Protocol B1851196

A COHORT STUDY TO EVALUATE IMMUNOGENICITY FOR CHILDREN AGED 5 MONTHS TO ≤60 MONTHS AT THE TIME OF CLINICAL PNEUMONIA DIAGNOSIS

Statistical Analysis Plan
(SAP)

Version: 1.2

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[redacted]

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 18Jul2019	Original (25Jul2018)	N/A	N/A
1.1/16Mar2020	Original (25Jul2018)		Add wording of subset for MOPA testing from Non- 13vPnC cohort and few editorial changes
1.2/22May2020	Original (25Jul2018)		Add wording of handling missing data and immunogenicity data below limit of quantification and a few editorial changes.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study B1851196. 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, Endpoints, and Estimands

To describe the antibody levels as measured by IgG and MOPA by 13vPnC vaccination status and vaccine-type (VT) carriage status, among children 5 months to ≤ 60 months of age with diagnosis of clinical pneumonia per local standard

2.1.1. Primary Estimand

The serotype-specific IgG geometric mean concentration (GMC) and MOPA geometric mean titers (GMT) for each of the pneumococcal serotypes measured at the time of diagnosis of clinical pneumonia

The primary estimand of this study will be the GMC and GMT for each cohort (refer to section 2.2 for each cohort). The estimand is defined according to the primary objective and is in alignment with the primary endpoint. It includes the following 2 attributes:

- Population: Patients who meet all study inclusion/exclusion criteria;
- Variable: IgG /MOPA;

2.2. Study Design

This is a cohort study designed to describe serotype-specific antibody levels by 13vPnC vaccination status (in children who completed at least 2 doses of 13vPnC, versus children that did not receive any 13vPnC) and vaccine type (VT) carriage status, among children 5 months to ≤ 60 months of age with clinical pneumonia. Thus, there will be four subgroups in this study: the 13vPnC cohort with VT carrier; the 13vPnC cohort without VT carrier; the unvaccinated cohort with VT carrier; and the unvaccinated cohort without VT carrier.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The serotype-specific IgG geometric mean concentration (GMC) and MOPA geometric mean titers (GMT) for each of the pneumococcal serotypes measured at the time of diagnosis of clinical pneumonia.

Serum levels of MOPA for each of the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) will be determined in all 13vPnC cohort subjects with adequate blood volume. In the non 13vPnC cohort, a sample of subjects with adequate blood volume will be selected, to be equal to the number of the 13vPnC cohort included for MOPA testing. This sample of subjects from Non-13vPnC cohort will be performed by randomly ordering all subjects with adequate serum volume and selecting the first number of subjects which is equal to the number of the 13vPnC cohort included for MOPA testing.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Population	Description
Enrolled	All participants who signed the informed consent document.
Evaluable	All participants who signed the informed consent document, met all inclusion/exclusion criteria, and had at least one immunogenicity assay value available for analysis.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

Not Applicable as this is a descriptive study.

5.2. General Methods

5.2.1. Analyses for Binary Endpoints

For carriage results, the exact 2-sided 95% confidence intervals (CIs) (Clopper-Pearson CIs) will be provided for the proportions of subjects with VT or serotype-specific carriage.

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)[1] and implemented in SAS PROC FREQ.

5.2.2. Analyses for Continuous Endpoints

For each of the 13 serotypes contained in 13vPnC Cohort and also Non-13vPnC Cohort, GMCs of IgG and GMT of MOPA will be calculated along with 2-sided 95% CIs, which will be constructed by back transformation of the CIs for the mean of the logarithmically transformed IgG/MOPA computed using Student's t distribution. In addition, the 2-sided 95% CI on the geometric mean ratios (GMRs) (the GMC of 13vPnC Cohort to the GMC of Non-13vPnC Cohort and the GMT of 13vPnC Cohort to the GMT of Non-13vPnC Cohort) for all 13 serotypes will be also provided and those 95% CIs will be constructed by back transformation of the CIs for the mean difference of the measures on the logarithmically transformed scale(IgG/MOPA) using Student's t distribution.

A multiple regression model will be used with the log concentration or log titers as a dependent variable. Independent variables will include cohort (13vPnC or unvaccinated), 13vPnC VT carriage status, and the interaction of the cohort and carriage status, as well as the confounding variables (age at enrollment, sex, season of enrollment). Adjusted GMCs (or GMTs) and adjusted geometric mean ratios (GMRs) along with 95% CI will be estimated based on this model. The (GMRs) will compare antibody levels between:

1. Within 13vPnC Cohort: VT-carrier + vs VT-carrier -
2. Within Non-13vPnC Cohort: VT-carrier + vs VT-carrier -
3. 13vPnC Cohort vs Non-13vPnC Cohort
4. Within VT-carrier +: 13vPnC Cohort vs Non-13vPnC Cohort
5. Within VT-carrier -: 13vPnC Cohort vs Non-13vPnC Cohort

Additionally, serotype-specific GMC/GMT (unadjusted) and associated 95% CI will be provided for each 13vPnC VT carriage status (Yes/No), for both 13vPnC cohort and unvaccinated cohort. GMRs (unadjusted) (GMC/GMT of VT- carrier + vs GMC/GMT of VT-carrier -) within 13vPnC Cohort and within unvaccinated Cohort, and GMRs (unadjusted) (GMC/GMT of 13vPnC Cohort vs GMC/GMT of Non-13vPnC Cohort) within

VT-carrier + group and within VT-carrier group and associated 95% CIs will be calculated using Student's t distribution for the mean difference of the measures on the logarithmically transformed scale (IgG/MOPA).

If model adjusted GMCs, GMTs, GMRs are not estimatable (e.g., due to limited data), then only unadjusted GMCs, GMTs, GMRs and associated 95% CIs will be presented.

5.3. Methods to Manage Missing Data

In general, nonmissing values will not be excluded from the analysis. However, certain statistical procedures that compare 2 or more variables, or values at more than 1 time point, for the same subject require all values to be available. In such cases, nonmissing values will be dropped to the extent necessary to perform the procedure.

5.3.1. Immunogenicity Data

Immunogenicity data collected for this study are the results of immunologic assays performed by the National Institutes for Food and Drug Control (NIFDC) on the blood samples collected.

The Lower Limit of Quantitation (LLOQ) in micrograms per mL (μg/mL) for each serotype is shown in Table 2.

Table 2. The LLOQ in Micrograms per mL from NIFDC

Serotype	LLOQ
1	0.02
3	0.03
4	0.02
5	0.03
6A	0.03
6B	0.03
7F	0.04
9V	0.02
14	0.04
18C	0.02
19A	0.02
19F	0.03
23F	0.03

Antibody concentrations above LLOQ are considered accurate and their quantitated values will be reported. The Limit of detection (LOD) was established as 50% of the LLOQ. Values below the LLOQ or denoted Below Limit of Quantification (BLQ) will be set to **0.5 × LOD** for analysis.

The NIFDC's OPA LLOQ in titers for all serotypes was set as 8. For the results of antibody titers that are below the LLOQ, or denoted as BLQ, **0.5 × LLOQ** will be assigned for analysis.

No other missing 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.

For each serotype's antibody concentrations or antibody titers, the number of subjects with missing values at each blood sampling point will be provided.

5.3.2. 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.

6. ANALYSES AND SUMMARIES

All summaries will be applied to evaluable population. Any subjects that are enrolled but did not meet study inclusion/exclusion criteria will be listed.

6.1. Primary Endpoint(s)

6.1.1. Primary Analysis

For each cohort, children will be assigned to 2 groups: Participant in whom a 13vPnC vaccine type (VT) strain has been isolated from the respiratory tract, and participant from whom a 13vPnC VT strain has not been isolated from the respiratory tract (VT carrier versus without VT carrier). Therefore, a total of 4 subgroups are available: 13vPnC cohort with VT carrier; 13vPnC cohort without VT carrier; unvaccinated cohort with VT carrier; unvaccinated cohort without VT carrier.

For each of the 13 serotypes contained in 13vPnC, the IgG concentration and MOPA titers will be transformed in logarithm scale. Crude (unadjusted) geometric mean concentrations (GMCs) and geometric mean titers (GMTs) and 95% confidence interval (CI) will be calculated for the 4 cohort/carriage subgroups.

6.1.2. Sensitivity/Supplementary Analyses

Not applicable.

6.2. Baseline and Other Summaries and Analyses

6.2.1. Baseline Summaries

Subjects demographics (collected information including, sex, residence, and number of siblings, if any) and medical history will be descriptively summarized.

6.2.2. Deep Upper Respiratory Aspirates Culture Summaries

The number and proportion of subjects with *S. pneumoniae* isolates detected will be summarized for both cohorts: the 13vPnC cohort and unvaccinated cohort. Additionally, the number and proportion of each serotype, serotype included in 13vPnC (VT), and serotypes not included in 13vPnC (non-VT) will be summarized for both cohorts.

6.2.3. Adverse Events

Any AEs reported in the study will be listed.

7. INTERIM ANALYSES

Interim data may be summarized if the assay data is available for subjects enrolled by certain cutoff date. Final report will be summarized after all data are available.

8. REFERENCES

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