Protocol B1851190

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

Statistical Analysis Plan
(SAP)

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1. VERSION HISTORY

This statistical analysis plan (SAP) for Study B1851190 is based on the protocol dated 05 Dec 2017.

Table 1.   Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B1851190. 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 Objective

To describe the safety profile of 13-valent pneumococcal conjugate vaccine (13vPnC) in pediatric subjects 6 to 17 years of age.

2.2. Study Design

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

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

- Local reactions within 7 days after vaccination.

- Systemic events within 7 days after vaccination.

- Adverse events (AEs) within 1 month after vaccination.

3.2. Secondary Endpoints

Not applicable.

3.3. Other Endpoints

Not applicable.

3.4. Safety Endpoints

3.4.1. Reactogenicity Endpoints

Reactogenicity data captured in the electronic diary (e-diary) after 13vPnC vaccination consist of local reactions (redness, swelling, and pain) and systemic events (fever, fatigue, headache, vomiting, diarrhea, muscle pain, and joint pain).

3.4.1.1. Local Reactions

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

Redness and swelling will be measured and recorded in measuring device units for 7 days following vaccination (Day 1 to 7), and then categorized using the scale shown in Table 2 below. The measurements will then be recorded in the e-diary.

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

Pain at the vaccine injection site will be assessed by the subject's parent(s)/legal guardian(s)/caregiver(s) as mild, moderate, or severe according to the grading scale in Table 2 below.

Table 2.   Grading Scale for Local Reactions

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

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

For events that were ongoing on the last day that the e-diary was completed, the end date will be collected in the CRF.

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, device units could be recorded with no or missing answer to the root question; or, redness/swelling could be recorded as yes with a measuring device unit of zero (if defaulted by the database). The combination of no with a device unit recorded will result in the answer to the root question being considered yes. The combination of yes with a device equal to 0 will result in the measuring device unit being considered ">0." A missing value for the root question with a positive value for measuring device units will result in the answer to the root question being considered yes. These rules are summarized in Table 3 below.

Table 3.   Data Conventions for Redness and Swelling in the Presence of Inconsistent or Missing Responses

Reported Response		Recoded Response	
Present	Measuring Device Units	Present	Measuring Device 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:

=•, if both variables (presence/absence and device units) are missing or otherwise unavailable, or if present and device units are missing;

=0 (absent), if not present and measuring device units are missing;

=1 (mild), if present and area is 0.5 to 2.0 cm (1 to 4 measuring device units), or if present and measuring device units are ">0";

=2 (moderate), if present and area is 2.1 to 7.0 cm (5 to 14 measuring device units);

=3 (severe), if present and area is >7.0 cm (>14 measuring device 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 measuring device units are >0;

=•, if values are a mixture of absent and missing for 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 pain at the injection site (tenderness) on each day, the following algorithm will be used:

=•, if tenderness is missing;

=0 (absent), if tenderness is not present;

=1 (mild), if does not interfere with activity;

=2 (moderate), if some interference with activity;

=3 (severe), if prevents daily routine activity.

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 4:

=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;

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

Table 4.   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
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

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;

=•, 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;

=•, 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 5 below.

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Table 5.   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 start of the first reported reaction to resolution of the last reported reaction, inclusive. 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.

3.4.1.2. Systemic Events, Including Fever

The systemic events reported in the e-diary following vaccination are fatigue, headache, vomiting, diarrhea, muscle pain, and joint pain. These will be recorded as present or absent. Fever is also included as a systemic event.

3.4.1.2.1. Fever

The subject's temperature will be recorded in the e-diary for 7 days following vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination). If more than 1 temperature was taken for a subject on the same day, the highest temperature will be recorded in the e-diary.

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

Temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis according to Table 6 below.

Table 6.   Ranges for Fever (All Subjects)

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

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) but ≤38.4°C (101.1°F)

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

=3, if temperature is ≥39.0°C (102.1°F) but ≤40°C (104.0°F)

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

Similar to the derivations specified for local reactions, any day, any fever, any fever on any day, and duration of fever will be derived. Duration will be calculated for any fever (temperature ≥38.0°C [≥100.4°F]). Each category of fever will be included as a separate event in summaries of systemic events.

3.4.1.2.2. Systemic Events

The presence of systemic events (fatigue, headache, vomiting, diarrhea, muscle pain, and joint pain) will be recorded in the e-diary daily for 7 days (Day 1 through Day 7, where Day 1 is the day of vaccination) after vaccination, using the grading scale in Table 7 below.

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

Table 7. Grading Scale for Systemic Events

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

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For fatigue (synonymous with tiredness in the e-diaries), headache, muscle pain, and joint pain on each day, an indicator variable will be created for them for each day separately, using the following algorithm:

= •, if fatigue, headache, muscle pain, or joint pain is missing

= 0 (none), if no fatigue, headache, muscle pain, or joint pain

= 1 (mild), if does not interfere with activity

= 2 (moderate), if some interference with activity

= 3 (severe), if prevents daily routine activity

For vomiting on each day, an indicator variable will be created for each day using the following algorithm:

= •, if vomiting is missing

= 0 (none), if no vomiting

= 1 (mild), if 1 to 2 times in 24 hours

= 2 (moderate), if more than 2 times in 24 hours

= 3 (severe), if requires intravenous hydration

For diarrhea on each day, an indicator variable will be created for each day using the following algorithm:

= •, if diarrhea is missing

= 0 (none), if no diarrhea

= 1 (mild), if 2 to 3 loose stools in 24 hours

= 2 (moderate), if 4 to 5 loose stools in 24 hours

= 3 (severe), if 6 or more loose stools in 24 hours

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 other systemic event on a given day, and whether or not the subject experiences any other systemic events on any day. Similar algorithms described in Section 3.4.1.1 will be used.

3.5. Study Conduct

3.5.1. E-Diary Completion

An 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 all 7 days 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 – Day 7."

An e-diary will be considered completed 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 – 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 ($\geq$75% to <100%)

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

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

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

3.5.2. Demographic, Medical History, and Baseline Characteristics Variables

The demographic variables are age at first vaccination visit (in years) at Visit 1, sex, race, and ethnicity. Age will be calculated as (first vaccination date – date of birth + 1)/365.25 and rounded to 1 decimal place. Medical history will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA).

Clinically significant findings for physical examination will be recorded as yes or no in the CRF.

3.5.3. Nonstudy Vaccinations

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

3.5.3.1. Concomitant Vaccines and Medication(s)

3.5.3.1.1. Prohibited During the Study

The following are prohibited during the study:

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

- Receipt of any other investigational product.

3.5.3.1.2. Permitted During the Study

The following are permitted during the study:

- Any other vaccine may be given according to local practice. If any vaccine other than 13vPnC is administered during the study, the name and date of administration will be documented in the CRF.

- Any medication, except those listed in Section 3.5.3.1.1, is permitted but will not be documented in the CRF.

4. ANALYSIS SETS

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

4.1. Full Analysis Set

The full analysis set (FAS) is all subjects who have been enrolled in the study, regardless of whether or not investigational product was received.

4.2. Safety Analysis Set

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

4.3. Other Analysis Sets

Not applicable.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

No formal statistical hypothesis test will be performed as this is a descriptive study and no formal hypotheses were predetermined. 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 in the study.

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Point estimates and nominal 95% confidence intervals (CIs) will be provided for all safety 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 CIs (Clopper-Pearson) for the various proportions of individual groups 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.

5.3. Methods to Manage Missing Data

5.3.1. Safety Data

Handling of missing information related to safety data, such as 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 – Day 7" data will be considered as nonmissing for analyses after vaccination. The proportion of subjects with missing reactogenicity data will also be summarized. The denominator will be the number of subjects who receive the scheduled vaccination.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Safety Endpoints

6.1.1.1. Primary Analysis

Endpoints: Safety endpoints in Section 3.1

- o Analysis time points**:**

  Endpoints for local reactions and systemic events: 7 days after each vaccination

  Endpoints for AEs and SAEs: from the signing of the informed consent document (ICD) to 1 month after vaccination

- o Analysis population: Safety population

- o Analysis methodology: Descriptive; also see Section 5.2.1

- o Supporting objective: Primary objective

Reporting results:

The number, proportion, and corresponding 95% CI will be presented.

6.2. Baseline and Other Summaries and Analyses

6.2.1. Demographic, Medical History, and Baseline Summaries

Descriptive summary reports for demographic characteristics will be provided for the FAS and safety analysis populations. Descriptive summary reports for medical history will be provided for the safety population only.

6.2.2. Study Conduct and Subject Disposition

The number and percentage of subjects who are vaccinated will be included in the subject disposition summary: subjects who withdraw during the vaccination phase, complete the vaccination phase, complete the study, and withdraw during the follow-up phase 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.

The number and percentage of subjects vaccinated will be tabulated.

A listing of noncompliant vaccine administration will be provided. The protocol deviations will also be listed. A listing of subjects who withdrew because of AEs will be provided.

All assigned subjects will be used to generate these tables. Subjects who sign the ICD but are screen failures will be also summarized.

6.2.3. E-Diary Completion

Variables defined in Section 3.5.1 will be summarized with descriptive statistics. The safety population will be used to generate this table.

6.3. Safety Summaries and Analyses

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

6.3.1. 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.

Descriptive summaries and listing of AEs will be provided. The descriptive statistics for AEs will be summarized as the number and percentage of subjects reporting at least 1 event of each preferred term with associated Clopper-Pearson 95% CIs (Section 5.2.1), arranged by system organ class, and will also be summarized as the number of occurrences of the events.

For the safety results in children 6 to 17 years of age in India, the exact 2-sided 95% CIs will be provided for AEs within 1 month after vaccination.

6.3.2. Reactogenicity Data

The derived endpoints (Section 3.4.1) for each local reaction and systemic event will be summarized.

The presence and maximum severity of each local reaction and systemic event, including fever, and any event within 7 days following vaccination with 13vPnC, will be summarized by proportions of subjects with the associated 95% Clopper-Pearson CIs.

The presence of each local reaction and systemic event, and any local reaction and systemic event, including fever, on each day and any day of Day 1 to Day 7 following vaccination with 13vPnC, will also be summarized by proportions of subjects with associated Clopper-Pearson CIs.

For each local reaction and systemic event, including fever, descriptive summary statistics of the maximum duration of each event will be provided. The maximum duration of each event for each subject will be calculated as the last day with the event minus the first day with the event + 1, ignoring any intervening days without the indicated event.

For the onset of each local reaction and systemic event, including fever, descriptive summary statistics will be provided.

6.3.3. 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) events.

6.3.4. Immediate AEs

Descriptive summaries and listing of subjects reporting AEs during the protocol-specified first 20-minute observation period will be provided. Also, Clopper-Pearson 95% CIs will be included with the percentages.

6.3.5. Physical Examinations

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

6.3.6. Nonstudy Vaccination

Nonstudy vaccination summaries will be provided with descriptive summaries. Each vaccine will be summarized according to the Anatomic Therapeutic Chemical (ATC) 4 classification system. The number and percentage of subjects receiving vaccine will be tabulated. The denominator for the percentages is the number of subjects in the vaccine group.

7. INTERIM ANALYSES

Not applicable.

8. REFERENCES

1.   Collett D. Modelling binary data. London: Chapman & Hall; 1991.