Vfend Special Investigation

- Investigation For Treatment of Invasive Fungal Infections in Pediatric Patients -

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

[redacted]

[redacted]

STUDY INFORMATION

Title	Special Investigation of Vfend - Investigation for Treatment of Invasive Fungal Infections in Pediatric Patients -
Protocol ID	A1501100
Protocol version identifier	Ver. 1.0
Date of last version of protocol	N/A
Active substance	Voriconazole
Medicinal product	Vfend 200 mg for Intravenous Use Vfend Tablets 50 mg Vfend Tablets 200 mg Vfend Dry Syrup 2800 mg
Research question and objectives	This study is intended to assess the following items, etc. for the safety and effectiveness of Vfend 200 mg for Intravenous Use, Vfend Tablets 50 mg, Vfend Tablets 200 mg, and Vfend Dry Syrup 2800 mg (hereinafter referred to as Product) in daily clinical practice for invasive fungal infections in children and review the necessity for further special investigation and post-marketing clinical study. - Unknown adverse reactions - Occurrence of adverse reactions under actual clinical settings - Factors considered to affect the safety and effectiveness of this product
Author	PPD Post Marketing Study Strategy and Management PMS Planning and Operation Group 1

[redacted]

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1. LIST OF ABBREVIATIONS

Acronym	Tittle
AE	adverse event
Al-P	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CRP	C-reactive protein
EDP	exposure during pregnancy
GGT	Gamma-glutamyltransferase
IEC	Independent Ethics Committee
IRB	institutional review board
NIS	Non interventional study
SRSD	Single Reference Safety Document

2. RESPONSIBLE PARTIES

The Good Post marketing Study Practice officer

Principal Investigator(s) of the Protocol

N/A

[redacted]

3. AMENDMENTS AND UPDATES

N/A

4. MILESTONES

Milestone	Planned date
Start of data collection	Jun 2015
End of data collection	Jun 2018
Final study report	To be decided

5. RATIONALE AND BACKGROUND

Vfend (nonproprietary name: voriconazole) is a new triazole therapeutic agent for invasive fungal infections developed by Pfizer UK Central Laboratory which has a similar structure as fluconazole.

Vfend selectively acts on fungal cells and demonstrates its antimycotic activity by inhibiting cytochrome P450-dependent 14α-demethylase in the ergosterol biosynthesis which is a component of fungal cell membranes.

Vfend 200 mg for Intravenous Use, Vfend Tablets 50 mg, and Vfend Tablets 200 mg were approved as drugs indicated for invasive aspergillosis, pulmonary aspergilloma, chronic necrotic pulmonary aspergillosis, candidaemia, esophageal candidiasis*, candidal peritonitis, bronchopulmonary candidiasis, cryptococcal meningitis, pulmonary cryptococcosis, fusariosis, and scedosporiosis on 11 April 2005.

Furthermore, since the options for antimycotic agents which can be used for pediatric patients are limited in Japan, "the Review Committee on Unapproved or Off-Labeled Drugs with High Medical Need" held in April 2010 evaluated that the pediatric indication of voriconazole had high medical need and requested the development of voriconazole for pediatric use. The pharmacokinetic study of voriconazole in pediatric patients was conducted in Japan and the pediatric indication of voriconazole was approved on 26 September 2014. In so doing, since the dosage and administration in children need to be adjusted per weight and the use of tablets in younger children is expected to be difficult, the approval of oral dry syrup was also obtained as a new dosage form.

Special Investigation of Vfend - Investigation for Treatment of Invasive Fungal Infections in Pediatric Patients - (hereinafter referred to as "this study") will be conducted to collect information on occurrence of adverse reactions by Vfend 200 mg for Intravenous Use, Vfend Tablets 50 mg, Vfend Tablets 200 mg, and Vfend Dry Syrup 2800 mg by type of diseases, etc., quality, effectiveness and safety under the actual clinical settings in daily clinical practice for children. The information collected from this study shall be used to provide proper use information and prepare documents for the application of re-examination.

This Study shall be conducted in strict compliance with the "Ordinance concerning Standards for Conducting Post-Marketing Study and Studies on Pharmaceutical 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 and Medical Device Act; pertinent to which, data may be publicly posted in 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, 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.

* Only for tablets and dry syrup

6. RESEARCH QUESTION AND OBJECTIVES

This study is intended to assess the following items, etc. for the safety and effectiveness of Vfend 200 mg for Intravenous Use, Vfend Tablets 50 mg, Vfend Tablets 200 mg, and Vfend Dry Syrup 2800 mg (hereinafter referred to as this product) in daily clinical practice for invasive fungal infections in children and review the necessity for further special investigation and post-marketing clinical study.

- Unknown adverse reactions
- Occurrence of adverse reactions under actual clinical settings
- Factors considered to affect the safety and effectiveness of this product

6.1. Safety Specifications

[Important identified risks] Hepatic toxicity, QT prolongation, ventricular tachycardia, ventricular fibrillation, arrhythmia, complete atrioventricular block, visual events, phototoxicity, peripheral neuropathy such as Guillain-Barre syndrome, renal disorder, hematologic disorder, interstitial pneumonia, cardiac failure, consciousness disorder

[Important potential risks] None

[Important missing information] Safety of pediatric use

7. RESEARCH METHODS

7.1. Study design

This study is a prospective multicenter cohort study conducted in patients receiving this product; for which, case report forms will be recorded based on data presented in medical records obtained in daily clinical practice.

7.2. Setting

Patients under the age of 15 years with severe or intractable fungal infection at the initiation of treatment with this product are subject to this study.

7.2.1. Inclusion criteria

1. Patients under the age of 15 years at the initiation of treatment with this product

2. Patients with invasive fungal infections

[redacted]

The indications, and dosage and administration of this product are as follows. The latest package insert should be referred to when administering this product.

[INDICATIONS]

Severe mycosis as follows:

- Invasive aspergillosis, Pulmonary aspergilloma, Chronic necrotic pulmonary aspergillosis.

- Candidemea, Esophageal candidasis*, Candidal peritonitis, Bronchopulmonary candidiasis.

- Cryptococcal meningitis, Pulmonary cryptococcosis.

- Fusariosis.

- Scedosporiosis. * Only for tablets and dry syrup

[DOSAGE AND ADMINISTRATION]

<for Intravenous Use>

Adult	Voriconazole is administered by intravenous drip infusion at the dose of 6 mg/kg twice daily on day 1 and 3 mg/kg or 4 mg/kg twice daily from day 2 onward.
Children (Aged 2 to <12 and ≥12 whose body weight is less than 50 kg)	9 mg/kg as voriconazole twice daily on day 1 and 8 mg/kg twice daily from day 2 should be given intravenously. Dose may be increased if poorly responded by 1 mg/kg at a time, and dose in intolerant patients should be reduced by 1 mg/kg at a time.
Children (Aged ≥12 whose body weight is 50 kg or more)	6 mg/kg as voriconazole twice daily on day 1 and 4 mg/kg twice daily from day 2 should be given intravenously.

<Tablet>

Adult (body weight ≥40 kg)	A recommended oral dose of voriconazole is 300 mg/dose twice daily between meals on day 1, and 150 or 200 mg/dose twice daily between meals on day 2 and thereafter. Dose may be increased depending on condition of patients or if poorly responded; provided that a total daily dosage should not exceed 400 mg/dose twice daily on day 1 and 300 mg/dose twice daily on day 2 and thereafter.

[redacted]

Adult (body weight <40 kg)	A recommended oral dose of voriconazole is 150 mg/dose twice daily between meals on day 1, and 100 mg/dose twice daily between meals on day 2 and thereafter. Dose may be increased from day 2 onward depending on condition of patients or if poorly responded; provided that a total daily dosage should not exceed 150 mg/dose twice daily.
Children (Aged 2 to <12 and ≥12 whose body weight is less than 50 kg)	After the administration of Voriconazole injection, a recommended maintenance oral dose of voriconazole following injection therapy is 9 mg/kg/dose twice daily between meals. Dose may be increased by 1 mg/kg at a time if poorly responded, and dose in intolerant patients should be reduced by 1 mg/kg at a time (unless the dosage was at its maximum 350 mg, in which case, dose should be reduced by 50 mg at a time). A total daily dosage should not exceed 350 mg/dose twice daily.
Children (Aged ≥12 whose body weight is 50 kg or more)	After the administration of Voriconazole injection, a recommended maintenance oral dose of voriconazole following injection therapy is 200 mg/dose twice daily between meals; which may be increased up to 300 mg/dose twice daily if poorly responded.

<Dry Syrup>

Adult (body weight ≥40 kg)	A recommended oral dose of voriconazole is 300 mg/dose twice daily between meals on day 1, and 150 or 200 mg/dose twice daily between meals on day 2 and thereafter. Dose may be increased depending on condition of patients or if poorly responded; provided that a total daily dosage should not exceed 400 mg/dose twice daily on day 1 and 300 mg/dose twice daily on day 2 and thereafter.
Adult (body weight <40 kg)	A recommended oral dose of voriconazole is 150 mg/dose twice daily between meals on day 1, and 100 mg/dose twice daily between meals on day 2 and thereafter. Dose may be increased from day 2 onward depending on condition of patients or if poorly responded; provided that a total daily dosage should not exceed 150 mg/dose twice daily.
Children (Aged 2 to <12 and ≥12 whose body weight is less than 50 kg)	After the administration of Voriconazole injection, a recommended maintenance oral dose of voriconazole following injection therapy is 9 mg/kg/dose twice daily between meals. Dose may be increased by 1 mg/kg at a time if poorly responded, and dose in intolerant patients should be reduced by 1 mg/kg at a time (unless the dosage was at its maximum 350 mg, in which case, dose should be reduced by 50 mg at a time). A total daily dosage should not exceed 350 mg/dose twice daily.

[redacted]

Children (Aged ≥12 whose body weight is 50 kg or more)	After the administration of Voriconazole injection, a recommended maintenance oral dose of voriconazole following injection therapy is 200 mg/dose twice daily between meals; which may be increased up to 300 mg/dose twice daily if poorly responded.

7.2.2. Exclusion criteria

Patients who correspond to the following must not be registered to this study.

- Patients who have been registered to this study before

7.2.3. Sites for this study

Sites with presence of doctors specialized in the target therapeutic area primarily in the following departments, at which, the product can be prescribed:

Departments of pediatrics, pediatric hematology, etc.

7.2.4. Planned investigation period

Investigation period: June 2015 to June 2018

Registration period: June 2015 to March 2018

(Registration will be discontinued even before the end of the registration period if the target number of patients is reached.)

7.2.5. Study procedure

7.2.5.1. Study methods

This study will be conducted with a central registration system.

7.2.6. Observation period

The observation period shall start on the day the treatment with this product begins and end on the day the treatment is completed; provided that it will be cut off at Week 16 of treatment (Day 112 counting from Day 1 as the day the treatment begins) if the treatment prolongs.

7.3. Variables

This study will be conducted in accordance with the following assessment schedule.

[redacted]

Table 1. Schedule of observation

Variables \ Timing		Baseline	Observation period	Termination of observation period
Background	ID number	●		
	Sex	●		
	Age at the time when the treatment of the targeted drug is initiated	●		
	Height/body weight	●		
	Hospitalization status (inpatient/outpatient)	●		
	Objective of treatment	●		
	Disease history	●		
	Presence/absence of fever unresponsive to antibacterial agents	●		
	Prior medications for infection for which this product is prescribed	●		
Presence/absence of pregnancy			●	
Targeted drug use record			●	
Therapeutic drugs and concomitant medications for careful administration/contraindication for infection			●	
Laboratory tests			●	
Final diagnosis (name of infection)			●	
Effectiveness evaluation				●
Completion (discontinuation) record				●
Confirmation of presence/absence of adverse events which correspond to major investigation items (presence/absence of occurrence of hepatic toxicity/visual events)			●	
Adverse events			●	

● : Data items

7.3.1. Background

Input the information at the initiation of this product.

(1) ID number
(2) Sex
(3) Age (at the time when the targeted drug is initiated)
(4) Height
(5) Body weight
(6) Hospitalization status (inpatient/outpatient)
(7) Objective of treatment (infection for which this product is prescribed)
- Treatment of mycosis/others
- Severity
(8) Disease history (information on diseases other than target diseases)
- Presence/absence and severity of hepatic function disorder, renal impairment

[redacted]

- Name of disease or syndrome, as well as history or pre-existing disease
(9) Presence/absence of fever unresponsive to antibacterial agents
(10) Prior medications for infection for which this product is prescribed (name of antifungal agent administered to the target disease from 2 weeks before treatment of this product until the day before the start date of treatment, route of administration, reason for discontinuation)

7.3.1.1. Presence/absence of pregnancy

Input the presence/absence of pregnancy from the start date of treatment until the completion of observation period (date of delivery (abortion) or expected date of delivery if the patient is pregnant).

7.3.2. Targeted drug use record

The following will be recorded for the treatment status of this product.

(1) Dosage form
(2) Dose
(3) Body weight used for calculation of adjustment of this product
(4) Frequency of dose
(5) Treatment period

7.3.3. Concomitant therapy

7.3.3.1. Therapeutic drugs and concomitant medications for precautions/contraindication for infection for which this product is prescribed

The following information will be recorded for therapeutic drugs and concomitant medications for careful administration/contraindication for infection for which this product is prescribed from the initiation of treatment with this product to the completion date of observation period.

(1) Drug name (product name)
(2) Route of administration
(2) Treatment period

7.3.4. Tests

7.3.4.1. Mycological test

Input assumed causative fungi used for diagnosis of invasive fungal infections (input for each collected material/assumed causative fungi).

(1) Testing material
(2) Testing method
(3) Assumed causative fungi (name of fungi, date of sample collection, fungal volume)
(4) Result of susceptibility test

7.3.4.2. Serological test

Input the results of serological test used for diagnosis of invasive fungal infections.

(1) Date of collection of sample used for diagnosis
(2) Testing method (β-D-glucan, D-arabinitol, candida antigen, candida mannan antigen, candida antibody, cryptococcus neoformans antigen, cryptococcus antibody, aspergillus antigen, aspergillus antibody etc.)
(3) Cut-off value
(4) Test results

7.3.4.3. Imaging test

Input the results of the imaging test which was conducted by the initiation of treatment with this product and used for diagnosis of invasive fungal infections (input for each test site).

(1) Test site
(2) Test date
(3) Presence/absence of findings suspected of invasive fungal infections

7.3.4.4. Plasma voriconazole concentration

If the plasma concentration of voriconazole was measured, input the test results.

(1) Date and time of blood collection
(2) Date and time of treatment with this product immediately before blood collection
(3) Plasma voriconazole concentration

7.3.4.5. Laboratory tests

Input the following test items and test items for adverse events.

[Observation items] White blood cell count, neutrophil count, platelet count, total bilirubin, AST, ALT, Al-P, GGT, CRP, BUN, serum creatinine

7.3.5. Final diagnosis (name of infection)

Diagnose the name of infection from clinical symptoms, results of mycological test, serological test, etc.

Follow the latest guideline for diagnosis and treatment of invasive fungal infections for determination of patients with definite diagnosis and suspected diagnosis.

7.3.6. Completion (discontinuation) record

If the observation is completed or discontinued before the end of the longest observation period (16 weeks), the reason should be recorded.

If an adverse event is selected for the reason, the information in details should be recorded in the adverse event column.

[Reason for completion]
- Cured (effective)

[Reason for discontinuation]
- Insufficient clinical effectiveness

- Adverse events
- No revisit
- Hospital transfer
- Other

7.3.7. Effectiveness evaluation

7.3.7.1. Clinical response

The clinical response of this product should be evaluated based on the clinical course excluding the mycological response at the end of the observation period.

If this product is used continuously for more than 16 weeks, the clinical response should be evaluated comprehensively at Week 16.

- Effective
- Not effective
- Indeterminate (In this case, the reason should be recorded.)

Reason in the case of indeterminate

- Because the diagnosis is not "invasive fungal infections" or "invasive fungal infections suspected"
- Other

7.3.7.2. Mycological response

The mycological response should be determined at the end of the observation period and the results should be recorded.

- Eradication: The causative fungi detected from the focus before treatment with this product has become negative
- Presumed eradication: In the case when the focus improved and the collection of test material became impossible
- Decreased: The causative fungi decreased
- No change: There is no change in causative fungi
- Increased: The causative fungi increased (including the case of microbial substitution)
- Indeterminate: In the cases when the follow-up was inadequate, the causative fungi were not detected, or the mycological test was "not conducted"

7.3.8. Adverse events

Confirm the status of adverse events from the initiation of treatment with this product to the completion of observation period, and record the following information. Upon discovery of an adverse event, the attending doctor should take appropriate actions, and promptly report to Pfizer Japan Inc. (hereinafter "Sponsor"), and if causal relation with this product cannot be ruled out, the doctor should follow up the event until the adverse event or its sequelae are resolved or stabilized at the level acceptable by the attending doctor and Sponsor.

Moreover, a study should be conducted on patients in whom a serious adverse reaction, or an adverse reaction not specified in the package insert occurred if it is determined necessary by Sponsor.

[redacted]

(1) Presence/absence of adverse event
(2) Name of adverse event
(3) Date of occurrence
(4) Action
(5) Seriousness
(6) Outcome
(7) Causality

[If the adverse event is associated with abnormal change in laboratory values, i.e., laboratory tests, the following information should also be recorded.]

(1) Laboratory parameter
(2) Site reference value
(3) Unit
(4) Date of test
(5) Results

7.3.9. Major investigation items

The following items will be major investigation items in this study.

(1) Hepatic toxicity

For patients who developed events related to hepatic toxicity including abnormal hepatic function test values, assess the occurrence status and the differences in patient background, dose, etc. between patients who can continuously receive treatment with this product and patients who must discontinue treatment with this product.

(2) Visual events

Set the presence or absence of visual events as an investigation item. Assess the occurrence status for patients who developed visual events and the differences in patient background, dose, etc. between patients who can continuously receive treatment with this product and patients who must discontinue treatment with this product.

7.3.9.1. Confirmation of presence/absence of adverse events that correspond to major investigation items

7.3.9.1.1. Presence/absence of hepatic toxicity

The presence/absence of hepatic toxicity including hepatitis, jaundice, hepatic failure, coma hepatic, ALT (GPT) increased, AST (GOT) increased, and γ-GTP increased should be recorded for target patients in this study. If aggravation or new occurrence of hepatic toxicity is observed, the information in details should be recorded in the adverse event column.

7.3.9.1.2. Presence/absence of occurrence of visual events

The presence/absence of aggravation or new occurrence of visual events including photophobia, vision blurred, and visual disturbance should be recorded for target patients in this study. If aggravation or new occurrence of visual event is observed, the information in details should be recorded in the adverse event column.

[redacted]

7.4. Data sources

In this study, the investigators extract the 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 target sample size was set out to 100 patients who developed hepatic toxicity or visual events which are major investigation items for whom differences between patients who can continuously receive this product and patients who must discontinue the treatment with this product can be evaluated.

In the reports of adverse reactions in the clinical study (study A1501096) conducted for Japanese children (from 2 years old to under 15 years old), there were 4 patients with hepatic toxicity including abnormal hepatic function test values (19.0%) and 9 patients with visual events (42.9%). If the number of patients to be collected is set out to be 100, the number of patients from whom these events can be detected at a probability of 95% or higher is estimated to be 13 patients and 35 patients respectively. The 100 patients is the number of patients from whom adverse reactions that occur at the frequency of 3% or higher can be detected in at least 1 patient at a probability of 95% or higher.

7.6. Data management

7.6.1. Data collection method

Data for this study shall be collected using a specific case report form provided by Pfizer. Investigator will complete promptly after observation period and submit them to the Pfizer.

7.6.2. Patient registration

7.6.2.1. Procedure of patient registration

(1) Registration

The following information regarding registration should be recorded in the registration forms if this product is given to patients who meet the following registration criteria; patients should be registered via FAX at the registration center until the target number of patients is registered. Patients should be registered via FAX within 2 weeks from the initiation of treatment with this product with the start date of treatment as Day 1.

1) Registration criteria

- Patients under the age of 15 years old at the initiation of treatment with this product

- Patients with invasive fungal infections

2) Registration data

[redacted]

Patient identification number, sex, age at the initiation of treatment, date on which treatment with this product begins, eligibility to registration criteria

[Patient Registration Center] FAX: 0120 - 007 - 233 (Accessible 24 hours a day)

(2) Exclusion from the registration

Patients found to not meet the registration criteria 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 and other medical records such as relevant test results, using an ineffaceable ink such as ballpoint pen.

7.6.3.2. Revision

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. Corrections in the CRF should be struck out with a double line (=) with a "correction seal" on the double line; the double line should be drawn so that the original contents prior to correction are legible.

7.6.3.3. Submission

CRFs should be submitted promptly upon completion in accordance with the procedures set out by Sponsor.

7.7. Data analysis

The details of analysis method on data collected in this study shall be described in the Statistical Analysis Plan to be separately prepared.

1) Definition of analysis set

The safety analysis set shall include patients for whom the registration in this study and administration of this product have been confirmed.

Two analysis sets, which are clinically-evaluable analysis set and mycological analysis set, shall be defined as the effectiveness analysis set. The clinically-evaluable analysis set includes patients for whom performance of clinical response was confirmed among patients in the safety analysis set. The mycological analysis set include

[redacted]

patients for whom microbiological response was assessed among patients in the clinically-evaluable analysis set.

2) Analysis method

(1) Safety analysis

The incidence of adverse reactions shall be calculated for each event. Also, the factors affecting the occurrence of adverse reactions shall be evaluated as necessary.

(2) Effectiveness analysis

The clinical response rate (the number of responders / the number of clinically-evaluable patients excluding indeterminate patients) and its 95% confidence interval shall be calculated for the clinically-evaluable analysis set. Also, the eradication rate (the number of patients with mycological eradication + presumed eradication / the number of patients for mycological analysis excluding indeterminate patients) and its 95% confidence interval shall be calculated for the mycological analysis set.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan of this study 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

Pfizer staff in charge of site 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 case report form 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 adverse events 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 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 routine medical practice. In doing so, the informed consent will not be used because the information collected from medical charts is anonymized and does not contain any information that identifies individual patients.

8.2. Patient withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or Sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved adverse events.

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

This study is excluded from the patient since it includes the scope of application of the "Good Post-Marketing Study Practice" (Ordinance of Ministry of Health, Labour and Welfare No. 171 of 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, each staff in charge of each site shall request each investigator to report events that need to be reported within 24 hours of discovery, and visit the investigator periodically within the study period to request for reporting.

The NIS AE Report Form will be handled as part of the case report form.

9.1. REQUIREMENTS

The table below summarizes the requirements for recording safety events on the case report form and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements should be described for the following 3 types of events.(1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving exposure to a Pfizer product, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse,

extravasations, and occupational exposure. These events are defined in the section “Definitions of safety events”.

Safety event	Recorded on the case report form	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 a Pfizer product, including exposure during pregnancy, 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) involving exposure to a Pfizer product

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

Safety events must be reported to Pfizer within 24 hours of awareness of the event by the investigator as described in the table above. 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 those 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. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. 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 informed consent, which is obtained prior to the patient's registration in the study, and lasts through the end of the observation period of the study; 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 a drug under study 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 a SAE occurring at any time after completion of the study and s/he considers the serious AE to be related to a Pfizer product, the SAE also must be reported to Pfizer Safety.

[redacted]

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 adverse event. For AEs with a causal relationship to a Pfizer product, 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 a Pfizer product caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether a Pfizer product caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that Anaemetro did not cause the event, this should be clearly documented on the case report form and the NIS AEM 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 adverse events include but are not limited to:

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

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

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

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event 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 adverse event by the investigator or sponsor.

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

9.4.2. SAE

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose or using a medical device that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute adverse events);
- 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.

[redacted]

- 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 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 exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy;

Exposure during pregnancy; An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) Anaemetro, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to Anaemetro (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 a Pfizer product 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 exposures during pregnancy 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 a Pfizer product, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred, must be submitted using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to a Pfizer product, 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 AEM 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

[redacted]

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 (e.g., 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 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product

Additional information regarding the exposure during pregnancy 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 breast feeding;

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 health care professional, patient, or consumer. Such events may be related to professional practice, health care 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 :

[redacted]

 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 extravasations 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 study 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.

[redacted]

11. ORGANIZATIONAL SYSTEM FOR STUDY IMPLEMENTATION

The organizational system in this study is equivalent to that for the operations such as the risk management plan and 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) Subcontractors

(1)Registration center
Company name: EP Pharma Line Co., Ltd.
Address: 3-27-12 Nishi-Ikebukuro, Toshima-ku, Tokyo

(2) Destination of case report and query forms, data management, and statistical analysis
Company name: EPS Corporation
Address: 8F Acropolis TOKYO, 6-29 Shinogawamachi, Shinjuku-ku, Tokyo

2) Scope of subcontract

Activities concerning registration center, destination of case report and query forms, data management, and statistical analysis, except for management activities.

13. ADDITIONAL MEASURES THAT MAY BE IMPLEMENTED BASED ON THE STUDY RESULTS AND CRITERIA FOR DETERMINATION OF THE INITIATION

The Drug Risk Management Plan should be reviewed and revised as necessary at each relevant milestone for the contents including the following information.

□The necessity to amend the protocol of this study including presence/absence of new safety specifications should be discussed.

□The necessity of risk minimization plan including that for new safety specifications should be discussed.

□Amendment of the risk minimization activities for the current safety specification should be discussed.

14. SCHEDULED TIMING OF MILESTONES AND THEIR RATIONALES FOR REPORTING OF STUDY IMPLEMENTATION STATUS AND EVALUATION OF OBTAINED RESULTS TO THE PMDA

[Planned milestone]

At the time of Periodic Safety Report

[Rationale]

To comprehensively evaluate the safety information

[redacted]

15. OTHER ASPECTS

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 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., the amendment of the package insert and implementation of a new special investigation or post-marketing clinical study should be considered.

16. CONTACT INFORMATION

16.1. 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	VFD-pedPMS@pfizer.com

17. REFERENCES

None.

18. LIST OF TABLES

19. LIST OF FIGURES

N/A

20. LIST OF STAND ALONE DOCUMENTS

N/A

[redacted]

21. ADDITIONAL INFORMATION

N/A