Prevenar 13® Suspension Liquid for Injection Drug Use Investigation

- Investigation in Adults Aged 65 Years or Older -

Protocol

Information on the Investigation

Title	Prevenar 13® Suspension Liquid for Injection Drug Use Investigation - Investigation in Adults Aged 65 Years or Older -
Protocol number	B1851121
Protocol version identifier	Revised version No. 2
Date of last version of protocol	25 March 2015
Nonproprietary name of the investigational drug	13-valent pneumococcal conjugated vaccine (non-toxic mutant of diphtheria toxin)
Brand name of the investigational drug	Prevenar 13® Suspension Liquid for Injection
Objectives	To understand the following matters under the actual use conditions after marketing concerning the safety of Prevenar 13® Suspension Liquid for Injection given as a single vaccination to elderly people (adults aged 65 years or older): 1) Understanding of actual use conditions 2) Understanding of the occurrence of adverse events (AEs)
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TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

Abbreviation	Term
23vPS	23-valent pneumococcal polysaccharide vaccine
AE	adverse event
EDP	exposure during pregnancy
IEC	Independent Ethics Committee
IRB	institutional review board
NIS	Non interventional study
SRSD	Single Reference Safety Document

2. PERSON RESPONSIBLE FOR THE INVESTIGATION

Postmarketing surveillance control manager

Investigator
Not applicable

3. AMENDMENTS AND UPDATE

Amendment number	Date	Amendment to the protocol contents/ others	Amended section	Summary of amendment	Reason
Revised version 1	25 February 2016	Additions	Section 12	Additions	Inadequate description
Version 2	25 March 2015	Other	Cover page, Sections 3, 7, 9, 11, 16, 17, 20 and 21	Description reorganization	Error entries and inadequate description
First version	3 February 2015	N/A	N/A	N/A	N/A

4. PLANNED PERIOD OF INVESTIGATION

Item	Planned date
Start date of the investigation	April 2015
End date of the investigation	October 2016
Date of preparation of the final report	Undecided

5. RATIONALE AND BACKGROUND

Prevenar 13® Suspension Liquid for Injection (hereinafter referred to as Prevenar 13) is a pneumococcal conjugated vaccine containing an active ingredient that is pneumococcal capsular polysaccharides of 13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F), conjugated to non-toxic mutant of diphtheria toxin (CRM197) as a protein carrier, and aluminium phosphate as an adjuvant and polysorbate 80 as an additive. In Japan, marketing approval for Prevenar 13 was granted in June 2013 for the indication: “Prevention of invasive infections due to *Streptococcus pneumoniae* (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) by assuming administration to infants at the age of 2 months, inclusive, to 6 years, exclusive. Furthermore, Prevenar 13 received additional approval in June 2014 for “prevention of infections due to *Streptococcus pneumoniae* (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) in the elderly.

A drug use investigation - investigation in adults aged 65 years or older - (hereinafter referred to as the investigation) of Prevenar 13® Suspension Liquid for Injection will be implemented to understand the below mentioned matters under the actual use conditions after marketing concerning the safety of Prevenar 13 given as a single vaccination to elderly people (adults aged 65 years or older). Information collected in the investigation will be used for providing information on proper use and preparing application data for reexamination. Therefore, the investigation shall be conducted in compliance with the “Ministerial Ordinance on Good

Postmarketing Study Practice" (Ordinance No. 171 of the Ministry of Health, Labour and Welfare [MHLW] dated December 20, 2004). Case data collected in the investigation will be reported to the MHLW pursuant to the "Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics." In that case, information such as the drug name, adverse reaction terms, gender, and age (age category) for applicable case data may be disclosed in a case list in the "Pharmaceuticals and Medical Devices Safety Information" and "Website for Provision of Pharmaceuticals and Medical Devices Information (http://www.info.pmda.go.jp)." Furthermore, collected case data will be disclosed if a request for disclosure is made to the MHLW in accordance with the "Law Concerning Disclosure of Information Retained by Administrative Bodies" (Law No. 42 dated May 14, 1999). In either case, however, information such as the names of physicians and institutions will not be subject to reporting, and thus will not be posted or disclosed.

6. RESEARCH QUESTION AND OBJECTIVES

To understand the following matters under the actual use conditions after marketing concerning the safety of Prevenar 13® Suspension Liquid for Injection given as a single vaccination to elderly people (adults aged 65 years or older):
1) Understanding of actual use conditions
2) Understanding of the occurrence of adverse events (AEs)

6.1. Safety Specifications

1) Safety in persons with immunocompromised state
2) Safety of concurrent vaccination with other vaccines
3) Safety in the elderly (adults aged 65 years or older) who received multiple vaccinations with Prevenar 13
4) Safety of Prevenar 13 in the elderly (adults aged 65 years or older) with a history of immunization with polyvalent pneumococcal capsular polysaccharide vaccines

7. METHOD

7.1. Design

This is a multicenter, open-label investigation in persons who are vaccinated with Prevenar 13. Case report forms (CRFs) will be completed based on medical records documenting data obtained mainly from usual routine medical examination. In order to collect accurate safety data, the "Health Survey Diary for Pneumococcal Vaccine" will be introduced to directly request vaccinees for collaboration.

7.2. Subjects

The subjects of the investigation will be vaccinees who meet the inclusion criteria and defined as registration criteria.

7.2.1 Inclusion criteria

1) Elderly persons (adults aged 65 years or older) who received Prevenar 13

2) Consent of vaccinees (that written informed consent showing that appropriate information on the investigation has been notified is signed and dated personally by the vaccinees to be included in the investigation [or their legal proxies])

The indication, and dosage and administration of Prevenar 13 are as follows. For administration of Prevenar 13, see the latest package insert:

[Indication]
Prevention of infections due to *Streptococcus pneumonia* (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F)
[Dosage and administration]
Prevenar 13 should be intramuscular injected at a dose of 0.5 mL.

7.2.2 Exclusion criteria

No exclusion criteria are specified in the investigation.

7.2.3 Investigation sites

This investigation will be implemented at approximately 100 sites mainly the department of internal medicine.

7.2.4 Planned period of the investigation

The planned period of the investigation is as follows:

Period of the investigation: April 2015 to October 2016

Registration period: April 2015 to September 2016

7.2.5 Investigation method

The investigation will be conducted using the continuous investigation method, with which vaccinees who meet the inclusion criteria will be continuously registered until the number of contracted cases is reached.

7.2.6 Observation period

The observation period will be a period up to 28 days after vaccination with Prevenar 13 (The day of vaccination will be defined as Day 0).

The investigator should evaluate AEs on or after Day 28 from the date of vaccination, by defining the day when the vaccinee first visits the hospital as the end day of observation. If the vaccinee does not visit the hospital, the investigator should make an inquiry to the vaccinee by phone and assess AEs. For the timing of confirmation by phone, see Table 2.

If the observation period does not meet the requirement of up to Day 28 after vaccination despite the use of the abovementioned method, and confirmation by phone cannot be made,

AEs should be evaluated with the period up to the date on which the investigator was able to confirm the information of the vaccinee for the last time regarded as the observation period.

In addition, the investigator should distribute the "Health Survey Diary for Pneumococcal Vaccine" to request vaccinees to record the results of observation during a period from the date of vaccination to Day 13 (The day of vaccination will be defined as Day 0). The diary should be retrieved at hospital visits on or after Day 13, and the investigator should interview the vaccinees to collect AEs.

Table 1. Method and timing of AE evaluation

Standard AE evaluation (at a visit)	AEs will be evaluated on or after Day 28 from the vaccination, whenever the vaccinee first visits the hospital.
Timing of AE evaluation by phone	Information on a vaccinee will be confirmed by phone if the vaccinee does not make a visit after the abovementioned period.
In the case where the observation period does not meet the requirement of 28 days after vaccination	If the observation period does not meet the requirement of up to Day 28 after the vaccination despite the use of the abovementioned method, and confirmation by phone cannot be made, AEs will be evaluated with the period up to the date on which the investigator was able to confirm the information of the vaccinee for the last time regarded as the observation period.

7.3. Investigation Items

Table 2 List of investigation items

		Registration form	CRF
Investigation items \ Time point		At registration	Observation period (from day of vaccination to Day 28)
Registration items	Information to identify the vaccinee	●	●
	Date of the vaccination with Prevenar 13	●	●
	Whether the registration criteria are met	●	
Investigation items	Body weight		●
	Inpatient/outpatient status		●
	Medical history (past history and complications)		●
	Details of treatment of immunodeficiency disorder		●
	History of immunization with 23vPS		●
	History of immunization with other vaccines		●
	Record of vaccination with Prevenar 13		●
	Body temperature at		●

	vaccination with Prevenar 13		
	Concurrently used vaccines		●
	Status of immunization with other vaccines		●
	End date of observation and discontinuation record		●
	AEs		●

7.3.1 Vaccinee background

1) The following information at vaccination with Prevenar 13 should be entered in the registration form:
   (1) Identification number (other than the medical record number)
   (2) Gender
   (3) Age (as of the day of vaccination with Prevenar 13)
   (4) Date of vaccination with Prevenar 13
   (5) Whether the registration criteria are met

2) The following information at vaccination with Prevenar 13 should be recorded in the CRF:
   (1) Body weight
   (2) Inpatient/outpatient status
   (3) Medical history (past history and complications)
   For vaccinees suffering from a disease*, the status of morbidity at vaccination with Prevenar 13 and the name of the disease will be entered.
   As for the status of morbidity, it will be entered as "past history" in the case where the vaccinee had the disease before vaccination with Prevenar 13 but the disease has been cured at the time of the first vaccination, and as a "complication" in the case where the vaccinee is suffering from the disease at the time of vaccination with Prevenar 13.
   * Disease: Chronic disease (including allergy), disease requiring treatment, disease or disorder associated with surgery, hospitalization, and sequela, or any other disease (or syndrome) considered to be a problem.
   (4) Details of treatment of immunodeficiency disorder
   (5) History of immunization with 23vPS
   (6) History of immunization with other vaccines

7.3.2 Record of vaccination with Prevenar 13

The following information should be entered for the status of vaccination with Prevenar 13:
1) Date of vaccination
2) Dose
3) Administration site
4) Route of administration
5) Serial number (lot number)

7.3.3 Concomitant therapies

Information on vaccines falling into the following should be entered:
1) Vaccines concurrently administered with Prevenar 13

(1) Name of concurrently administered vaccine
(2) Administration site

2) Vaccines administered before Day 28 after vaccination with Prevenar 13 (The day of vaccination will be defined as Day 0.)
(1) Name of vaccine
(2) Date of vaccination

7.3.4 Test

1) Body temperature
Body temperature at vaccination with Prevenar 13 should be entered.

7.3.5 End date of observation and discontinuation record

The investigator should enter Day 28 from the vaccination or any day after Day 28 (The day of vaccination will be defined as Day 0), whenever the vaccinee first visits the hospital (the date on which the investigator was able to confirm the information of the vaccinee), as the end date of observation. If the end day of observation does not meet the requirement of up to Day 28 from vaccination, the reason for discontinuation should be input.

7.3.6 Efficacy evaluation

No efficacy evaluation will be performed in the investigation.

7.3.7 AEs

The investigator should record the below mentioned information after checking the occurrence of AEs during the AE collection period. Particularly, the vaccinees should be explained to notify local and systemic reactions, if occurred, to the investigator. If AEs are identified, the investigator should take appropriate therapeutic actions, immediately inform the sponsor, and monitor the outcome and course until symptoms resolve, as a rule.
If the sponsor determines it necessary in vaccinees with serious adverse reactions, adverse reactions such as local and systemic reactions in the investigation, adverse reactions not specified in the package insert, etc., a detailed investigation should be separately performed.
(1) Whether or not AEs occurred
(2) AE term
(3) Date of onset
(4) Severity
(5) Therapeutic action taken or not taken (if taken, its detail)
(6) Seriousness
(7) Outcome
(8) Causal relationship with Prevenar 13

[Assessment of severity]
The investigator should record the maximum severity during the period from the onset of the AE to the confirmation of its outcome using mild, moderate, or severe (for pyrexia, mild, moderate, severe or possibly life-threatening). The severity will be defined as follows (Table 3):

Table 3 Definition of severity

	Absent	Mild	Moderate	Severity	Possibly life-threatening
Injection site erythema and swelling	< 2.5 cm	≥ 2.5 cm, ≤ 5.0 cm	> 5.0 cm, ≤ 10.0 cm	> 10.0 cm	-
Pyrexia	< 37.5°C	≥ 37.5°C, ≤ 38.4°C	≥ 38.5°C, ≤ 38.9°C	≥ 39.0°C, ≤ 40.0°C	> 40.0°C
Other AEs	-	Not interfering with the normal function of the vaccinee	Interfering with the normal function of the vaccinee to some degree	Significantly interfering with the normal function of the vaccinee	-

[If an AE of pyrexia occurs, the following information should be additionally entered:]
(1) Date of measurement
(2) Body temperature
Be sure to record the maximum body temperature during the period from the onset of pyrexia to its resolution.

[In the case of AEs related to laboratory tests, etc. and abnormal changes in test values, the following should be additionally entered:]
(1) Name of test
(2) Site reference value
(3) Unit
(4) Date of measurement
(5) Results

7.3.8 Priority investigation items

No priority investigation item is specified in the investigation.

7.4 Data Source

In the investigation, the investigator will extract necessary information in accordance with the protocol using information in medical records and the "Health Survey Diary for Pneumococcal Vaccine."

7.5 Target Sample Size

7.5.1 Planned sample size of the investigation

600 persons (number of persons to be registered)

7.5.2 Rationale

In the age group of 65 years or older in a clinical study, B1851088 (noninferiority study) involving elderly subjects (adults aged 65 years or older) without history of immunization with pneumococcal vaccines and a clinical study, 6115A1-3004 (open-label study) involving

adults aged 50 years or older conducted in Japan, the incidence of local reactions reported by the subjects using an electronic diary during 14 days after vaccination with Prevenar 13 was 55.8% and 63.6%, respectively, and the incidence of systemic reactions was 37.9% and 52.6%, respectively. In the two studies, the incidence of AEs (adverse reactions) related to Prevenar 13 reported by the investigators during approximately one month after vaccination with Prevenar 13 was 3.9% (13/333) and 6.6% (9/136), respectively. The results of comparison between Japanese and overseas clinical study data revealed no new risk factor requiring attention in the Japanese subjects aged 65 years or older. In the Japanese clinical studies, 518 elderly subjects aged 65 years or older (B1851088, n = 382; and 6115A1-3004, n = 136) received Prevenar 13, and 469 subjects included in the safety set (B1851088, n = 333; and 6115A1-3004, n = 136) were evaluated for safety. Consequently, for the safety of Prevenar 13 under actual use conditions after marketing, a planned sample size of the investigation was set to 600 persons to collect and examine safety information from a subject scale equivalent to those of the Japanese clinical studies.

7.6 Data Management

7.6.1 Data collection method

In the investigation, data entry and verification will be carried out using the drug postmarketing surveillance data collection system (EDC; hereinafter referred to as the system) on the internet.

7.6.2 Case registration

7.6.2.1 Case registration procedures

After receiving individual user ID and password for the investigator, he/she will register persons on the vaccinee registration screen of the system. In addition, the investigator will explain the vaccinees to use the “Health Survey Diary for Pneumococcal Vaccine” and receive their consent before case registration. Case registration shall be carried out as soon as Prevenar 13 is given to the vaccinees.

7.6.2.2 Confirmation of registered cases

After the number of registered cases reaches the number of contracted cases, the investigator should check the contents of the “Continuous Investigation Confirmation Form” provided by the sponsor and affix his/her name and seal on or sign the confirmation form.

7.6.3 Points to consider for completing, correcting and submitting the CRF

7.6.3.1 Data entry method

The investigator should enter data to the system based on medical records upon confirming the investigation items and send the data after digital signing.

7.6.3.2 Correction method

If an inquiry (reinvestigation) concerning the entered data is made by the sponsor, the investigator will confirm the medical records again, and as necessary, correct the entered data and send it.

7.6.3.3 Submission method

The CRFs should be sent as soon as data are entered in accordance with procedures specified by the sponsor.

7.7 Data Analyses

1) Safety analysis set
The safety analysis set will include persons who meet the registration criteria for vaccinees and whose safety data are obtained after vaccination with Prevenar 13.

2) Method of safety analysis
The incidence (the number of vaccinees with adverse reactions/the number of vaccinees in the safety analysis set) of adverse reactions (vaccination-related AEs) will be the primary analysis endpoint, which will be tabulated. In addition, the incidence of adverse reactions will be tabulated by variable of vaccinee background, etc. to examine factors affecting the onset of adverse reactions.

The details of analysis methods should be as specified in a separately prepared statistical analysis plan.

The detailed methods for statistical analyses of data collected in the investigation will be presented in the statistical analysis plan for the investigation which will be retained by Pfizer. In the statistical analysis plan, the plan summarized in the protocol may be changed, but the definition of the primary endpoint and/or important changes in its analysis will be reflected in a protocol revision.

7.8 Quality Control

Prior to the implementation of the investigation, the person in charge of the site will explain details such as the protocol to the investigator and request him/her to prepare CRFs based on medical records.

7.9 Limitation of Study Methods

The following matters may be assumed for the investigation:
1) Because no control group is established, there is a limitation in determining whether or not vaccination with Prevenar 13 increases the risk of AEs or adverse reactions.
2) Background information may not be adequately collected so that confounders may not be fully taken into account.
3) Since this is an investigation to collect data from medical records, specified data may not be collected or lack.

7.10 Other Necessary Matters

Not applicable

8 PROTECTION OF VACCINEES TO BE INCLUDED IN THE INVESTIGATION

8.1 Information and Consent of Vaccinees to Be Included in the Investigation

Any personnel who is involved in the investigation shall guarantee the protection of the personal information of vaccinees to be included in the investigation and prevent that the names of vaccinees to be included in the investigation are not mentioned in forms to be completed provided by Pfizer, reports, publications or other documents possibly disclosed, except for the case where such is required by laws. Pfizer shall maintain high level confidentiality to protect personal information when transferring data.

The informed consent form shall be in compliance with regulatory and legal requirements of the countries where the investigation is conducted.

The informed consent form to be used for the investigation and any change made during the investigation period shall be approved by Pfizer. The informed consent form shall be approved by the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) before its use at necessary sites.

The investigator shall adequately explain the vaccinees to be included in the investigation or their legal proxies about the contents and objectives of the investigation and potential risks associated with participation in it. The investigator or person designated by the investigator should receive written consent of the vaccinees to be included in the investigation or their legal proxies prior to implementing investigation-related activities. The investigator should retain the original of the informed consent form signed by the vaccinees to be included in the investigation.

8.2 Criteria and Procedures for Discontinuation of the Investigation in the Vaccinees to Be Included in the Investigation

The vaccinees to be included in the investigation may terminate their participation in the investigation at any time if they wish to do so. Also, the investigator or Pfizer may discontinue their participation in the investigation at their discretion at any time because of safety, behaviors of the vaccinees to be included in the investigation, or management reasons. In any event, the outcome of the vaccinees to be included in the investigation should be recorded whenever possible. The investigator shall confirm the reason for discontinuation, and follow up the course of the vaccinees to be included in the investigation if there are AEs not resolved.

In the case where the participation of the vaccinees to be included in the investigation is terminated and their consent for information disclosure in the future is withdrawn, no evaluation or collection of additional data thereafter shall be carried out. Pfizer may retain and continue using data collected before withdrawal of consent.

8.3 Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)

No review of the investigation by the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) is mandatory.

8.4 Ethical Conduct of the Investigation

This section is not applicable to the investigation because it is within the scope of application of the "Ministerial Ordinance on Good Postmarketing Study Practice" (Ordinance No. 171 of the MHLW dated December 20, 2004).

9 MANAGEMENT AND REPORTING OF AES/ADVERSE DRUG REACTIONS (ADRS)

The handling of each event when the investigator learned events related to safety information is specified below.

Events required to be reported to the sponsor within 24 hours should be notified using a given AEs report form (NIS AE Report Form).

The person in charge of the site should request the investigator to report events, which are required to be reported within 24 hours by him/her, at the start of the investigation, and periodically visit the investigator to request for reporting during the investigation period.

The AE report form (NIS AE Report Form) should be handled as part of the CRF.

9.1 Report Requirements

The following table summarizes requirements for recording of safety events in the CRF and reporting of safety events to Pfizer Safety Division using the NIS AE Report Form (Non-Interventional Study Adverse Event Report Form). These requirements are described for the following three types of events: (1) serious adverse events (SAEs), (2) non-serious AEs (if applicable), and (3) drug exposure-related scenario including exposure during pregnancy, exposure during breastfeeding, misdosing, overdosing, drug misuse, extravasation, and occupational exposure. These events are defined in the Section "Definition of Safety Events."

Safety events	To record in the CRF	**To report within 24 hours after learning the event to Pfizer Safety Division using the NIS AE Report Form**
SAEs	All	All
Non-serious AEs	All	None
Prevenar 13 exposure-related scenario including exposure during pregnancy, exposure during breastfeeding, misdosing, overdosing, drug misuse, extravasation, lack of pharmacological effect, and occupational exposure	(Regardless of accompanying AEs) all, **excluding occupational exposure**	(Regardless of accompanying AEs) all

The investigator shall confirm the outcome of each AE and obtain adequate information to determine whether or not the event corresponds to the criteria for SAEs (see the Section "SAEs" below).

The safety events listed in the above table shall be reported to Pfizer within 24 hours after the investigator is aware of it whether or not the investigator judges that the event is related to Prevenar 13. Particularly, SAEs resulting in death or being life-threatening shall be promptly notified to Pfizer regardless of the degree of their information obtained. This reporting period is also applicable to the case where new additional (follow-up investigation) information for a submitted safety event report is obtained. In a rare case where the investigator is not promptly aware of the onset of safety events, the investigator shall report the event within 24 hours after learning it and record the first date and time when he/she is aware of the event.

For safety events deemed as serious and safety events specified in the right column of the above table that shall be reported to Pfizer within 24 hours after learning the events, the investigator shall perform a follow-up investigation and report follow-up information if any to Pfizer in accordance with the reporting period of within 24 hours. Furthermore, the investigator may be requested from Pfizer to urgently obtain specific follow-up information. Such information is required to be more detailed information than that to be recorded in the CRF. In general, this information includes complete medical evaluation on the AE and adequately detailed information enabling to independently assess the causal relationship. Information (e.g., concomitant medications and complications) on the event shall be also provided. If the vaccinees died, a summary of available autopsy findings shall be promptly submitted to Pfizer or the person to whom Pfizer has outsourced the activity.

9.2 Reporting Period

The reporting period of safety events in each vaccinee shall be at least 28 days (calendar days) after administration of Prevenar 13 starting from the first administration of Prevenar 13 to the vaccinee or if the vaccinee has already received Prevenar 13, from the time of obtaining his/her consent to the end of the observation period in the investigation. If the types of safety events listed in the above table occurred during the said period, a report shall be submitted to Pfizer Safety Division (or the person to whom Pfizer has outsourced the activity). If the vaccinees have received Prevenar 13 on the end day of the observation period, the reporting period will be prolonged for 28 days (calendar days) after the end of observation. In the majority of cases, the date of informed consent is the same as the date of registration. Under some circumstances, there may be a time difference between the date of informed consent and the date of registration. In such a situation, when consent is received from vaccinees, but they are not registered in the investigation (e.g., the vaccinees changed their mind about taking part in the investigation), the reporting period is terminated on the day when a decision not to register the vaccinees is made.

In the case where the investigator learned that SAEs occurred at any time after the completion of the investigation, if the SAEs are determined to be related to Prevenar 13, the SAEs shall be also reported to Pfizer Safety Division.

9.3 Assessment of the Causal Relationship

The investigator will be required to assess and record the causal relationship. Furthermore, he/she shall obtain adequate information for assessing the causal relationship for each AE.

For AEs related to Prevenar 13, the investigator will be required to carry out a follow-up investigation until the event or its associated sequela resolves, or becomes stable to the extent it can be accepted by the investigator, and Pfizer agrees with the judgement.

The assessment of the causal relationship by the investigator should be made based on whether or not Prevenar 13 may have reasonably caused the AE or be of its cause. When the final assessment of the causal relationship by the investigator is “unknown” and whether or not Prevenar 13 has caused the event cannot be determined, the safety event shall be reported within 24 hours.

When the investigator cannot identify the cause of the event but judges that Prevenar 13 has not caused the event, such a fact should be specified in the CRF and NIS AE Report Form.

9.4 Definition of Safety Events

9.4.1 AEs

An AE is any untoward medical occurrence in a vaccinee administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Example AEs are listed below but are not limited to the following:

Abnormal test findings (for criteria for abnormal test findings to correspond to AEs, see below)

- Clinically significant symptoms and signs
- Changes in physiological test findings
- Hypersensitivity
- Progression/ worsening of the primary disease
- Lack of pharmacological effect
- Drug abuse
- Drug dependency

Furthermore, signs and symptoms due to the following causes may be included:

- Drug overdosing
- Treatment discontinuation
- Drug misuse
- Off-label use
- Drug interactions
- Extravasation
- Exposure during pregnancy
- Exposure during breastfeeding
- Misdosing
- Occupational exposure

<u>Abnormal test findings</u>

Criteria for determining abnormal test findings that should be reported as AEs are as follows:

- When symptoms related to tests results are present
- When an additional diagnostic test or medical/surgical treatment is required
- When a change of the dose of Prevenar 13, treatment discontinuation, or addition of treatment with concomitant medications or other treatment is made based on test results
- When the investigator or Pfizer judged abnormal test findings to be AEs.

The persistence of simple abnormal values not falling into any of the above criteria is not an AE. Also, it is unnecessary to report abnormal values due to test errors as AEs.

9.4.2 SAEs

An SAE is any untoward medical occurrence in a vaccinee administered a pharmaceutical or nutrition product (including products for children) at any dose that corresponds to the following events that:

- results in death;
- is life-threatening;
- requires hospitalization or prolongation of existing hospitalization (For conditions not corresponding to AEs, see below);
- results in persistent or significant disability/incapacity (that significantly interferes with the ability to execute usual living function); or
- results in congenital anomaly/birth defect.

Medical and scientific judgement should be exercised in deciding whether or not the event is medically important. Medically important events may not be immediately life-threatening or result in death but may jeopardize the vaccinee or may require intervention to prevent one of the other outcomes listed in the definition above. These should be reported as SAEs.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Furthermore, when transmission of infectious substance via Pfizer products is suspected, it is deemed as serious whether it is pathogenic or non-pathogenic. Such events may be suspected from clinical signs or laboratory findings suggesting infection in vaccinees exposed to Pfizer products. The term “suspected infection transmission” is considered to be a synonym of “infection transmission.” These cases are deemed as unexpected events and handled by the Safety Department to be a serious emergency priority case. In addition, for such a case, reporting of a product defect, if appropriate, shall be also considered.

<u>Hospitalization</u>

Hospitalization is defined as new admission to the hospital or medical institution equivalent to this (even if the hospital stay is less than 24 hours) or the prolongation of an existing hospitalization period. Transfer to another department or emergency/intensive care unit in the hospital (e.g., transfer from the psychiatric ward to the internal medicine ward, from the

internal medicine ward to the intensive care unit for coronary diseases, and from the neurological ward to the tuberculosis ward) is also included in hospitalization. Treatment in the emergency unit is not always included in hospitalization, but events resulting in treatment in the emergency unit should be assessed for medical importance.

Hospitalization not accompanying a medical AE is not an AE and thus not subject to reporting. For example, it is not necessary to report the following hospitalization not accompanying a medical AE:

- Hospitalization due to social reasons (e.g., The patient/subject has no accommodation.)
- Management hospitalization (e.g., for once-yearly health check-up)
- Voluntary hospitalization not due to acute changes in clinical conditions (e.g., voluntary plastic surgery)
- Hospitalization for follow-up not accompanying medical AEs
- Hospitalization for the treatment of disease existing since before the start of the investigation that is not related to the onset of new AEs or worsening of the pre-existing disease (e.g., detailed examination for abnormal laboratory values that have been noted since before treatment initiation)
- Protocol-specified hospitalization during the investigation period (e.g., tests and treatment stipulated in the protocol)

9.4.3 Scenarios of events that shall be reported within 24 hours to the Safety Department, Pfizer

Scenarios concerning exposure during pregnancy, exposure during breastfeeding, misdosing, overdosing, drug misuse, extravasation, lack of pharmacological effect and occupational exposure are described below.

Exposure during pregnancy

Exposure during pregnancy (EDP) occurs in the following cases:

- where a women became pregnant or aware of being pregnant while she is on or directly exposed to Prevenar 13 (e.g., environmental exposure); or where a women became pregnant or aware of being pregnant after discontinuation or direct exposure to Prevenar 13 (maternal exposure).

Examples of environmental exposure include direct contact with Pfizer products by pregnant women (e.g., A nurse reports that she became pregnant, and she has been exposed to chemotherapeutics until that time.);

- where a man was exposed to Prevenar 13 through treatment or environmental exposure before or around conception; or where a man was exposed while his partner is pregnant (paternal exposure).

In principle, prospective and retrospective EDP reports from any information source shall be notified whether or not they are AEs. At that time, the procedures for SAE reporting shall be followed.

In the case where the vaccinees or their partners are found to have become or be pregnant during the Prevenar 13 treatment period, this information shall be submitted to Pfizer using the NIS AE Report Form and EDP Supplemental Form whether or not it is an AE.

Furthermore, information on environmental exposure of pregnant women to Prevenar 13 (e.g., a pregnant subject mistakenly inhaled a cytotoxic drug or touched a spilled drug) shall be also handed in using the NIS AE Report Form and EDP Supplemental Form. These reports shall be made whether or not it is an AE.

Information to be submitted shall include the expected date of delivery (for information on abortion, see below).

A follow-up investigation on general pregnancy information should be carried out. Furthermore, a follow-up investigation on information on the outcome of EDP should be performed for all EDP reports in which the outcome of pregnancy is unknown. A follow-up investigation on pregnancy should be implemented until delivery or the termination of pregnancy (e.g., artificial abortion), and the outcome should be reported to Pfizer. This information should be submitted as a follow-up investigation on an early EDP report. If a newborn was born, whether or not the newborn has external malformation should be assessed. If an abortion is carried out, the reason should be clarified, and if clinically possible (unless congenital anomaly is confirmed by tests and reported), whether or not the aborted child has external malformation should be evaluated by gross observation.

If the outcome of pregnancy meets the criteria for SAEs [i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal death, neonatal death, and congenital anomaly (in the case of live-born infant, aborted fetus, intrauterine fetal death and neonatal death)], the procedures for SAE reporting shall be followed.

Follow-up information on the outcome of pregnancy to be reported as an SAE is as follows:

- Spontaneous abortion includes miscarriage and missed abortion.
- Neonatal death within one month after birth should be reported as an SAE regardless of the causal relationship. Furthermore, the death of an infant after one month after birth, which is determined by the investigator to be related or probably related to drug exposure, should be reported as an SAE.

Follow-up information on EDP may be required. A detailed follow-up investigation on the outcome of delivery (e.g., Follow-up investigation on the presence or absence of developmental delay of a premature baby) should be handled for individual subjects.

In the case of paternal exposure, the subjects will receive the “Disclosure of information on partners during pregnancy” that should be given to their partners. The fact that this document to be given to the partners has been provided to the subjects shall be recorded.

Exposure during breastfeeding

A scenario of exposure during breastfeeding shall be reported whether or not it is an AE. Particularly, if Pfizer products (e.g., vitamins) approved to be used in breastfeeding women are administered in accordance with the approved dosage regimens, no report of exposure during breastfeeding will be prepared. However, if AEs related to administration of these drugs occurred in infants, the AEs should be reported with exposure during breastfeeding.

Misdosing

Misdosing is an event leading to improper use of a drug under supervision of healthcare professionals, vaccinees or consumers, or adversely affecting vaccinees that can be prevented. Such an event is related to medical acts, products, treatments and systems including prescription, prescription notification, product labels, packages and names, combinations, preparation, distribution, administration, education, monitoring and use.

Examples of misdosing are as follows:

- Prevented misdosing whether or not it directly affected vaccinees (e.g., careless/wrong administration mistakenly using dosage and administration not presented on a product label or prescription by healthcare professionals or vaccinees/consumers)
- Mixing up of names (e.g., brand name)

The investigator shall submit the following misdosing whether or not there are related AEs/SAEs:

- Misdosing related to exposure of vaccinees to the product whether or not misdosing accompanies AEs
- Misdosing not directly involving vaccinees (e.g., possible misdosing or near miss including potential or prevented misdosing). If misdosing is not involved in exposure of vaccinees to the product, a misdosing report should be prepared based on the following minimum criteria:
- Identifiable reporter
- Suspected product
- Misdosing event

Overdosing, drug misuse and extravasation

The investigator should report overdosing, drug misuse and extravasation associated with the use of Pfizer products to Pfizer whether or not they are AEs/SAEs.

Lack of pharmacological effect

The investigator should report a lack of pharmacological effect of Pfizer products to Pfizer whether or not it is an AE/SAE or for any indications of Pfizer products.

Occupational exposure

The investigator should occupational exposure to Pfizer products to Pfizer whether or not it is an AE/SAE.

9.5 Single Reference Safety Document

A single reference safety document (SRSD) refers to a document presenting information on a known safety profile and is the package insert of Prevenar 13 in the investigation. The sponsor should assess safety information reported by the investigator during the investigation period with the use of the SRSD.

In addition, the investigator should follow prescription and dosing guidance based on the SRSD.

10 PLAN FOR THROUGH NOTIFICATION OF RESULTS AND PUBLICATION

Investigation results may be presented at academic conferences or in papers for providing information on proper use.

Report of problems

In the case of new information on the prohibition of the use of Prevenar 13 or any restrictions (e.g., discontinuation of distribution) by regulatory agencies supervising any region in the world, or when the investigator learned new information affecting the benefit and risk assessment of Prevenar 13, such information should be promptly notified to the sponsor.

If the investigator took emergency safety measures to protect vaccinees registered in the investigation from immediate hazards and noticed major violation of the protocol, he/she should promptly notify it to the sponsor.

11 ORGANIZATION SYSTEM FOR THE IMPLEMENTATION OF THE INVESTIGATION

The organization system will be the same as that for postmarketing surveillance activities presented in the risk management plan (RMP). The person responsible for the investigation will be the Director of the Postmarketing Investigation Planning and Management Department.

12 NAME AND ADDRESS OF THE PERSON TO WHOM THE ACTIVITIES ARE OUTSOURCED, AND OUTSOURCED ACTIVITIES

1) Address: 24-1 Nihonbashi Hakozaki-cho, Chuo-ku, Tokyo

Name of company: CAC Exicare Corporation

Scope of outsourced activities: Activities for registration, reception of CRFs, monitoring, data management, tabulations/analyses, etc.

2) Address: 2-4-32 Aomi, Koto-ku, Tokyo

Name of company: Fujitsu FIP Corporation

Scope of outsourced activities: EDC (e.g., Establishment and operation of a data collection system)

13 POSSIBLE ADDITIONAL MEASURES TO BE TAKEN BASED ON THE RESULTS FROM THE INVESTIGATION AND CRITERIA FOR DECIDING THEIR INITIATION

At milestones, the RMP including the following items should be reviewed:

• To evaluate whether or not it is necessary to amend the details of risk minimization activities for the current safety specifications;
• To examine whether or not it is necessary to amend the details of this protocol (e.g., the continuation of the investigation and the implementation of an additional investigation) including the presence or absence of new safety specifications; and
• To consider whether or not it is necessary to establish a risk minimization plan for a new safety specification.

14 IMPLEMENTATION STATUS OF THE INVESTIGATION AND EVALUATION OF OBTAINED RESULTS, OR PLANNED MILESTONES FOR MAKING REPORTS TO THE PMDA AND THEIR RATIONALES

Safety will be assessed and reported at the time of submitting periodic safety reports and the end of the investigation.

15 OTHER NECESSARY MATTERS

1) Protocol revision

The necessity for revising the protocol should be examined in consideration of new evidence becoming available according to the progress of the investigation, and the protocol should be revised as needed. In addition, when partial changes in the dosage and administration or indications are approved during the reexamination period (excluding the case where a reexamination period is newly designated), the necessity of protocol revision should be reviewed, and the revision should be made as needed.

2) Actions for problems and questions if any

When the onset of serious and unexpected ADRs is suggested, the incidence of ADRs greatly increased, any efficacy or safety issue is identified as compared with those before approval, or the onset of different ADRs is suggested, a revision of the package insert and the implementation of a new special drug use investigation or postmarketing clinical study should be considered.

16 CONTACT INFORMATION

16.1 Where to Contact for the Contents of Investigation

Name	Postmarketing Investigation Planning and Management Department, Pfizer Japan Inc.
Address	Shinjuku Bunka Quint Bldg., 3-22-7 Yoyogi, Shibuya-ku, Tokyo 151-8589
E-mail address	PRV_Adult_EDC_PMS@pfizer.com

16.2 Where to Contact for the EDC System

Name	PostMaNet CSD, Fujitsu FIP Corporation
Reception hours	Monday through Friday: 9:00 to 21:00 (excluding national holidays)

Phone number	0120-002-593

17 REFERENCES

None

18 LIST OF TABLES

19 LIST OF FIGURES

Not applicable

Table of contents of independent documents

Not applicable

Follow-up information

Not applicable