Non-Interventional Study Protocol
B1851121

Prevenar13 (registried) Suspension Liquid for Injection
Drug Use Investigation
-adults aged 65 years or older-

Statistical Analysis Plan

Version: 1.1

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TABLE OF CONTENTS

1. REVISION FROM THE PREVIOUS VERSION

Version/ Date/ Author(s)	Summary of Changes/Comments
1.0 28-AUG-2015 PPD	Original
1.1 08-DEC-2016 PPD	5.4 Subgroup • Described the name of documents to identify hepatic dysfunction, renal dysfunction and immunocompromised complication. • Added a subgroup to assess the safety of subjects ineligible for vaccination as described in the package insert.
	8.2.1 Summary of vaccinees/Disposition of vaccinees • Corrected typographical error.
	8.2.1. Summary of vaccinees/Listing of discontinuation and withdrawal • Deleted calculation of proportion because of multiple choices allowed for the reason for discontinuation. • Corrected typographical error.
	8.2.2. Characteristics and treatment history of vaccinees/Vaccinee characteristics • Added references for definition of hepatic dysfunction, renal dysfunction and immunocompromised complication.
	8.2.3.1 Adverse reaction/Details of adverse reaction • Added calculation by severity.
	8.2.3.1 Adverse reaction/Timing of onset of adverse reaction • The day of vaccination of Day 1 as specified in the SAP was changed to Day 0 in consistent with the survey protocol. • Timing of onset category was revised to avoid difficulties in assessment by the timing of onset caused by decreasing number of vaccinees.
	8.2.3.3. Subgroup analysis • Added analyses to evaluate the safety in specific populations of vaccinees in detail.
	9. Listing • Added listings of specific subgroups of vaccinees who experienced adverse reactions.

2. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis plan for drug use results survey of Prevenar13® Suspension Liquid for Injection (hereinafter, Prevenar13). Excerpts from the protocol for drug use results survey are indicated in italics in this SAP.

2.1. Survey Design

[Vaccinees to be surveyed]

Elderly subjects (adults aged 65 years or older) receiving Prevenar13 as indicated in Indication and Dosage and Administration

[Indication]

Prevention of infection caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

[Dosage and Administration]

Each 0.5 ml dose is to be injected intramuscularly.

[Survey method]

This survey is to be conducted with consecutive eligible subjects registered until the contracted number of subjects is reached.

[Proposed survey period]

This survey is to be conducted as follows:

Survey period: April 2015 – October 2016

Registration period: April 2015 – September 2016

[Priority survey items]

No priority survey items in this survey.

[Number of vaccinees to be surveyed and its rationale]

600 vaccinees (to be registered)

In two clinical studies conducted in Japan B1851088 (non-inferiority study) in pneumococcal vaccine naive elderly subjects (adults aged 65 years or older) and 6115A1-3004(open study) in adults aged 50 years or older, the incidences of local reactions were 55.8% and 63.6%, respectively, and those of systemic reactions were 37.9% and 52.6% as reported via e-diary for 14 days following Prevenar13 vaccination in 65 years or older age group. In addition, the incidences of adverse events whose causal relationship to Prevenar13 cannot be ruled

out (adverse reactions) as reported by investigators in both studies for about 1 month following Prevenar13 vaccination were 3.9% (13/333 subjects) and 6.6% (9/136 subjects), respectively. Comparison of these results from clinical studies in Japan with those from overseas clinical studies identified no risk factor requiring additional attention in Japanese aged 65 years or older. In clinical studies in Japan, 518 elderly subjects aged 65 years or older (382 in B1851088 study and 136 in 6115A1-3004 study) received Prevenar13 and the safety was assessed for 469 subjects included in safety population (333 in B1851088 study and 136 in 6115A1-3004 study). To collect and evaluate safety information of Prevenar13 in post-marketing use for similar number of vaccinees compared to the clinical studies in Japan, 600 vaccinees are to be surveyed.

2.2. Survey Objective

To understand the following items in terms of safety of a single dose of Prevenar13 in elderly (adults aged 65 years or older) in post-marketing use.

1. *Actual usage*

2. *Occurrence of adverse events*

3. INTERIM ANALYSIS AND FINAL ANALYSIS

In this survey, interim analysis is to be periodically performed for periodic safety reports. At the interim analysis, only the items required for periodic safety reports are to be analyzed in the statistical analysis specified in the SAP. Additionally, final analysis is to be performed for re-examination filing. At the final analysis, all analyses specified in the SAP are to be performed.

4. HYPOTHESIS AND DECISION RULE

4.1. Statistical Hypothesis

Since this survey is not confirmatory in nature, statistical hypothesis testing is to be performed in an exploratory fashion, if applicable. The resulting p-value is to be assessed as a descriptive statistic and the significance level is not defined. However, the threshold may be established post hoc for screening.

4.2. Statistical Decision Rule

No statistical decision rule is to be set in this survey.

5. ANALYSIS POPULATION

5.1. Safety Analysis Population

Safety analysis population includes eligible subjects who receive Prevenar13 vaccination and have available safety information. However, subjects are to be excluded if any of the following apply:

a. CRF could not be collected at all (indicated in the report as “CRF not collected”).

b. There was a breach or incompleteness of contract (indicated in the report as “breach or incompleteness of contract”).

c. There was a breach of registration (indicated in the report as “breach of registration”).

d. There was no report on administration of the vaccine to be surveyed (indicated in the report as “no information on administration”).

e. There was no report on adverse event information (indicated in the report as “no adverse event information”).

For details on each criterion, “Guidance on criteria for inclusion or exclusion of analysis population and data handling in drug use results survey” is to be followed.

5.2. Efficacy Analysis Population

Efficacy analysis population is not used since efficacy is not assessed in this survey.

5.3. Other Analysis Population

No analysis population other than safety analysis population is used in this survey.

5.4. Subgroup

Safety analysis by subgroup is to be performed for the following subject characteristics:

- Gender [male, female] (reference population: male).
- Hepatic dysfunction [no, yes] (reference population: no): Hepatic dysfunction is identified in accordance with separately prescribed “procedure for extracting hepatic or renal dysfunction”.
- Renal dysfunction [no, yes] (reference population: no): Renal dysfunction is identified in accordance with separately prescribed “procedure for extracting hepatic or renal dysfunction”.
- Age at the time of vaccination [≥65, <70; ≥70, <75; ≥75, <80; ≥80, <85; ≥85] (reference population: ≥65, <70).

Safety analysis by subgroup is to be performed for the following other characteristics:

- Immunocompromised complication [no, yes] (reference population: no): Complication is identified in accordance with separately prescribed “definition of ‘immunocompromised’ in P13 adults”.
- Simultaneous vaccination with other vaccine [no, yes] (reference population: no).
- More than once Prevenar13 vaccination [once, more than once] (reference population: once).

- Prior vaccination of polyvalent pneumococcal polysaccharide vaccines [no, 1 year ago from the day before Prevenar13 vaccination, 1-5 years ago, more than 5 year ago, unknown date] (reference population: no).

- Subjects ineligible for vaccination: Subject population ineligible for vaccination as described in the package insert. Criteria for subjects ineligible for vaccination is based on separately prescribed "procedure for extracting subjects ineligible for vaccination". Reference population is not used since there is no category within the subgroup.

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

- Adverse reaction: Adverse event whose causal relationship is confirmed by investigator or sponsor.

- Adverse event: Adverse event regardless of causal relationship.

- Priority survey items: No priority survey items in this survey.

6.2. Efficacy Endpoints

Efficacy is not assessed in this survey.

6.3. Other Endpoints

No endpoint other than safety endpoint is used in this survey.

6.4. Covariate

There is no covariate identified from previous clinical study data, etc. or potential covariate in terms of the safety of Prevenar13.

7. HANDLING OF MISSING DATA

When seriousness, corrective treatment and outcome of adverse events are missing, these data are handled as "unknown" for counting.

Since laboratory testing is not mandatory in this survey, laboratory test value or date of measurement is not imputed.

Data not yet cleaned are to be handled as follows:

- Missing data: Handled as missing both in the counting and listing (category variable classified as "unknown").

- Inconsistent data: Handled as missing both in the counting and listing. However, a list of handling data is separately prepared.

- No signature: Data included in the CRF without a signature of contracting investigator (including CRF with a signature of person other than contracting investigator only) are to be handled as missing both in the counting and listing.

8. STATISTICAL METHOD AND STATISTICAL ANALYSIS

8.1. Statistical Method

8.1.1. Analysis of Continuous Data

Summary statistics (number of vaccinees, mean, standard deviation, median, maximum and minimum) are to be calculated.

8.1.2. Analysis of Categorical Data

Frequency (number of vaccinees) and its proportion of each category are to be calculated.

8.1.3. Analysis of Binary Data

Frequency and its proportion are to be calculated. Two-sided 95% confidence interval (exact method) is to be calculated for obtaining the confidence interval of the proportion.

To compare the proportion between subgroups, risk ratio and its 95% confidence interval are to be calculated. In addition, risk ratio and its 95% confidence interval are to be shown in the figure (See Section 10.1).

Statistical hypothesis testing is not to be formally performed in this survey. If statistical hypothesis testing becomes necessary, Fisher's exact test is to be performed for association with nominal scale data, Cochran-Armitage test (exact method) for association with ordinal scale data.

8.2. Statistical Analysis

8.2.1. Summary of Vaccinees

- **Number of institutions and vaccinees to be surveyed by establishment category**

Number of institutions and vaccinees with their proportion by establishment category are to be calculated for the vaccinees whose CRFs collected:

- National, public and private university hospital;
- National hospital established by MHLW;
- Prefectural and municipal hospital;
- Public institution;
- Hospital established by corporations and individuals not described above;
- Private practice/clinic.

Additionally, mean, minimum and maximum of the number of vaccinees per institution are to be calculated.

- **Disposition of vaccinees**

Numbers of vaccinees are to be calculated by those registered, those who completed the survey and those included in the safety analysis population. Also, number of vaccinees are to be calculated by those whose CRFs not collected and those excluded from the safety analysis population as well as by reason for exclusion.

- **Listing of discontinuation and withdrawal**

Numbers of subjects who discontinued vaccination and its proportion are to be calculated in the safety analysis population as well as by reason for exclusion.

- **Listing of subjects excluded from safety analysis population**

Listing of subjects excluded from safety analysis population and the reason for exclusion is to be prepared.

8.2.2. Characteristics and Treatment History of Vaccinees

- **Vaccinee characteristics**

The following characteristics are to be calculated in the safety analysis population in accordance with Section 8.1:

- Gender [male, female];
- Age (continuous);
- Age [<65; ≥65, <70; ≥70, <75; ≥75, <80; ≥80, <85; ≥85];
- Inpatient/outpatient status at the time of initial vaccination [inpatient, outpatient];
- Weight [<40 kg; ≥40 kg, <50 kg; ≥50 kg, <60 kg; ≥60 kg, <70 kg; ≥70 kg, <80 kg; ≥80 kg];
- Complication [no, yes];
- Immunocompromised complication [no, yes]: See Section 5.4 for definition of immunocompromised complication;
- Hepatic dysfunction [no, yes]: See Section 5.4 for definition of hepatic dysfunction;
- Renal dysfunction [no, yes]: See Section 5.4 for definition of renal dysfunction;
- More than once Prevenar13 vaccination [once, more than once];

- Simultaneous vaccination with other vaccine [no, yes];
- Prior vaccination of polyvalent pneumococcal polysaccharide vaccines [no, 1 year ago from the day before Prevenar13 vaccination, 1-5 years ago, more than 5 year ago, unknown date].

The following number of vaccinees and its proportion are to be calculated by System Organ Class (SOC) and Preferred Term (PT) in the safety analysis population:

- Disposition of medical history;
- Disposition of complication.

The following number of vaccinees and its proportion are to be calculated in the safety analysis population:

- Disposition of vaccines before Prevenar13 vaccination;
- Disposition of vaccines after Prevenar13 vaccination.

- **Prevenar13 vaccination data**

The following Prevenar13 vaccination data are to be collected in the safety analysis population:

- Dose [0.5 ml, other];
- Location [upper arm, other];
- Route [intramuscular, other];
- Body temperature at the time of vaccination [<37.5°C, ≥37.5°C, not measured].

- **Simultaneous vaccination data**

Simultaneous vaccination data are to be collected in the safety analysis population:

- Name of vaccine simultaneously administered [Prevenar13 alone, name of vaccine simultaneously administered];
- Location [Prevenar13 alone, location of simultaneous vaccination].

8.2.3. Safety Analysis

8.2.3.1. Adverse Reaction

- **All adverse reaction**

Number of vaccinees experiencing adverse reactions and its proportion are to be calculated. Number of vaccinees experiencing adverse reactions and its proportion are also to be calculated by SOC and PT.

Number of adverse reactions is to be calculated. However, the same adverse reaction which occurred more than once in the same vaccinee is to be calculated as 1 adverse reaction.

- **Serious adverse reaction**

Number of vaccinees experiencing serious adverse reactions and its proportion are to be calculated by SOC and PT.

- **Details of adverse reaction**

Number of vaccinees experiencing adverse reactions and its proportion are to be calculated by SOC and PT for the following data:

- Seriousness [serious, non-serious];
- Expected/unexpected [expected, unexpected];
- Corrective treatment [yes, no];
- Outcome [not recovered, recovered with sequelae, recovering, resolved/recovered, unknown];
- Severity [mild, moderate, severe].

If the same adverse reaction (the same PT) occurred more than once in the same vaccinee, number of vaccinees experiencing the adverse reactions is to be calculated as follows:

- Seriousness: Serious if both serious and non-serious reactions occurred;
- Expected/unexpected: Unexpected if both expected and unexpected reactions occurred;
- Number of days to onset: Number of days to onset of the first reaction;
- Corrective treatment: Yes if vaccinees experienced both reactions requiring and not requiring treatment;
- Outcome: Outcome of the reaction lastly occurred in the vaccine;

- Severity: If the vaccinee experienced reactions with more than one severity, select one in the following order of priority: severe, moderate and mild.

- **Timing of onset of adverse reaction**

Number of vaccinees experiencing adverse reactions and its proportion are to be calculated by timing of initial onset [Day 0, Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Days 7-27, on or after Day 28] by SOC and PT. Proportion of vaccinees experiencing adverse reactions is to be calculated as the proportion to total number of vaccinees included in the safety analysis population for all the timing of onset.

- **Occurrence of adverse reactions by inclusion of/exclusion from safety analysis population**

For the vaccinees whose CRFs collected, a listing of adverse reactions in the vaccinees excluded from safety analysis population is to be prepared. Additionally, number of vaccinees experiencing adverse reactions is to be calculated by inclusion of/exclusion from safety analysis population by SOC and PT.

- **Local reaction**

Number of vaccinees experiencing local reactions and its proportion are to be calculated by SOC and PT. See Section 10.2.1 for definition of local reaction.

- **Systemic reaction**

Number of vaccinees experiencing systemic reactions and its proportion are to be calculated by SOC and PT. See Section 10.2.2 for definition of systemic reaction.

- **Pyrexia**

Number of vaccinees experiencing pyrexia and its proportion are to be calculated by presence or absence of immunocompromised complication and simultaneous vaccination with other vaccine. See Section 10.2.3 for definition of pyrexia.

8.2.3.2. Adverse Event

- **All adverse events**

Number of vaccinees experiencing adverse events and its proportion are to be calculated by SOC and PT.

- **Adverse events by seriousness**

Number of vaccinees experiencing serious adverse events and its proportion are to be calculated by SOC and PT. Also, number of vaccinees experiencing non-serious adverse events and its proportion are to be calculated by SOC and PT.

8.2.3.3. Subgroup Analysis

Number of vaccinees experiencing at least one adverse reaction and its proportion are to be calculated by subgroups as defined in Section 5.4 (excluding subjects ineligible for vaccination). To assess the association between vaccinee characteristics and occurrence of adverse reactions, risk ratio and its 95% confidence interval are to be calculated as described in Section 8.1.3.

To evaluate the safety in specific populations of vaccinees in detail, analyses are to be performed in the following subgroups.

- **Vaccinees with hepatic dysfunction, renal dysfunction and simultaneous vaccination with other vaccine**

Number of vaccinees experiencing adverse reactions and its proportion are to be calculated by SOC and PT in each subgroup.

- **Vaccinees with immunocompromised complication**

Number of vaccinees experiencing adverse reactions, local and systemic reactions and adverse events with its proportion are to be calculated by SOC and PT.

- **Vaccinees with prior vaccination of polyvalent pneumococcal polysaccharide vaccines**

Number of vaccinees experiencing adverse reactions, local and systemic reactions and adverse events with its proportion are to be calculated by SOC and PT by prior vaccination of polyvalent pneumococcal polysaccharide vaccines [1 year ago from the day before Prevenar13 vaccination, 1-5 years ago, more than 5 year ago, unknown date].

- **Vaccinees with immunocompromised complication and prior vaccination of polyvalent pneumococcal polysaccharide vaccines**

Number of vaccinees experiencing adverse reactions, local and systemic reactions with its proportion are to be calculated by SOC and PT by prior vaccination of polyvalent pneumococcal polysaccharide vaccines [1 year ago from the day before Prevenar13 vaccination, 1-5 years ago, more than 5 year ago, unknown date].

- **Subjects ineligible for vaccination**

Reports described below are to be prepared for subjects ineligible for vaccination (See Section 5.4) and used as a reference for reporting safety information of these subjects. If there are less than 10 subjects ineligible for vaccination, however, safety information of these subjects are to be reported with a listing of vaccinees and other forms, and reports described below are not to be prepared.

Number of subjects ineligible for vaccination as described in the package insert and its proportion are to be calculated. In addition, number of the following subjects ineligible for vaccination as described in the package insert which would be identifiable in this survey is to be calculated:

- Subjects with apparent pyrexia;
- Subjects with documented serious acute disease.

Number of subjects ineligible for vaccination with at least one adverse reaction is to be calculated.

8.2.3.4. Exploratory Analysis

Additional analysis may be performed as necessary. Results from exploratory analysis will be reported only if they provide important interpretation.

8.2.4. Efficacy Analysis

No efficacy analysis is to be performed in this survey.

9. LISTING

The following listings are to be prepared:

- Listing of vaccines;
- Listing of vaccinees (safety analysis population);
- Listing of vaccinees who experienced adverse events;
- Listing of vaccinees who experienced adverse reactions;
- Listing of vaccinees excluded from safety analysis population who experienced adverse reactions;
- Listing of vaccinees experiencing serious adverse reactions;
- Listing of vaccinees experiencing serious adverse events;
- Listing of vaccinees with hepatic dysfunction who experienced adverse reactions;
- Listing of vaccinees with renal dysfunction who experienced adverse reactions;
- Listing of vaccinees with immunocompromised complication who experienced adverse reactions;
- Listing of vaccinees with prior vaccination of polyvalent pneumococcal polysaccharide vaccines who experienced adverse reactions;

- Listing of vaccinees with immunocompromised complication and prior vaccination of polyvalent pneumococcal polysaccharide vaccines who experienced adverse reactions.

Additionally, the following listings are to be included in the attached forms of periodic safety reports:

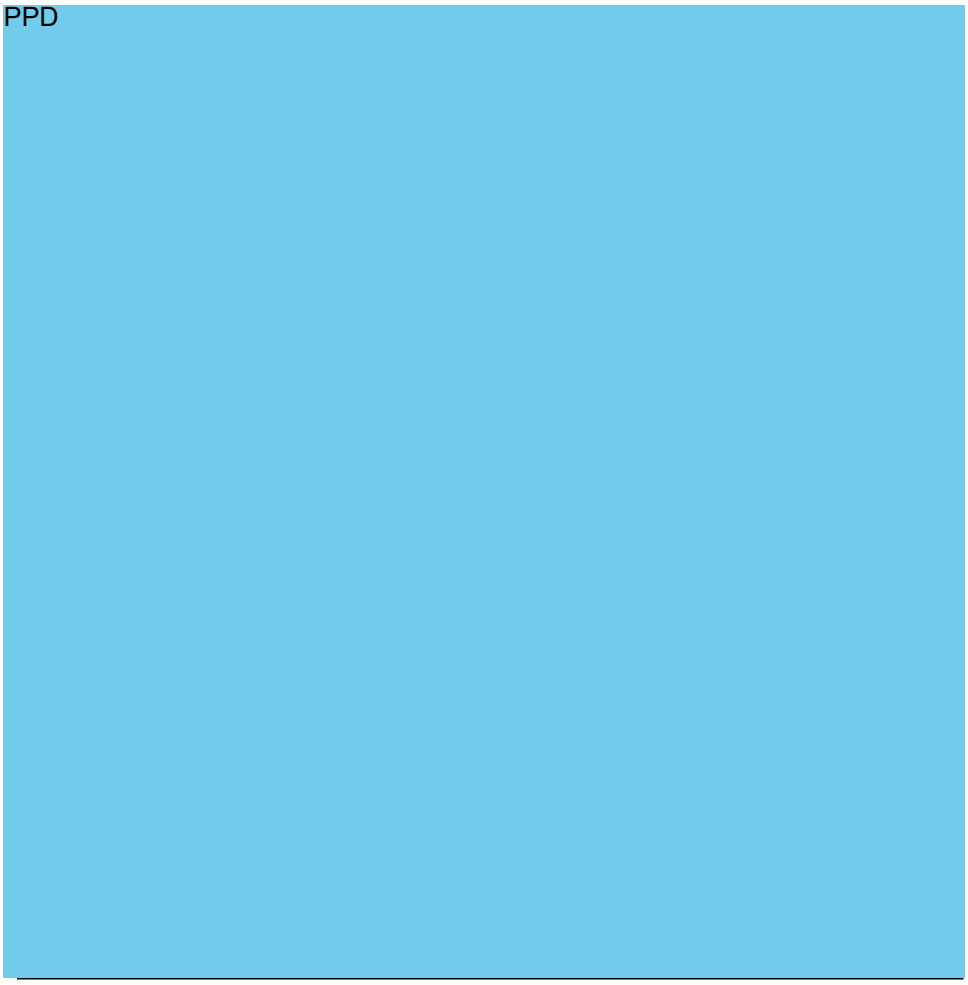
- Attached form 3 (Listing of occurrence of ADR/Infection case report);
- Attached form 2 (Listing of occurrence of ADR/Infection);
- Attached form 10 (Attached form 2-2) (Listing of occurrence of serious adverse events).

If there are at least 10 subjects ineligible for vaccination (See Section 5.4), listings including the following information are to be prepared:

- Case number;
- Criteria for subjects ineligible for vaccination;
- Name of institution;
- Date of vaccination;
- Completion/discontinuation of observation and reason for discontinuation if applicable;
- Presence or absence of adverse reactions;
- Details of each adverse reaction: name of adverse reaction (SOC and PT), date and timing of onset (calculated with day of vaccination as Day 0), date and timing of outcome (calculated with day of vaccination as Day 0), severity, corrective treatment, seriousness and outcome.

10. APPENDIX

10.1. Appendix 1: Example of a Chart of Risk Ratio of Incidence of Adverse Reactions by Subgroups



10.2. Appendix 2: Definition of Events

10.2.1. Local Reaction

Local reaction is defined as an adverse reaction coded as Primary High Level Term of "vaccination site reactions".

10.2.2. Systemic Reaction

Systemic reaction is defined as an adverse reaction coded as PT of either "nausea", "vomiting", "diarrhoea", "headache", "fatigue" or "myalgia" by reference to the current FDA "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials; September 2007" at the start of this survey.

10.2.3. Pyrexia

Pyrexia is defined as an adverse reaction coded as PT of either "hyperthermia", "hyperpyrexia", "pyrexia", or "body temperature increased".