AMEPAROMO CAPSULES 250 mg Drug Use Investigation

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

[redacted]

[redacted]

STUDY INFORMATION

Title	AMEPAROMO Capsules 250 mg Drug Use Investigation
Protocol ID	B3391001
Protocol version identifier	2
Date of last version of protocol	27 APR 2015
Active substance	Paromomycin sulfate
Medicinal product	AMEPAROMO Capsules 250 mg
Research question and objectives	This study will be conducted to investigate the safety and effectiveness of AMEPAROMO Capsules 250 mg in daily medical practice in terms of: 1) Adverse reactions unexpected from precautions (unknown adverse reactions); 2) Occurrence of adverse reactions under daily medical practice; and 3) Factors that may affect safety, effectiveness and other relevant matters.
Author	PPD Post Marketing Study Strategy and Management PPD

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[redacted]

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
EDP	Exposure during pregnancy
IEC	Independent Ethics Committee
IRB	Institutional review board
N/A	Not applicable
NIS	Non-interventional study
SRSD	Single Reference Safety Document

2. RESPONSIBLE PARTIES

The Japan Good Post marketing Study Practice officer

Principal Investigator(s) of the Protocol
N/A

3. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
Version 2	02 June 2016	Other amendment(s)	12	Changes in the contents of outsourced activities	Because the contents of outsourced activities were changed

4. MILESTONES

Milestone	Planned date
Start of data collection	May 2015
End of data collection	Until the target sample size is achieved or one year prior to the reexamination period after the start of the study, whichever is earlier
Final study report	To be decided

5. RATIONALE AND BACKGROUND

AMEPAROMO (nonproprietary name, paromomycin sulfate) has been positioned as one of the standard drugs for the treatment of intestinal amebiasis in Japanese and overseas guidelines because it is rarely absorbed by [redacted]

the digestive tract following oral administration and thus can act on *Entamoeba histolytica* (protozoa and cysts) in the intestinal lumen at high concentrations. In Japan, paromomycin preparations were approved and distributed for the indications including Shigellosis during a period from the 1960's to 1990's, but thereafter, because the approval was withdrawn, drugs, which were normally used in foreign countries, were not available in Japan. As its countermeasure, the current "Study on the establishment of medical responses through optimal treatments with orphan drugs for imported tropical diseases and infestations" Group (Research Group of Tropical Diseases and Parasitic Diseases) has taken the responsibility to import paromomycin preparations since 1998 to organize a system paying consideration that these drugs can be available for the treatment of patients with amebiasis. Under these circumstances, the Japanese Association for Infectious Diseases and the Research Group of Tropical Diseases and Parasitic Diseases submitted a request for the development of paromomycin preparations for the indication of intestinal amebiasis in Japan, and it was reviewed by the "Evaluation Committee on Unapproved or Off-labeled Drugs with High Medical Needs," Ministry of Health, Labour and Welfare (MHLW). In December 2010, in response to the development request from the MHLW, Pfizer Japan Inc. undertook the development of "AMEPAROMO Capsules 250 mg," and approval was granted to the indication, "intestinal amebiasis," in December 2012.
In foreign countries, a paromomycin preparation has been sold by Parke-Davis GmbH (current Pfizer Inc.) in Germany since 1961 and approved and distributed in 18 countries including the EU countries as of August 2012.

The drug use investigation of AMEPAROMO Capsules 250 mg (hereinafter referred to as "this study") shall be conducted to collect or confirm information on the occurrence by type of adverse reaction associated with AMEPAROMO in daily medical practice, and information on the quality, effectiveness and safety of AMEPAROMO. The information collected from this study shall be used to provide proper use information and prepare documents for the reexamination application. This study shall be therefore implemented in strict compliance with the "MHLW Ordinance on the Standard for Post-Marketing Studies and Clinical Trials of Medical Products" (MHLW Ordinance No. 171 dated December 20, 2004). Data obtained from the patients registered in this study will be reported to the MHLW pursuant to the Pharmaceutical Affairs Law; pertinent to which, data may be publicly posted in the MHLW's "Pharmaceuticals and Medical Devices Safety Information" and "Pharmaceuticals and Medical Devices Information Website (http://www.info.pmda.go.jp)" as a listing of patients with adverse reactions, which will present the names of drugs, adverse reactions, sex, age (increment of 10 years), and other relevant information. Furthermore, data collected may also be disclosed if the MHLW is required to disclose such information in accordance with the "Act on Access to Information Held by Administrative Organs" (Law No. 42 dated May 14, 1999) provided that in no event will the names of physicians, medical institutions, and other personal information be subject to such disclosure, nor will it be posted or disclosed in any form or shape.

6. RESEARCH QUESTION AND OBJECTIVES

AMEPAROMO Capsules 250 mg (hereinafter referred to as "AMEPAROMO") have been distributed over 50 years in foreign countries and demonstrated a high safety profile. Also, it was sold over 20 years in Japan. Furthermore, AMEPAROMO is a drug rarely absorbed by the intestinal tract and causes very few adverse reactions that are concerned for aminoglycoside antibiotics. Its use is recommended for the prevention of recurrence in textbooks and guidelines worldwide.
The safety and effectiveness of AMEPAROMO have been evaluated in Japanese subjects, and it has been assessed as effective with no special safety concern as a drug for the treatment of intestinal amebiasis.
The evaluation of AMEPAROMO in Japan was, however, made in limited patients performed as a group research by the Research Group of Tropical Diseases and Parasitic Diseases. In addition, the number of patients with intestinal amebiasis targeted by AMEPAROMO is extremely limited so that medical institutions where treatment is actually given after marketing are also assumed to be limited.

In the light of these, this study will be mainly requested to institutions having the results of AMEPAROMO treatment and will collect the additional effectiveness and safety evidence of AMEPAROMO under actual conditions of use after marketing by specifying criteria.
This study will investigate the safety and effectiveness of AMEPAROMO in daily medical practice in terms of: 1) Adverse reactions unexpected from precautions (unknown adverse reactions); 2) Occurrence of adverse reactions under daily medical practice; and 3) Factors that may affect safety, effectiveness and other relevant matters.

7. RESEARCH METHODS

7.1. Study design

This study is a multicenter open-label study conducted in patients receiving AMEPAROMO, for which case report forms (CRFs) will be recorded based on data presented in medical records obtained in daily medical practice.

7.2. Setting

Patients who satisfy all of the inclusion criteria are subject to this study.

7.2.1. Inclusion criteria

Patients who have never been treated with AMEPAROMO

The indication, dosage and administration of AMEPAROMO are as mentioned below. See the latest package insert when using AMEPAROMO.

INDICATION
Intestinal amebiasis
[PRECAUTIONS CONCERNING INDICATIONS]
AMEPAROMO should not be used for the treatment of parenteral amebiasis because AMEPAROMO acts only on protozoa and cysts in the intestine.
DOSAGE AND ADMINISTRATION
The usual dosage for adults is 1500 mg (potency) of paromomycin sulfate administered orally after meals, divided into 3 doses per day for 10 days.

7.2.2. Exclusion criteria

There are no exclusion criteria for this study.

7.2.3. Sites for this study

This study will be implemented at 20 to 30 sites including the department of infectious diseases and department of internal medicine.

7.2.4. Planned investigation period

This study will be conducted during the following period:

Investigation period: From May 2015 until the target sample size is achieved or one year prior to the reexamination period after the start of the study, whichever is earlier

Registration period: From May 2015 until the target sample size is achieved or one year and 3 months prior to the reexamination period after the start of the study, whichever is earlier.

7.2.5. Study methods

7.2.5.1. Study system

This study will be implemented using a central registration system.

7.2.6. Observation period

The observation period shall start on the day the treatment with AMEPAROMO begins (Day 1) and end on Day 10 during which patient background information, records on AMEPAROMO treatment, records on concomitant therapies, and records on the treatment status and discontinuation of AMEPAROMO shall be entered in CRFs. When the treatment is discontinued during the observation period, the observation period shall be until the day when AMEPAROMO treatment is discontinued.

7.3. Variables

The investigator will conduct this study in accordance with the following variables/schedule of observation.

Table 1. Variables/schedule of observation

		Registration Form	CRF		
Variables \ Timing		At the time of registration	Initiation of treatment	Completion of observation period	Up to 3 months after the completion of observation period
Background	ID number	●			
	Sex	●			
	Age on the start date of AMEPAROMO treatment	●			
	Enrollment criterion	●			
	Start date of AMEPAROMO treatment	●			
	Targeted disease		●		
	Hospitalization status (inpatient/outpatient)		●		
	Body height		●		
	Body weight		●		
	Medical history		●		
	Records on previous treatment drugs		●		
	Pregnancy status [female only]			●	
Targeted drug use record			●	●	
Concomitant therapy			◄———	———►	
Study discontinuation record				●	
Effectiveness evaluation	Examination of cysts after AMEPAROMO treatment			◄———	———►
	Clinical response to AMEPAROMO (assessed by the investigator)			◄———	———►
Adverse events			◄———	———►	

7.3.1. Background

(1) Input the information on the start day of treatment with AMEPAROMO.

[1] ID number

[2] Sex

[3] Age on the start date of AMEPAROMO treatment

[redacted]

[4] Start date of AMEPAROMO treatment

[5] Body height

[6] Body weight

[7] Targeted disease

- Name of disease
- Severity
- Initial onset or recurrence

[8] Hospitalization status (inpatient/outpatient)

[9] Medical history (information except for the targeted disease)

- Presence or absence of human immunodeficiency virus (HIV) infection
- Name of disease or syndrome other than the above
  By history or complication*
  *Enter chronic diseases (including allergies), diseases requiring treatment, diseases or impairment accompanying surgery, inpatient treatment or sequelae, and the names of diseases or syndromes that may be other problems. If these were cured prior to AMEPAROMO treatment, they are "history," and if such diseases, etc. still persist at the time of treatment, they are "complications."

[10] Records on previous treatment drugs for intestinal amebiasis

- Name of drug (product name)
- Route of administration
- Daily dose
- Treatment period
- Effectiveness evaluation

(2) Input the following information during a period from the start day of AMEPAROMO treatment to the end day of the observation period or the day of treatment discontinuation:

- Pregnancy status and date of delivery/expected date (female only)

7.3.2. Targeted drug use record

Input the following information for the targeted drug:

[1] Dose

[2] Frequency of doses per day

[3] Treatment period

7.3.3. Concomitant therapy

7.3.3.1. Drug therapy

Input the following information on all drugs used during the observation period. If adverse events (AEs) occurred, drugs administered for the treatment of AEs will be also entered:

[1] Name of drug (product name)
[2] Route of administration
[3] Treatment period
[4] Presence or absence of treatment for AEs

7.3.3.2. Non-drug therapy

Input the following information on all treatments other than drugs used during the observation period. If AEs occurred, non-drug therapies administered for their treatment will be also documented:

[1] Name of therapy
[2] Therapy period
[3] Presence or absence of treatment for AEs

7.3.4. Study discontinuation record

Whether or not AMEPAROMO treatment could be completed should be checked. If AMEPAROMO treatment could not be completed, the date of the final observation should be entered, and the main reason for discontinuation corresponding to the items below should be chosen and documented. If an AE is selected for the reason, detailed information should be recorded in the AE column.

[Reason for discontinuation]

・Insufficient clinical response
・AEs
・Not making revisits
・Hospital/department transfer
・Others

7.3.5. Effectiveness evaluation

[1] Examination of cysts after AMEPAROMO treatment

After the completion of the observation period (or treatment discontinuation), an examination of cysts will be carried out, and the result should be recorded. The result of cyst examination shall be within 3 months after the end day of the observation period (or day of treatment discontinuation)

・Examination performed
－Date of sample collection
－Result of cyst examination: Negative, positive or indeterminate

[redacted]

・Examination not performed

[2] Clinical response to AMEPAROMO (assessed by the investigator)

After the completion of the observation period (or treatment discontinuation), the clinical response to AMEPAROMO should be comprehensively assessed based on the course of the general condition, laboratory findings and other relevant data after the start of AMEPAROMO treatment, and the results should be recorded:

・Effective
・Not effective
・Indeterminate (The reason should be recorded.)

7.3.6. Adverse events

After confirming the occurrence of AEs from the start day of treatment with AMEPAROMO to the end day of the observation period, input the following information. Upon occurrence of any AE, the investigator should take appropriate measures, and promptly report to Pfizer Japan Inc. (hereinafter referred to as the "Sponsor"), and if the causal relationship with AMEPAROMO cannot be ruled out, the investigator should follow up the event until the AE or its sequelae are resolved or stabilized at the level acceptable to the investigator and Sponsor.
In addition, a study should be separately conducted in detail on patients in whom a serious adverse reaction, or an adverse reaction not described in the package insert occurred if it is determined necessary by the Sponsor.

・Presence/absence of AE
・Name of AE
・Date of onset
・Intervention
・Seriousness
・Outcome of the AE to date
・Causal relationship with AMEPAROMO

When an adverse reaction such as diarrhea occurred, and changes in intestinal flora were checked, input the following additional information:

・Result of changes in intestinal flora

If the AE is associated with abnormal change in laboratory values, i.e., clinical laboratory tests, input the following information:

・Laboratory parameter
・Site reference value
・Unit
・Date measured
・Results

[redacted]

Supplement: An AE can be any unfavorable event (including a clinically significant abnormal change in a laboratory value) in a patient occurred after administration of AMEPAROMO whether or not considered related to AMEPAROMO. A serious adverse event (SAE) is an event that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is other medically important events or events possibly resulting in disability.

7.3.7. Major investigation items

N/A

7.4. Data sources

In this study, the investigator extracts necessary information from the medical record in accordance with the protocol.

7.5. Study size

7.5.1. Planned sample size

100 patients

7.5.2. Rationale for sample size

The number of patients who will receive AMEPAROMO may be extremely small, but 100 patients were chosen as a sample size that can be collected during a certain period of time from the viewpoint of the feasibility of the study.

7.6. Data management

7.6.1. Data collection method

The data for this study will be collected using a specific CRF provided by the Sponsor. The investigator will complete the CRFs within the reporting period after the completion of observation period and submit them to the Sponsor.

7.6.2. Patient registration

7.6.2.1. Procedure of patient registration

(1) Registration

The following registration items should be completed in the registration forms for patients who meet the enrollment criterion and are given AMEPAROMO; patients should be registered via FAX at the registration center until the contracted number of patients is registered. The patients should be registered as soon as they received AMEPAROMO.

[redacted]

1) Enrollment criterion

Patients who meet the following criterion should be registered:

・Patients who have never received AMEPAROMO

2) Items to be recorded in the registration form

ID number, sex, age on the start date of AMEPAROMO treatment, the start date of AMEPAROMO treatment and enrollment criterion

Registration Center
Fax No.: PPD
Receivable hours: Available 24 hours a day
Reception hours: 9:00 to 15:00 from Monday through Friday (excluding national holidays and from December 29 to January 4)
*When a fax is received after 15:00, it is considered to have received on the following business day.

(2) Exclusion from the registration

Patients found to not meet the enrollment criterion after the registration form is received at the registration center will be excluded from the registration.

7.6.3. Reminders concerning completion, revision, and submission of case report form

7.6.3.1. Completion

The investigator shall, upon confirming the study items, complete the CRF based on medical charts using a pen, ballpoint pen, or other inerasable means.

7.6.3.2. Revision

When correcting information entered in the CRF, the investigator will strike out with double lines (=) with a “correction seal” on the double lines; the double lines should be drawn so that the original contents prior to correction are legible. Also, upon receiving Sponsor's inquiry on the contents of the CRF (query forms), the investigator will again confirm the contents of medical records described earlier, and as required, correct relevant sections and resubmit the form. When correcting information on effectiveness and safety evaluations, in principle, the reason and date of correction should be also documented.

7.6.3.3. Submission

After all the study items are entered or corrected, the investigator should check the contents of the completed CRF and query form again, enter the name and affix his/her seal or signature.

7.7. Data analysis

(1) Definition of analysis set

[redacted]

The safety analysis set shall include patients for whom administration of AMEPAROMO has been confirmed. The effectiveness analysis set shall include evaluable patients (patients who are determined to be properly assessed) in accordance with a separately specified statistical analysis plan (SAP).

(2) Methods of analysis

1) Analysis for safety evaluation
For the safety analysis set, the occurrence of main adverse reactions and incidence of adverse reactions (proportion of patients with treatment-related AEs) will be the main analysis items.

2) Analysis for effectiveness evaluation
For the effectiveness analysis set, [proportion of cyst negative] will be the main analysis item.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed and maintained by Pfizer. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

7.8. Quality control

The site staff will explain the contents of the protocol, etc. to the investigator prior to the implementation of this study and ask the investigator to prepare a CRF based on medical charts.

7.9. Limitations of the research methods

The following matters are considered for this study:
1) Since no control group is set in the study, there is a limit to the judgment on whether or not a risk of developing AEs and adverse reactions increases due to the administration of the study drug.
2) The consideration for confounding factors may not be adequate because the background information may not be sufficiently obtained.
3) Since this is a study that collects the information described in medical charts, the set data may not be collected or there may be missing information.

7.10. Other aspects

N/A

8. PROTECTION OF HUMAN SUBJECTS

8.1. Patient information and consent

All parties will ensure the protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

In this study, the information will be collected by transcribing medical chart information described in daily medical practice. In doing so, the informed consent will not be required because the information collected from medical charts is anonymized and does not contain any information that identifies individual patients.

8.2. Patient withdrawal

N/A

8.3. Institutional review board (IRB)/independent ethics committee (IEC)

In this study, the review by the IRB/IEC is not essential.

8.4. Ethical conduct of the study

Not applicable. This study is included in the scope of application of the "MHLW Ordinance on the Standard for Post-Marketing Studies and Clinical Trials of Medical Products" (MHLW Ordinance No. 171 dated December 20, 2004).

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The handling of each event in the case where the investigator becomes aware of any event concerning the safety information should be prescribed as follows:

For an event that needs to be reported to the Sponsor within 24 hours, the investigator must report it using the designated “Non-Interventional Study AE Report Form” (hereinafter referred to as “NIS AE Report Form”).

At the initiation of study, the site staff should request the investigator to report events that need to be reported within 24 hours of awareness, and visit the investigator periodically during the investigation period to request for reporting.

The NIS AE Report Form will be handled as part of the CRF.

9.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the NIS AE Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) SAEs; (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy (EDP), exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section “Definitions of safety events.”

Safety event	Recorded on the CRF	Reported on the NIS AE Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to AMEPAROMO, including EDP, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE (see section "Serious adverse events" below).

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to AMEPAROMO**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

9.2. Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of AMEPAROMO, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of AMEPAROMO; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered AMEPAROMO on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation.

If the investigator becomes aware of an SAE occurring at any time after completion of the study and he/she considers the SAE to be related to AMEPAROMO, the SAE also must be reported to Pfizer Safety.

9.3. Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each AE. For AEs with a causal relationship to AMEPAROMO, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that AMEPAROMO caused or contributed to an AE. If the investigator's final determination of causality is "unknown" and he/she cannot determine whether AMEPAROMO caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but he/she determines that AMEPAROMO did not cause the event, this should be clearly documented on the CRF and NIS AE Report Form.

9.4. Definitions of safety events

9.4.1. Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an AE);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- EDP;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

<u>Abnormal test findings</u>

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

[redacted]

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

9.4.2. Serious adverse events

An SAE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute AEs);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

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.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for the treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)

9.4.3. Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving EDP, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An EDP occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) AMEPAROMO, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to AMEPAROMO (maternal exposure).
   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to AMEPAROMO prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective EDP reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with AMEPAROMO, this information must be submitted to Pfizer, irrespective of whether an AE has occurred using the NIS AE Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to AMEPAROMO in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AE Report Form and the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow-up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within one month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after one month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to AMEPAROMO.

Additional information regarding the EDP may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the

[redacted]

healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);

- Confusion with regard to invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.

- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:

    - An identifiable reporter;

    - A suspect product;

    - The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

9.5. Single reference safety document

A Single Reference Safety Document (SRSD) refers to a document that contains the information on the known safety profile. The package insert of this product will be the SRSD in this study. Pfizer Japan Inc. will evaluate the safety information reported by the investigator during the investigation period using the SRSD.

The investigator will also prescribe the drug and give the drug administration guidance based on the SRSD.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study results may be published during scientific meetings, in research paper, etc. for the purpose of providing proper use information, etc.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

11. ORGANIZATIONAL SYSTEM FOR STUDY IMPLEMENTATION

The organizational system in this study is equivalent to that for the operations regarding the post-marketing study. The director of the Post Marketing Study Strategy and Management will be responsible for post-marketing study.

12. NAME, ADDRESS AND OUTSOURCED OPERATIONS OF THE PERSON WHO WAS CONTRACTED WITH THE OPERATIONS

1) Contractors

PPD

Name: PPD

Scope of the outsourced operations: Registration activities, reception of CRF and query form, data management, and statistical analysis (operational jobs excluding the management of postmarketing surveillance)

Address: PPD

Name: PPD

Scope of the outsourced operations: Data management (operational jobs excluding the management of postmarketing surveillance)

13. OTHER NECESSARY MATTERS

1) Amendment of the protocol

Based on the new knowledge to be obtained according to the progress of this study, the need for amendment of the protocol will be examined and the protocol will be amended if necessary. Also, the need for amendment of the protocol will be examined and the protocol will be amended as necessary even if the partial change in the dosage and administration or indication is approved during the reexamination period (except the case when the reexamination period is newly designated), etc.

2) Actions to be taken if any problem or question is observed

In the cases where the onset of any serious and unknown adverse reaction is suggested, a significant increase in the frequency of adverse reactions is observed, any problem is found in the effectiveness and safety of the drug compared to those prior to the approval, the onset of a different kind of adverse reaction is suggested, etc.,

[redacted]

implementation of a special drug use investigation or post-marketing clinical study should be considered to detect or confirm the cause and to verify the assumption, etc. derived from the deliberations.

14. CONTACT INFORMATION

14.1. Contact information for the contents of the study

Name	Pfizer Japan Inc. Post Marketing Study Strategy and Management
Address	Shinjuku Bunka Quint Building 3-22-7 Yoyogi Shibuya-ku, Tokyo 151-8589
E-mail address	PPD

15. REFERENCES

N/A

16. LIST OF TABLES

17. LIST OF FIGURES

N/A

18. LIST OF STAND ALONE DOCUMENTS

N/A

19. ADDITIONAL INFORMATION

N/A