-dose infant series and the toddler dose separately.

The infant evaluable immunogenicity population will include all subjects who:

1. met all eligibility criteria,
2. were aged 6 weeks (42 to 72 days, inclusive) at the time of the first vaccination,
3. have received 3 doses of vaccine that was randomly assigned to them,

4. have post–Dose 3 blood drawn within 27 to 56 days, inclusive, after the third vaccination,

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

6. have no other major protocol violations.

The toddler evaluable immunogenicity population will include all subjects who:

1. met all eligibility criteria,

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

3. have post–Dose 4 blood drawn within 27 to 56 days, inclusive, after the fourth vaccination,

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

5. have no other major protocol violations.

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

### 4.2. All-Available Immunogenicity Populations

The all-available immunogenicity population will be defined for the 3-dose infant series and the toddler dose separately.

The infant all-available immunogenicity population will include all subjects who have at least 1 valid and determinate assay result after Dose 3. The toddler all-available immunogenicity population will include all subjects who have at least 1 valid and determinate assay result after Dose 4.

### 4.3. Safety Analysis Populations

Separate safety populations will be defined for the infant series and the toddler dose. Each safety population will include all subjects who receive at least 1 dose of the investigational product for the indicated regimen. In each population 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. However, subjects who receive both vaccines during the infant series will be assigned to their randomized vaccine group for this compilation of AEs or SAEs.

Subjects who lack any safety data for a particular vaccination will be excluded from analysis.

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Subjects vaccinated but not randomized will be included in the safety population for safety analysis. The results from these subjects will be reported under the group corresponding to the vaccine they actually received.

### 4.4. Other Populations

Not applicable.

## 5. GENERAL METHODOLOGY AND CONVENTIONS

### 5.1. Hypotheses and Decision Rules

No formal statistical hypothesis test will be performed. There are also no formal statistical decision rules for this study and a descriptive estimation approach will be used to assess all study objectives regarding safety and immunogenicity in the study.

Point estimates and nominal 95% confidence intervals (CIs) will be provided for all safety and immunogenicity endpoints at each planned analysis.

No formal multiplicity adjustments will be applied due to multiple endpoints or multiple looks of the same endpoint.

### 5.2. General Methods

Unless otherwise explicitly stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum. Descriptive statistics for categorical variables are the percentage (%) and the numerator (n) and the denominator (N) used in the percentage calculation.

#### 5.2.1. Analyses for Binary Data

The exact CI (Clopper-Pearson CI) for a single proportion of an individual group will be computed using the F distribution. If r is the number of responses and n is the number of subjects, then it follows that p=r/n is the estimate of the proportion of responses. An exact 95% CI can be computed by solving the following 2 equations. For the lower limit $P_L$,

$$P_L = \frac{rF_L}{(rF_L + (n - r + 1))}$$

and for the upper limit $P_u$,

$$P_u = \frac{(r+1)F_u}{(n-r) + (r+1)F_u}$$

where $F_L$ is the quantile from the F distribution for α=0.025, with numerator degrees of freedom equal to 2r and denominator degrees of freedom equal to 2(n–r+1). $F_U$ is the quantile from the F distribution for α=0.975, with numerator degrees of freedom equal to 2(r+1) and denominator degrees of freedom equal to 2(n–r). When r equals 0, $F_L$ should be set equal to 1.0 so $P_L$ equals 0. When r equals n, $F_U$ should be set equal to 1.0 so $P_U$ equals 1.0.

The CI using the F distribution is described in Collett (1991) and implemented in SAS PROC FREQ.

Similarly, for the safety results, the exact 2-sided 95% CIs will be provided by vaccine group for all primary safety endpoints, ie, proportions of subjects reporting local reactions, systemic events, and AEs.

The 2-sided 95% CI on MDV minus PFS will be compiled using the method of Chan and Zhang (1999), but only for tier 1 and tier 2 events.

### 5.2.2. Analyses for Continuous Data

For each vaccine group, the GMCs and GMTs and the associated 95% CIs at 1 month after the infant series and 1 month after the toddler dose will be provided. The GMC or GMT will be calculated as the mean of the assay results after making the logarithmic transformation and then back transformation to the antilog scale. Two-sided 95% CIs will be constructed by back transformation of the CI for the mean of the logarithmically transformed assay results computed based on the Student t distribution.

For the GMCs, 2-sided 95% CIs for the ratio of 2 geometric means (MDS divided by PFS) will be compiled by back transformation of the CIs for the mean difference of the 2 logarithmically transformed assay results computed using the Student t distribution. The mean difference of the logarithmically transformed results is equivalent to the mean of the ratio on the logarithmic scale: log (x/y) = (log x) – (log y).

Similarly, for the GMTs, 2-sided 95% CIs for the ratio of 2 geometric means (MDS divided by PFS) will be constructed.

Reverse cumulative distribution curves (RCDCs) will be presented graphically by vaccine group (MDV, PFS) for each serotype-specific pneumococcal IgG antibody concentration and OPA titer after the infant series and after the toddler dose.

## 5.3. Methods to Manage Missing Data

### 5.3.1. Immunogenicity Data

The LLOQs by serotype for Pfizer's Luminex-based immunoassay were set as shown in Table 8.

**Table 8. LLOQs for the Luminex-Based Immunoassay**

| Serotype | LLOQ (µg/mL) |
|---|---|
| 1 | 0.002 |
| 3 | 0.004 |
| 4 | 0.005 |
| 5 | 0.002 |
| 6A | 0.005 |
| 6B | 0.015 |
| 7F | 0.003 |
| 9V | 0.013 |
| 14 | 0.005 |
| 18C | 0.002 |
| 19A | 0.038 |
| 19F | 0.012 |
| 23F | 0.009 |

Abbreviation: LLOQ = lower limit of quantitation.

The OPA LLOQ titer for each serotype is as follows: 1, 18; 3, 12; 4, 21; 5, 29; 6A, 37; 6B, 43; 7F, 113; 9V, 141; 14, 35; 18C, 31; 19A, 18; 19F, 48; and 23F, 13.

Any antibody concentration or antibody titer below the LLOQ will be assigned to the lower limit of detection (LOD), defined as 0.5 × LLOQ. No other assay data will be imputed in the analyses. All immunogenicity analyses will be performed after the imputation of the antibody concentrations or antibody titers that are below the LLOQ.

### 5.3.2. Safety Data

Handling of missing information related to safety data, such as a missing or partially missing date, will be in accordance with Pfizer reporting standards.

For derived variables in reactogenicity data, if any day of the 7-day e-diary is available, the "Day 1 to Day 7" data will be considered to be nonmissing for analysis after each dose. The proportion of subjects with missing reactogenicity data will also be summarized by each dose in the infant series and the toddler dose for each vaccine group. The denominator will be the number of subjects who receive the scheduled vaccination.

# 6. ANALYSES AND SUMMARIES

## 6.1. Primary Endpoint(s)

**Endpoints:** Safety endpoints in Section 3.1.

- Analysis intervals**:**

  Endpoints for local reactions and systemic events: 7 days after each dose of the infant series and the toddler dose.

  Endpoints for AEs: from the first dose up to 1 month after the infant series. Also from the toddler dose up to 1 month after the toddler dose.

  Endpoints for SAEs: from the first dose up to 1 month after the toddler dose.

  Endpoint for newly diagnosed chronic medical conditions: from 1 month after the infant series up to the toddler dose.

- Analysis population**:** Infant or toddler safety population, as relevant. SAE analysis will include subjects in either the infant or toddler safety population.

- Analysis methodology**:** Descriptive.

- Supporting objective: Primary objective.

**Reporting Results:**

The number, proportion, and corresponding 95% CI will be presented for each vaccine group for each infant dose and the toddler dose.

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

## 6.2. Secondary Endpoints

**Endpoints:** Immunogenicity endpoints in Section 3.2.

**Endpoint:** The proportion of subjects with IgG concentration equal to or above the defined threshold for each of the pneumococcal serotypes measured.

- Analysis time points**:** 1 Month after the infant series and 1 month after the toddler dose.

- Analysis populations**:** Evaluable immunogenicity populations (infant and toddler) and all-available immunogenicity populations (infant and toddler).

- Analysis methodology**:** Descriptive.

- Supporting objective: Secondary objective.

**Reporting Results:**

The numerator and denominator used for percentage, the percentage, and associated 95% CI will be presented for each vaccine group for the infant series and the toddler dose. The differences (MDV minus PFS) in percentage and corresponding CIs for the infant series and the toddler dose will also be presented.

**Endpoint:** The serotype-specific IgG GMC for each of the pneumococcal serotypes measured.

- Analysis time points**:** 1 Month after the infant series and 1 month after the toddler dose.
- Analysis population**:** Evaluable immunogenicity populations and all-available immunogenicity populations.
- Analysis methodology**:** Descriptive.
- Supporting objective: Secondary objective.

**Reporting Results:**

The number of subjects, GMC, and associated 95% CI will be presented for each vaccine group for the infant series and the toddler dose. The geometric mean ratios (MDV divided by PFS) and corresponding CIs will also be presented.

**Endpoint:** The serotype-specific OPA GMT for each of the pneumococcal serotypes measured.

- Analysis time points**:** 1 Month after the infant series and 1 month after the toddler dose.
- Analysis populations**:** Evaluable immunogenicity populations and all-available immunogenicity populations.
- Analysis methodology**:** Descriptive.
- Supporting objective: Secondary objective.

**Reporting Results:**

The number of subjects, GMT, and associated 95% CI will be presented for each vaccine group for the infant series and the toddler dose. The geometric mean ratios (MDV divided by PFS) and corresponding CIs will also be presented.

**Endpoint:** The proportion of subjects achieving a serotype-specific OPA titer ≥ LLOQ for each of the pneumococcal serotypes measured.

- Analysis time points**:** 1 Month after the infant series and 1 month after the toddler dose.
- Analysis populations**:** Evaluable immunogenicity populations and all-available immunogenicity populations.
- Analysis methodology**:** Descriptive.
- Supporting objective: Secondary objective.

**Reporting Results:**

The numerator and denominator used for percentage, the percentage, and associated 95% CI will be presented for each vaccine group for the infant series and the toddler dose. The differences (MDV minus PFS) and corresponding CIs will also be presented for both the infant series and the toddler dose.

AEs occurring prior to the first vaccination will be excluded from AE analysis, unless the severity increases after dosing. AEs occurring between the informed consent document signoff and prior to the first vaccination will be summarized separately.

Any AE that starts in the infant series and continues past the toddler dose will be assigned only in the infant series.

For tier 1 and tier 2 events, the proportion of AEs observed in each vaccine group will be presented along with the point estimates and associated 95% CIs of the risk difference (the difference of incidence rates) between MDV and PFS. The 95% CIs will be calculated using the Chan and Zhang method described in Section 5.2.1.

For tier 1 events, p-values from Chan and Zhang's method will be calculated and included in the presentations. AEs will be arranged in the output sorted in descending order of point estimates of the risk difference (the difference of incidence rates) within system organ class.

### 6.3. Baseline and Other Summaries and Analyses

#### 6.3.1. Study Conduct: Subject Disposition, Vaccine Administration, Blood Samples, and Screen Failures

The numbers and percentages of subjects who are randomized will be included in the subject disposition summary: screening, open-label vaccine administration, and follow-up will be summarized. The reasons for withdrawal will also be tabulated. The reasons for withdrawal will be those specified in the database; no rewording/recoding will be done.

Subjects excluded from the evaluable immunogenicity population will also be summarized with reasons for exclusion.

The numbers and percentages of subjects randomized, vaccinated, and providing blood samples within the prespecified time frame, as well as before and after the specified time frame, will be tabulated for each vaccine group and for the total.

A listing of noncompliant vaccine administration will be provided. The protocol deviations will be listed. Subjects who do not receive the vaccine as randomized will be listed. A listing of subjects who withdrew because of AEs will be provided.

All randomized subjects will be used to generate these tables. All of the summary tables will be presented for each vaccine group and for the total.

Subjects who sign the informed consent document but are screen failures will be also summarized separately for each vaccine group.

### 6.3.2. Demographic, Medical History, and Baseline Characteristics

Descriptive summary reports for demographic characteristics will be provided for each vaccine group for the evaluable immunogenicity (infant and toddler), all-available immunogenicity (infant and toddler), and safety (infant and toddler) populations.

Descriptive summary reports for medical history will be provided for each vaccine group for the infant safety population only.

### 6.3.3. E-Diary Completion

Variables defined in Section 3.5.2 will be summarized with descriptive statistics for each vaccine group and for the total (ie, MDV and PFS combined) after each dose in the infant series and after the toddler dose. The respective safety populations will be used.

### 6.3.4. Analyses of Missing Immunogenicity Values

For each serotype, the number of subjects with missing values at each blood sampling point will be provided. Missing antibody concentrations and IgG concentrations will be compiled separately.

## 6.4. Other Safety Summaries and Analyses

All safety analyses will be summarized based on the safety populations in accordance with Pfizer reporting standards.

### 6.4.1. Adverse Events

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an AE or a group of AEs. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

The 3-tier approach is discussed in Section 3.5.1. The statistical methodology is described in Section 5.2.1.

Besides the primary safety endpoints described in Section 3.1, incidences of SAEs will also be compiled for the intervals from the first vaccination up to 1 month after the infant series, from 1 month after the infant series up to the toddler dose, and from the toddler dose up to 1 month after the toddler dose. The first 2 intervals will be analyzed using the infant safety population. The third interval, from the toddler dose up to 1 month after the toddler dose, will be analyzed using the toddler safety population.

### 6.4.2. Unscheduled Visits (Unplanned Visits) for Severe Reactions

A listing will be generated for all of the subjects with unscheduled/unplanned visits because of severe (Grade 3) reactions.

### 6.4.3. Physical Examinations, Including Vital Signs

Descriptive summary tables will be provided in accordance with Pfizer reporting standards.

### 6.4.4. Nonstudy Vaccinations and Nonstudy Medications

Nonstudy vaccinations will be summarized descriptively. Nonstudy medications are not collected in this study.

## 7. INTERIM ANALYSES

No formal interim analysis will be conducted. 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.

## 8. REFERENCES

1. Collett D. *Modelling Binary Data*. London: Chapman & Hall; 1991.

2. Chan ISF, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. *Biometrics.* 1999;55(4):1201-9.