Protocol C3571001

A PHASE 1/2, RANDOMIZED, OBSERVER-BLINDED TRIAL TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A MULTIVALENT PNEUMOCOCCAL CONJUGATE VACCINE IN HEALTHY ADULTS 50 THROUGH 85 YEARS OF AGE

Statistical Analysis Plan (SAP)

Version: 2.0

Author: PPD (SAP author –Pfizer)

Date: 30-Jan-2018

[redacted]

TABLE OF CONTENTS

[redacted]

LIST OF TABLES

[redacted]

APPENDICES

[redacted]

1. AMENDMENTS FROM PREVIOUS VERSION(S)

Revision History

Version	Date	Author(s)	Summary of Changes/Comments
Version 1.0	04-Oct-2017	PPD	Version 1
Version 2.0	30-Jan-2018	PPD	Section 3: Terms with "prevaccination" and "postvaccination" changed to "before" and "after" vaccination.
			Section 3: Text describing unblinded descriptive analyses of safety data after Visit 1 revised to clarify that only safety data on or after the visit occurring 1 month after vaccination will analyzed; ie, safety data obtained before the visit will not be reanalyzed.
			Section 5.2.1.1: The names of the evaluable immunogenicity populations shortened to "Stage 1 evaluable," "Stage 2 Month 1 evaluable," CCI [redacted]
			Section 5.2.1.1: Text added explaining expanded blood draw window as consistent with the Prevnar 13 program.
			Section 5.2.1.2: The names of the all-available immunogenicity populations shortened to "Stage 1 all-available," "Stage 2 Month 1 all-available," CCI [redacted]
			Section 5.4.2: Terms with "prevaccination" and "postvaccination" changed to "before" and "after" vaccination.
			Section 6.1.1: Text added that while redness or swelling <2.5 cm will be assigned as "none," such values will still be reported in the listings.
			Section 6.1.1: CCI [redacted]
			Section 6.1.1: Duration of local reactions ≥21 measuring device units will also be compiled.
			Section 6.1.1: Table 2 footnote text "any nonzero caliper measurement" changed to "any nonzero measurement," because "caliper" is not used in the protocol.
			Section 8.2.1: Text added that explains that local reaction and systemic event tables will be generated without e-diary data confirmed to have been entered in error. However, the maximum severity table will be regenerated with the erroneous data included.
			Section 8.2.1.1: Duration (total days) will be obtained for every event, not just a subset of events.

Revision History

Version	Date	Author(s)	Summary of Changes/Comments
			Section 8.2.2: Names of the evaluable populations shortened by removing "immunogenicity" from them.
			Section 8.2.2: CCI [redacted].
			Section 8.2.2: CCI [redacted]
			Section 8.2.3.2: Added text "Racial designation will be summarized by categories recorded in the database. Subjects with white race or who do not have a recorded racial designation will be assigned to "other."
			Section 8.2.3.3: Added text noting that concomitant medications for the treatments of SAEs or NDCMCs will be summarized.
			Various: The term "study vaccination" changed to "vaccination."
			Various: Terms with "prevaccination" and "postvaccination" revised to "before" and "after" vaccination.

[redacted]

2. INTRODUCTION

CCI [redacted]

The purpose of this study is to assess the safety and tolerability of c7vPnC in healthy adults 50 through 85 years of age. This study represents the initial evaluation of c7vPnC in humans. In addition to safety, immunogenicity of c7vPnC will also be described.

2.1. Study Design

This is a 2-stage, Phase 1/2, randomized, active-controlled, observer-blinded study with a 2-arm parallel design. It is planned to be conducted at investigator sites in the United States. The purpose of Stage 1 is to provide first-in-human (FIH) safety and immunogenicity data with the investigational pneumococcal vaccine c7vPnC in healthy adults 50 to 64 years of age, and it serves as the Phase 1 part of the study. Stage 2 functions as the Phase 2 part of the study and will provide additional safety and immunogenicity data with c7vPnC in healthy adults 65 to 85 years of age, compared to the licensed 23-valent pneumococcal polysaccharide vaccine (PPSV23).

Stage 1:

In Stage 1 of the study, approximately 66 (approximately 60 evaluable, assuming a 10% dropout rate) healthy adults 50 through 64 years of age with no history of pneumococcal vaccination will be enrolled, screened, and randomized equally in a 1:1 ratio to receive a dose of c7vPnC or licensed tetanus, diphtheria, and acellular pertussis vaccine (Tdap) as the control vaccine. CCI [redacted] Each subject will participate in Stage 1 of the study for approximately 7 months. Subjects will be enrolled and have blood drawn for baseline safety laboratory testing (hematology and tests for liver and renal function) at the screening visit (14 to 2 days prior to vaccination). On Day 1 (Visit 1), subjects will have blood drawn for immunogenicity assessments, receive investigational product, be observed for 30 minutes after vaccination, and receive safety follow-up and electronic diary (e-diary) instructions. Prompted local reactions (redness, swelling, and pain at the injection site) and systemic events (fever, headache, fatigue, muscle pain, and joint pain) occurring within 14 days after vaccination will be collected each day in the e-diary. Approximately 1 month after vaccination (Visit 2), subjects will return to the study site for safety follow-up (ie, collection of adverse events [AEs], including nonserious AEs, serious adverse events [SAEs], and newly diagnosed chronic medical conditions [NDCMCs]) CCI [redacted] and

[redacted]

immunogenicity). A telephone contact will occur 6 months after vaccination (Visit 3) to collect any SAEs or NDCMCs that occurred since the 1-month follow-up visit.

CCI [redacted]

Stage 2:

In Stage 2 of the study, approximately 440 (approximately 400 evaluable, assuming a 10% dropout rate) healthy adults 65 through 85 years of age previously vaccinated with Prevnar 13 ≥2 months prior to investigational product administration, as part of their routine medical care, will be enrolled and randomized equally in a 1:1 ratio to receive a dose of c7vPnC or PPSV23 as the control vaccine. Each subject will participate in Stage 2 of the study for approximately 12 months. On Day 1 (Visit 1), subjects will have blood drawn for immunogenicity assessments, receive investigational product, be observed for 30 minutes after vaccination, and receive safety follow-up and e-diary instructions. Prompted local reactions and systemic events occurring within 14 days after vaccination will be collected each day in the e-diary. Subjects will return to the investigator site for safety follow-up (AEs [including nonserious AEs, SAEs, and NDCMCs]) and a blood draw for immunogenicity approximately 1 month after vaccination (Visit 2). A telephone contact will occur 6 months after vaccination (Visit 3) to collect any SAEs or NDCMCs that occurred since the 1-month follow-up visit. Subjects will return approximately 12 months after vaccination (Visit 4) C C [redacted] and any SAEs or NDCMCs occurring in the interim since the 6-month telephone contact will be recorded.

CCI [redacted] safety and immunogenicity data reviews/analyses will be performed at various time points as described in Section 9 of the study protocol.

The study duration (first subject enrolled in Stage 1 until last subject completing Stage 2) will be approximately 20 months.

[redacted]

2.2. Study Objectives

The primary objectives of this study are to describe the safety profile of c7vPnC within each study stage.

The secondary objectives of this study are to describe the immunogenicity of c7vPnC within each study stage.

CCI [redacted]

3. INTERIM ANALYSES, FINAL ANALYSES, AND UNBLINDING

During this multistage study, the following analyses will occur:

Stage 1

1. Unblinded descriptive analyses of Stage 1 safety data through the visit occurring 1 month after vaccination to permit start of Stage 2.

2. Unblinded immunogenicity data from the visit occurring 1 month after vaccination from Stage 1 will be analyzed when data are available. Analyses will be descriptive.

3. Unblinded descriptive analyses of the safety data from the visit occurring 1 month after vaccination through the visit occurring 6 months after vaccination will be conducted when data are available.

Stage 2

1. Unblinded descriptive analyses for the visit occurring 1 month after vaccination for Stage 2 will be conducted when the safety and immunogenicity data are available.

2. Unblinded descriptive analyses of the safety data from the visit occurring 1 month after vaccination through 6 months and 12 months after vaccination will be conducted when data are available.

CCI [redacted]

Investigator sites and laboratory personnel directly conducting the immunogenicity assays will remain blinded until the study database has been locked and unblinded.

[redacted]

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

No formal statistical hypothesis testing will be performed. A descriptive estimation approach will be used to assess the safety and immunogenicity objectives in the study.

4.2. Statistical Decision Rules

Statistical decision rules will not be utilized in this study. All analyses are considered descriptive.

5. ANALYSIS SETS

Analysis sets for safety and immunogenicity data are defined in Section 5.1 and Section 5.2, respectively.

5.1. Safety Analysis Population

In Stage 1, the safety population will include all subjects who receive at least 1 dose of c7vPnC or Tdap. However, subjects who lack any safety data for an indicated analysis may be excluded from that analysis.

In Stage 2, the safety population will include all subjects who receive at least 1 dose of c7vPnC or PPSV23. However, subjects who lack any safety data for an indicated analysis may be excluded from that analysis.

Subjects will be assigned to vaccine groups corresponding to the vaccine actually received within each of the 2 study stages. The safety population will be the only analysis population for the primary endpoints for each study stage.

5.2. Other Analysis Sets

5.2.1. Immunogenicity Analysis Population

5.2.1.1. Evaluable Population

CCI evaluable populations are defined: the Month 1 evaluable population in each of Stage 1 and Stage 2CCI [redacted]. The evaluable population for each study stage will include any subject:

- who does not meet any exclusion criteria and meets all inclusion criteria,
- who has no major protocol deviations as determined by the clinician, and
- who receives the assigned vaccine, as randomized.

[redacted]

Additionally, for the Month 1 evaluable populations in Stage 1 and Stage 2,

- whose Visit 2 blood collection 1 month after vaccination is within 27 to 49 days, inclusive, after vaccination, and
- who has at least 1 valid and determinate assay result for at least 1 serotype for Visit 2.

  The blood draw window has been expanded by 1 extra day before and 14 days after the protocol-specified blood draw window of 28 to 35 days, as has been established by precedent in the Prevnar 13 development program.

CCI [redacted]

Individual samples may be excluded from statistical analysis plan (SAP)-specified immunogenicity analysis for reasons including, but not limited to, improper handling, insufficient volume, and inability to obtain a valid assay result; however, such a subject will still otherwise be included in the evaluable population, provided all other criteria are met.

The names for the evaluable populations will be "Stage 1 evaluable population," "Stage 2 Month 1 evaluable population," CCI [redacted]

The evaluable populations will be the primary analysis populations for immunogenicity results.

5.2.1.2. All-Available Immunogenicity Population

All-available immunogenicity populations will be defined for each blood draw collection visit after vaccination. Each all-available population will include all subjects who receive vaccine and have at least 1 valid and determinate assay result at the indicated visit. The all-available immunogenicity populations will be the secondary analysis populations for immunogenicity results. Subjects will be assigned to their randomized vaccination.

The names for the all-available populations will be "Stage 1 all-available population," "Stage 2 Month 1 all-available population," CCI [redacted]

[redacted]

5.3. Investigational Product Misallocations

All analyses will exclude data from subjects who are randomized but do not receive investigational product.

If a subject receives an investigational product that is not consistent with the investigational product to which he or she is randomized, for example, receives vaccine other than as randomized, then the subject will be reported under the investigational product that he or she actually received for all safety analyses, where applicable.

5.4. Protocol Deviations

A full list of protocol deviations will be compiled and reviewed to identify major and minor deviations prior to database lock.

5.4.1. Deviations Assessed Prior to Randomization

At screening in Stage 1 and prior to randomization in Stage 1 and Stage 2, the investigator will assess subjects against the inclusion and exclusion criteria as set out in Section 4.1 and Section 4.2 of the protocol.

5.4.2. Deviations Assessed After Randomization

Major deviations from the protocol will be reviewed for the protocol-specified unblinded analyses. Each major deviation will be evaluated regarding inclusion in safety or immunogenicity population before conducting the indicated unblinded analysis. The Stage 1 unblinded analyses will be performed on the safety data through 1 month after vaccination, the immunogenicity data from the visit occurring 1 month after vaccination, and the safety data through the visit occurring 6 months after vaccination (when the applicable data set is available). The Stage 2 unblinded analyses will be performed on the safety and immunogenicity data through 1 month after vaccination, the safety data through the visits occurring 6 months and 12 months after vaccination, CCI [redacted]
Inclusion or exclusion of subjects from the indicated populations will not be changed for later unblinded analyses.

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

The safety endpoints, which are primary endpoints of the study, include:

- Proportions of subjects reporting prompted local reactions within 14 days after vaccination (redness, swelling, and pain at the injection site), for each study stage.

- Proportions of subjects reporting prompted systemic events within 14 days after vaccination (fever, headache, fatigue, muscle pain, and joint pain), for each study stage.

[redacted]

- Proportions of subjects reporting AEs within 1 month after vaccination, for each study stage.

- Proportions of subjects reporting SAEs and NDCMCs within 6 months after vaccination (both Stage 1 and Stage 2) and within 12 months after vaccination (Stage 2 only).

6.1.1. Local Reactions

Within each study stage, the local reactions assessed and reported in the e-diary are redness, swelling, and pain at the injection site, from Day 1 to Day 14 following vaccination, where Day 1 is the day of vaccination.

Subjects will record presence or absence of redness and swelling. If present, the reaction will be measured and recorded in measuring device units (range: 1 to 21+). Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. The reaction will be categorized for analysis as mild, moderate, or severe based on the grading scale in Table 1 below. Redness or swelling less than 2.5 cm will be assigned as "none," but such values will still be reported in the listings.

Pain at the vaccine injection site will be assessed by the subject as mild, moderate, or severe according to the grading scale in Table 1.

Note that Grade 4 severities will not be collected in the e-diary but will be collected as AEs on the case report form (CRF). Grade 4 will not be analyzed as part of local reactions.

For each local reaction, the maximum severity grade of the reaction based on the severity grading scale of the local reactions in Table 1 will be derived for the e-diary collection period (Day 1 to Day 14, where Day 1 is the day of vaccination) as follows:

= missing, if all values are missing for Day 1 to Day 14;

= 0 (or none), if the subject reports all reactions as "no" or a combination of missing and "no" for all Days 1 to 14 or (redness and swelling only) if the largest diameter is <5 measuring device units (ie, <2.5 cm);

= highest grade (maximum severity) within 14 days after vaccination (Day 1 to Day 14) among severity grades where the answer is not "no" for at least 1 day during Days 1 to 14.

[redacted]

Table 1. Grading Scales for Local Reactions

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4
Redness (erythema)	5 to 10 measuring device units = 2.5 to 5.0 cm	11 to 20 measuring device units = 5.5 to 10.0 cm	≥21 measuring device units = ≥10.5 cm	Necrosis or exfoliative dermatitis
Swelling (edema)	5 to 10 measuring device units = 2.5 to 5.0 cm	11 to 20 measuring device units = 5.5 to 10.0 cm	≥21 measuring device units = ≥10.5 cm	Necrosis
Pain at injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization

Abbreviation: e-diary = electronic diary.
Note: If the size of the redness and/or swelling falls between 2 measuring device units, the higher measuring device unit number will be recorded in the e-diary.

Presence or Absence

For the data summary of the presence (yes or no) of a local reaction during Day 1 to Day 14 following vaccination, where Day 1 is the day of vaccination, the following variables are required:

- Maximum severity of each local reaction on any day (Day 1 to Day 14);
- Presence (yes or no) of each local reaction on each day (Day 1 to Day 14);
- Presence (yes or no) of each local reaction on any day (Day 1 to Day 14);
- Presence (yes or no) of any local reaction on each day (Day 1 to Day 14);
- Presence (yes or no) of any local reaction on any day (Day 1 to Day 14);
- Presence (yes or no) of each severe (Grade 3) (as defined in Table 1) local reaction on each day and any day (Day 1 to Day 14);
- Duration of each local reaction (duration will be calculated both from the first to the last day and also as total days with the indicated event);
- Onset day of each local reaction;
- [redacted].

[redacted]

For each local reaction, Table 2 below explains the algorithm to derive the presence of a reaction (yes or no) during Day 1 to Day 14 following vaccination, where Day 1 is the day of vaccination.

Table 2. Derived Variables for Each Local Reaction Within the Time Interval

Variable[a]	Yes (1)	No (0)	Missing (.)
Any Day 1 to 14	Subject reports the reaction as present ("yes") on any Day 1 to 14. For redness and swelling this includes any nonzero measurement.	Subject reports the reaction as "no" on all 14 Days 1 to 14 or as a combination of "no" and missing on all 14 Days 1 to 14.	Reaction data are missing on all 14 Days 1 to 14.

a. The variable will be derived for each of the local reactions (redness, swelling, pain at the injection site) and also for each of the severe local reactions within Day 1 to Day 14 following vaccination.

For any local reaction on any day, a similar rule applies as specified below in Table 3:

Table 3. Derived Variables for Any Local Reaction Within the Time Interval

Variable[a]	Yes (1)	No (0)	Missing (.)
Any Day 1 to 14	Subject reports "yes" or "mild" or greater for any local reaction on any Day 1 to 14.	Subject reports "no" on all 14 Days 1 to 14 or as a combination of "no" and missing on all 14 Days 1 to 14 on all 3 local reactions.	All 3 local reaction values are missing on all 14 Days 1 to 14.

a. The variable will be derived for any local reaction (any redness, swelling, pain at the injection site) and also for any severe local reaction within Day 1 to Day 14 following vaccination.

Duration (From First Day to Last Day Reported)

The duration of each local reaction will be calculated as the number of days from the start of the first reported reaction to the resolution of the last reported reaction, inclusive. Days with redness or swelling with diameter <2.5 cm will be excluded. Resolution is the last day on which the reaction is recorded in the e-diary if the reaction lasted 14 days or less, or the date the reaction ended if it continued beyond Day 14 (the latter will be collected on the CRF). If there is no known date when the reaction ended, then duration will be missing (unknown). Subjects with no reported reaction have no duration because it is not applicable.

Duration of reactions ≥21 measuring device units will also be compiled.

Duration (Total Days Reported)

The duration (total days) of each local reaction will be calculated as the number of days with the reported reaction, including days after Day 14 (if any). Days with redness or swelling with diameter <2.5 cm will be excluded.

[redacted]

If there is no known date when the reaction ended, then duration (total days) will be missing (unknown). Subjects with no reported reaction have no duration because it is not applicable.

Total days of reactions ≥21 measuring device units will also be compiled.

Onset

The onset day of each local reaction and any local reaction will be derived. Days with redness or swelling with diameter <2.5 cm will be excluded.

For the onset day of each local reaction, if subjects report severity change of the local reaction, only the first day of reporting that specific local reaction will be counted.

For the onset day of any local reaction, the first day of reporting any severity of any local reaction will be counted.

CCI

[redacted]

6.1.2. Systemic Events and Fever

Within each study stage, the systemic events assessed and recorded in the e-diary are headache, fatigue, muscle pain, and joint pain, from Day 1 to Day 14 following vaccination, where Day 1 is the day of vaccination.

For each systemic event, the maximum severity grade of the event based on the severity grading scale in Table 4 will be derived for the e-diary collection period (Day 1 to Day 14, where Day 1 is the day of vaccination) as follows:

= missing, if all values are missing for Day 1 to Day 14;

= 0, if the subject reports all reactions as "no" or a combination of missing and "no" for all Days 1 to 14;

= highest grade (maximum severity) within 14 days of vaccination (Day 1 to Day 14) among severity grades where the answer is not "no" for at least 1 day during Days 1 to 14.

[redacted]

The symptoms of systemic events will be assessed by the subject as mild, moderate, or severe according to the severity grading scales of each systemic event in Table 4 below. Grade 4 will not be collected in the e-diary but will be collected as an AE on the CRF. Grade 4 will not be analyzed as part of systemic events.

Table 4. Grading Scales for Systemic Events

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4
Fatigue (tiredness)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization
Muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization

Abbreviation: e-diary = electronic diary.

Oral temperature will be collected in the evening daily for 14 days following vaccination (Days 1 to 14, where Day 1 is the day of vaccination) and at any time during the 14 days that fever is suspected. Fever is defined as an oral temperature of ≥100.4°F (≥38.0°C). The highest temperature for each day will be recorded in the e-diary. In the event of a fever on Day 14, temperature will be collected 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 5 below:

Table 5. Ranges for Fever

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

Maximum severity for fever over Days 1 to 14 will be defined as >104.0°F (>40.0°C).

For each systemic event, the following endpoints and variables will be derived for analyses following the same rules as for local reactions in Section 6.1.1, where applicable:

- Maximum severity of each systemic event or fever on any day (Day 1 to Day 14);
- Presence (yes or no) of each systemic event or fever on each day (Day 1 to Day 14);

[redacted]

- Presence (yes or no) of each systemic event or fever on any day (Day 1 to Day 14);
- Presence (yes or no) of any systemic event or fever on any day (Day 1 to Day 14);
- Presence (yes or no) of each severe (Grade 3 as defined in Table 4) systemic event (this will include fever >104.0°F [>40.0°C]) on each day and on any day (Day 1 to Day 14);
- Duration of each systemic event or fever (duration will be calculated both from the first to the last day and also as total days with the indicated event);
- Onset day of each systemic event or fever;

CCI [redacted]

For the purposes of deriving the variable "any systemic event" on any day (Day 1 to Day 14) or each day, the systemic events headache, fatigue, muscle pain, and joint pain will be included, and fever will be included as one of the possible systemic events.

6.1.3. Use of Antipyretic/Pain Medication

Within each study stage, the use of antipyretic/pain medication to treat fever or pain is also recorded in the e-diary from Day 1 to Day 14 following vaccination, where Day 1 is the day of vaccination.

For the use of antipyretic/pain medication, the following endpoints and variables will be derived for analyses following the same rules as for local reactions in Section 6.1.1, where applicable:

- Presence (yes or no) of use of antipyretic/pain medication on each day (Day 1 to Day 14);
- Presence (yes or no) of use of antipyretic/pain medication on any day (Day 1 to Day 14);
- Duration of use of antipyretic/pain medication;
- Onset day of use of antipyretic/pain medication.

The use of antipyretic/pain medication will be summarized and included in the systemic event summary tables, but will not be considered a systemic event.

CCI [redacted]

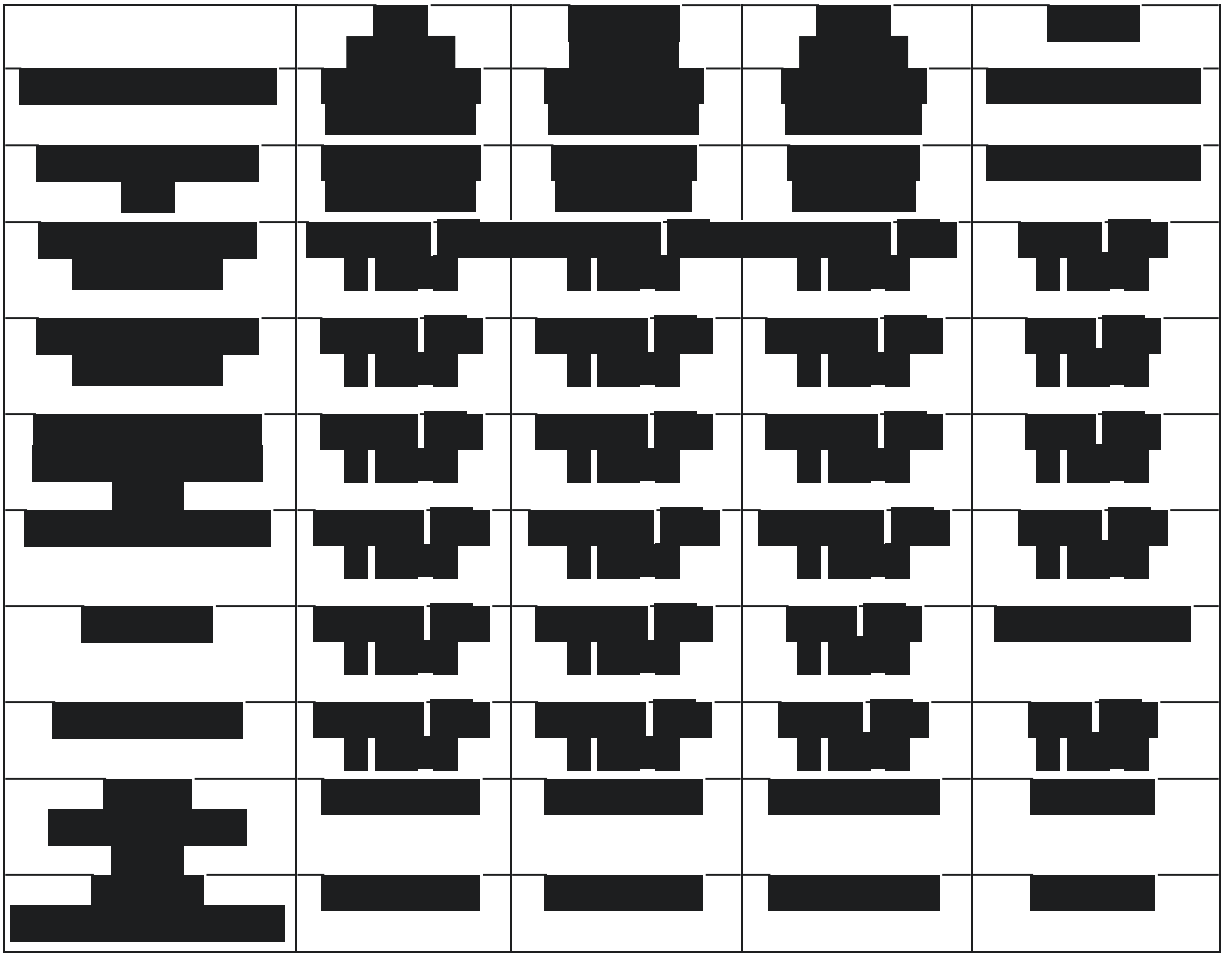
[redacted]

6.1.4. Adverse Events

AEs will be captured and reported in accordance with Pfizer reporting standards.

AEs will be assessed up to 1 month after vaccination within each of Stage 1 and Stage 2, separately. SAEs and NDCMCs will be assessed throughout the study and collected by a telephone call at 6 months after vaccination within each of Stage 1 and Stage 2, and collected during a clinic visit at 12 months after vaccination for Stage 2 only.

CCI



CCI [redacted]

[redacted]

6.2. Immunogenicity Endpoints

The immunogenicity endpoints are the secondary and exploratory endpoints of the study.

6.2.1. Secondary Endpoints

- Pneumococcal serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) measured at 1 month after vaccination, for each study stage.
- Pneumococcal serotype-specific OPA geometric mean fold rises (GMFRs) measured from before vaccination to 1 month after vaccination, for each study stage.

CCI [redacted]

[redacted]

CCI [redacted]

6.2.3. Immunogenicity Variables

Immunogenicity variables collected for this study are the results of assays performed on the blood samples collected. The results of these assays are CCI antibody titers (OPA) C CI [redacted]

OPA Titer

OPA titers for the complementary 7 pneumococcal serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) will be determined in all subjects for each blood sample at Day 1 prior to vaccination (baseline) and 1 month after vaccination (Stage 1 and Stage 2). CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

CCI

CCI

CCI

CCI [redacted]

6.4. Covariates

None.

7. HANDLING OF MISSING VALUES

For the analysis of the immunogenicity endpoints, missing values will be retained as missing and will not be imputed.

Handling of missing values for local reactions and systemic events, including fever, is described in Section 6.1.1 and Section 6.1.2.

7.1. Concentrations Below the Limit of Quantitation

Refer to Section 6.2.3.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

All analyses will be descriptive. 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.

No formal hypothesis testing will be performed.

8.1.1. Analyses for Binary Endpoints

Exact 2-sided 95% confidence intervals (CIs) (Clopper-Pearson CIs) will be provided by vaccine group for all primary safety endpoints, ie, proportions of subjects reporting local reactions, systemic events, and AEs (including SAEs and NDCMCs).

CCI [redacted]

The exact CIs for the various proportions 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 response. An exact 95% CI can be computed by solving the following 2 equations. For the lower limit p_L,

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

[redacted]

and for the upper limit p_U,

$$p_U = \frac{(r+1)F_U}{(n-r)+(r+1)F_U} \quad p_U = \frac{(r+1)F_U}{(n-r)+(r+1)F_U}$$

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.

The CI using the F distribution is described in Collett (1991) and implemented in SAS PROC FREQ. For a 95% CI, the quantiles, F_L and F_U, are from the F distribution for α=0.025 and α=0.975, respectively.

8.1.2. Analyses for Continuous Immunogenicity Endpoints

Geometric Mean

The secondary immunogenicity endpoints, which include OPA titers, CCI [redacted] will be summarized as GMTs CCI [redacted] for each pneumococcal serotype by each vaccine group at each blood sampling time point within each study stage. The associated 95% CIs of GMTs CCI [redacted] will also be provided.

The GMT CCI [redacted] will be calculated as the mean of the assay results after making the logarithmic transformation and then back transformation to its original scale. Two (2)-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.

Geometric Mean Fold Rise

OPA titers CCI [redacted] measured from before vaccination to 1 month after vaccination (Stage 1 and Stage 2), CCI [redacted] CCI [redacted] will be summarized as GMFRs for each pneumococcal serotype by each vaccine group. The GMFR will be calculated by dividing the later assay result by the earlier assay result for each subject with valid assay results from both sampling time points, then applying the same geometric mean calculations and the associated 95% CI calculations as described above.

Evaluable GMFRs from before vaccination to 1 month after vaccination (Stage 1 and Stage 2) will be limited to subjects in the respective Month 1 evaluable population. CCI [redacted]

[redacted]

CCI [redacted] All-available GMFRs will be calculated using parallel membership in the appropriate all-available population(s).

CCI [redacted]

[redacted]

8.2. Statistical Analyses

8.2.1. Safety Analysis

All safety summaries will be provided by vaccine group, for Stage 1 and Stage 2 separately. No statistical comparisons are planned for safety data. The safety endpoints detailed in Section 6.1 will be summarized as described below. The analyses will consist of subjects from the safety population for each study stage.

Local reaction and systemic event tables will be generated without e-diary data that have been confirmed by the subject to have been entered in error. However, the maximum severity table will be regenerated with the erroneous data included.

8.2.1.1. Local Reactions, Systemic Events, and Fever

The derived endpoints for each local reaction (Section 6.1.1), systemic event, and fever (Section 6.1.2) during Day 1 to Day 14 following vaccination, where Day 1 is the day of vaccination, will be summarized as the proportions of subjects with the associated 95% Clopper-Pearson CIs (Section 8.1.1) and descriptive statistics for each vaccine group.

The presence and maximum severity of each event and any event within 14 days following vaccination will be summarized by proportions of subjects with the associated 95% Clopper-Pearson CIs and descriptive statistics for each vaccine group.

Another set of summaries for the presence of each event and any event, and for events that are severe in grade, on each day and any day of Day 1 to Day 14 following vaccination will also be provided by day for each vaccine group in the proportions of subjects with the associated 95% Clopper-Pearson CIs, by each event and any event.

Figures of the bar charts plotting the proportions of subjects for each derived event will be plotted by day for each vaccine group. The bar charts will be divided into severity subgroups to highlight the proportions of subjects by severity.

For redness and swelling, the maximum reported diameters in centimeters (cm) will be summarized according to the severity categories specified in Table 1, for each vaccine group.

[redacted]

For each local reaction and systemic event, including fever, the duration of each event will be summarized using descriptive statistics for each vaccine group. Duration will be calculated as the last day minus the first day + 1, including any intervening days without the indicated event. Only subjects actually reporting the event will be included in the summary statistics. Bar charts plotting the proportions of each event each day will be inspected for possible skips, ie, the event tends to appear, disappear, then reappear. If skips are observed, then duration (total days) will be calculated as the total number of days on which the subject experienced the indicated event.

Duration (from the first day to the last day reported) will be obtained for every event. Duration (total days) will also be obtained for every event.

The onset day of each local reaction and systemic event, including fever, will be summarized using descriptive statistics for each vaccine group.

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A listing will be provided for the subjects with severe (Grade 3) local reactions, systemic events, or fever >104°F (>40°C), or for any other unscheduled/unplanned safety assessment.

8.2.1.2. Use of Antipyretic/Pain Medication

The derived endpoints for use of antipyretic/pain medication (Section 6.1.3) will be summarized as the proportions of subjects with the associated 95% Clopper-Pearson CIs (Section 8.1.1) for each vaccine group, summaries of the use of antipyretic/pain medication on "any Day 1 to Day 14" within 14 days following vaccination, summaries of the use each day of Day 1 to Day 14, and descriptive statistics for the duration (total days) and the onset day of use of antipyretic/pain medication. Supportive bar charts will also be produced.

8.2.1.3. Adverse Events

Descriptive summaries and listings of AEs will be provided. The descriptive statistics for AEs will be the number and percentage of subjects reporting at least 1 event of each preferred term with the associated Clopper-Pearson 95% CI (Section 8.1.1), arranged by system organ class. The number of occurrences of the event will also be compiled.

The AEs will be summarized for each vaccine group from vaccination until the visit for the blood collection 1 month after vaccination, for each of Stage 1 and Stage 2. In addition, tables with the same descriptive statistics for related AEs and AEs characterized as severe will also be compiled as described above.

[redacted]

SAEs and NDCMCs (defined in Section 8 of the protocol) will also be summarized for each vaccine group.

1. from vaccination until Visit 2 (1 month after vaccination) for each stage;
2. from vaccination until the 6-month follow-up for each stage;
3. from vaccination until the 12-month follow-up (Stage 2 only);
4. from Visit 2 (1 month after vaccination) until the 6-month follow-up for each stage;
5. from the 6-month follow-up until 12 months after vaccination (Stage 2 only).

The day of Visit 2 (1 month after vaccination) will be used to split the interval from vaccination to the 6-month follow-up. SAEs occurring on the day of the 1-month blood draw will be assigned to the interval "within 1 month after vaccination."

AEs occurring immediately after vaccination, ie, within 30 minutes, will also be summarized for each stage.

AEs occurring after informed consent and before vaccination will be summarized for each stage.

Subjects in the safety population will be summarized according to the vaccine actually received.

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8.2.2. Immunogenicity Analysis

All analyses for the immunogenicity data, which are the secondary CCI [redacted] endpoints, will be descriptive in nature.

If the number of subjects in the Month 1 evaluable population is 90% or more of the number of all-available subjects, then compilation of the all-available statistics for Visit 1 and Month 1 may be omitted. This applies to both Stage 1 and Stage 2.

[redacted]

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For each of Stage 1 and Stage 2, the number and percentage of subjects randomized and included in each immunogenicity population (defined in Section 5.2) will be tabulated for each vaccine group and for the total. Reasons for exclusions from the immunogenicity population will be summarized using the number and percentage of subjects.

OPA GMTs CCI [redacted] with their associated 95% CIs will be summarized separately before vaccination and 1 month (Stage 1 and Stage 2) CCI [redacted] after vaccination for each pneumococcal serotype by each vaccine group. Geometric means will be compiled in the evaluable population, using the detailed statistical method of geometric mean described in Section 8.1.2. The geometric means may also be compiled for the all-available populations.

Similarly, the OPA CCI [redacted] GMFRs, calculated from before vaccination to 1 month after vaccination (Stage 1 and Stage 2) CCI [redacted] with their associated 95% CIs, will be obtained for each pneumococcal serotype by each vaccine group. Only subjects with valid assay results from both sampling time points will be included. GMFRs will be obtained for the evaluable populations. The GMFRs may also be compiled for the all-available populations. GMFRs will be compiled using the detailed statistical method of geometric mean described in Section 8.1.2.

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[redacted]

8.2.3. Analyses of Study Conduct

8.2.3.1. Subject Disposition, Vaccination Administration, and Blood Samples

In each study stage, the number and percentage of subjects randomized, completing the study, and withdrawing from the study will be summarized for each vaccine group and for the total sample. In addition, the reasons for withdrawal from the study will also be summarized.

Listings of noncompliant vaccine administration and subjects who do not receive the vaccine as randomized will be provided.

The number and percentage of subjects randomized and providing blood samples within the protocol-specified time frame as described in Section 5.2.1.1, as well as before and after the specified blood sample time frame in each of Stage 1 and Stage 2, will be tabulated for each vaccine group and for the total.

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

8.2.3.2. Demographic, Medical History, and Baseline Characteristics Variables

The descriptive statistics of demographic characteristics will be summarized by sex, race, and age at randomization, within each study stage.

Age at randomization in years will be derived as (randomization date – date of birth + 1) / 365.25 and truncated to the nearest integer.

For sex, ethnicity, race, and racial designation, the summary statistics will be the number and percentage of subjects within each vaccine group, and for the total. The categories will be those recorded in the database. Racial designation will be summarized by categories recorded in the database. Subjects with white race or who do not have a recorded racial designation will be assigned to "other." For age at the time of randomization, the mean, median, minimum, maximum, and standard deviation will be provided for each vaccine group. These tabulations will be performed for all subjects and the safety, evaluable, and all-available populations.

Baseline medical history information will be summarized and categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) within each study stage. The number and percentage of subjects randomized with at least 1 diagnosis of each preferred term, arranged by system organ class, will be tabulated for each vaccine group and for the total.

In Stage 2 only, the timing of vaccination history of Prevnar 13 prior to vaccination will be summarized by the time interval of <2 months, ≥2 months to <6 months, ≥6 months to <12 months, ≥1 year to <2 years, or ≥2 years, prior to vaccination, for both Stage 2 evaluable populations and the all-available population. A listing of the timing of vaccination history of Prevnar 13 prior to vaccination for Stage 2 will also be provided.

8.2.3.3. Nonstudy Vaccines and Concomitant Treatments

Nonstudy vaccines and concomitant medications for the treatment of SAEs or NDCMCs taken from after signing the informed consent document (ICD) until conclusion of each study stage will be categorized according to the World Health Organization (WHO) Drug Dictionary (WHODD) and summarized.

CCI

9. REFERENCES

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

2. Food and Drug Administration. *Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*. Silver Spring, MD: Food and Drug Administration; September 2007.

Appendix 1. Abbreviations

The following is a list of abbreviations that may be used in this statistical analysis plan.

Abbreviation	Term
AE	adverse event
BLQ	below the limit of quantitation
c7vPnC	complementary 7-valent pneumococcal conjugate vaccine
CI	confidence interval
CRF	case report form
e-diary	electronic diary
FDA	Food and Drug Administration
FIH	first-in-human
CCI [redacted]	[redacted]
GMFR	geometric mean fold rise
GMT	geometric mean titer
ICD	informed consent document
ID	identification
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
NDCMC	newly diagnosed chronic medical condition
OPA	opsonophagocytic activity
PPSV23	23-valent pneumococcal polysaccharide vaccine
CCI [redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
Tdap	tetanus, diphtheria, and acellular pertussis vaccine
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

[redacted]