Vfend Special Investigation

- For prophylaxis of invasive fungal infections in pediatric and adults –

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

[redacted]

[redacted]

STUDY INFORMATION

Title	Vfend Special Investigation －For prophylaxis of invasive fungal infections in pediatric and adults－
Protocol number	A1501106
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 prophylactic administration of this product for invasive fungal infections in children and adults and review the necessity for further special investigation and post-marketing clinical study. - Unknown adverse reactions including those associated with long-term use - Occurrence of adverse reactions under actual clinical settings including long-term use. - Factors considered to affect the safety and effectiveness of this product
Author	Post-marketing Study Strategy and Management PMS Planning and Operation Group 1 PPD

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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	October 2015
End of data collection	October 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 action 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, candidemia, esophageal candidiasis*, candidal peritonitis, bronchopulmonary candidiasis, cryptococcal meningitis, pulmonary cryptococcosis, fusariosis, and scedosporiosis on April 11, 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 September 26, 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.

While the prophylactic administration of antifungal agents for patients with hematopoietic stem cell transplantation is recommended in the domestic and overseas guidelines, considering the fact that the prophylactic administration of voriconazole is recommended especially for invasive aspergillosis as one of the options, etc., the application for additional indication for prophylaxis of deep mycosis in patients with hematopoietic stem cell transplantation was submitted and the approval was obtained on August 24, 2015.

The Special Investigation of Vfend - For prophylaxis of invasive fungal infections in children and adults - (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 in daily clinical practice for prophylactic administration of this product for invasive fungal infections in children and adults. The information collected from this study shall be used to provide proper use information and prepare documents for the application of re-examination.

[redacted]

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 "Pharmaceutical and Medical Device 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 product) in daily clinical practice for prophylactic administration of this product for invasive fungal infections in children and adults and review the necessity for further special investigation and post-marketing clinical study.

- Unknown adverse reactions including those associated with long-term use
- Occurrence of adverse reactions under actual clinical settings including long-time use
- 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, atrioventricular block complete, visual events, phototoxicity, peripheral neuropathy such as Guillain-Barre syndrome, renal failure, blood disorder, interstitial pneumonia, heart failure, consciousness disturbed

[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 the product; for which, case report forms will be recorded based on data presented in medical records obtained from daily clinical practice.

7.2. Setting

Patients who were administered this product for the purpose of prophylaxis of invasive fungal infections at the initiation of administration of this product

7.2.1. Inclusion criteria

1. Patients who have not developed invasive fungal infections at the time of initiation of administration of this product (patients with medical history of invasive fungal infections can be registered)

2. Patients with history of hematopoietic stem cell transplantation or patients who plan to receive hematopoietic stem cell transplantation

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

Prophylaxis of invasive fungal infections in patients undergoing HSCT (Hematopoietic Stem Cell Transplantation)

[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 depending on condition of patients or 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.

[redacted]

<Tablet>

Adult (body weight ≥40 kg)	A recommended oral dose of voriconazole is 300 mg 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 the 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 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 depending on condition of patients or 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 depending on condition of patients or if poorly responded.

<Dry Syrup>

Adult (body weight ≥40 kg)	A recommended oral dose of voriconazole is 300 mg 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 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 depending on

[redacted]

	condition of patients or 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 depending on condition of patients or 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 hematology, pediatrics, pediatric hematology, etc.

7.2.4. Planned investigation period

Investigation period ：October 2015 to October 2018

Registration period ：October 2015 to August 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 administration of this product begins and ends on the day the administration is completed; provided that the patients will be followed until the last day of the investigation period as long as possible if the administration period 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 administration of the targeted drug is initiated	●		
	Height/body weight	●		
	Hospitalization status (inpatient/outpatient)	●		
	Objective of administration	●		
	History of hematopoietic stem cell transplantation	●		
	Disease history	●		
	Prior antifungal agents administered for prophylaxis of invasive fungal infections	●		
Presence/absence of pregnancy			●	
Targeted drug use record			●	
Concomitant medications, concomitant medications for careful administration/contraindication, and immunosuppressants for prophylaxis of invasive fungal infections			●	
Tests			●	
Effectiveness evaluation				●
Completion (discontinuation) record				●
Confirmation of presence/absence of adverse events that 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 administration of the targeted drug is initiated)
(4) Height
(5) Body weight
(6) Hospitalization status (inpatient/outpatient)
(7) Objective of administration (infection for which this product is prescribed)
-Primary prophylaxis* / secondary prophylaxis** / others
*Primary prophylaxis: Prophylaxis of patients without history of fungal infection

[redacted]

**Secondary prophylaxis: Prophylaxis of patients with history of fungal infection
(8) History of hematopoietic stem cell transplantation (before initiation of administration or immediately after initiation of this product)
- Date of hematopoietic stem cell transplantation, type of transplantation (autograft, allogeneic full transplantation/allogeneic mini-transplantation), source of transplantation (bone marrow/cord blood/peripheral stem cell)
- Occurence of GVHD (graft versus host disease)
- Disease indicated for transplantation/severity
(9) Presence/absence and severity of hepatic function disorder, renal impairment
(10) Disease history（medical history and complications）
- Name of disease or syndrome, as well as history or pre-existing disease
(11) Antifungal agents administered from the date of hematopoietic stem cell transplantation to the day before the start date of administration for prophylaxis of invasive fungal infections (name of antifungal agent, 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 administration until the completion of observation period.

7.3.2. Targeted drug use record

The following will be recorded regarding administration of this product.

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

7.3.3. Concomitant therapy

7.3.3.1. Concomitant medications for prophylaxis of invasive fungal infections, mediations listed in precautions for coadministration / contraindication for coadministration and immunosuppressants

The following information will be recorded for concomitant medications for prophylaxis of invasive fungal infections, concomitant medications for precautions for coadministration /contraindications for coadministration, and immunosuppressants from the initiation of administration of this product until the completion date of observation period.

(1) Drug name (product name)
(2) Daily dose
(3) Route of administration
(4) Administration period

7.3.4. Tests

7.3.4.1. Plasma voriconazole concentration

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

[redacted]

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

7.3.4.2. 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. Completion (discontinuation) record

If the administration of this product is completed or discontinued, the reason will be recorded excluding the case where the administration is continued.

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

〔Reason for completion〕
- Completion of prophylaxis
- If the objective of administration is changed from prophylaxis to treatment, completion of administration of this product for treatment.

〔Reason for discontinuation〕
- For the onset of invasive fungal infections
- Adverse events (other than invasive fungal infections)
- No return to hospital
- Hospital transfer
- Other

7.3.6. Effectiveness evaluation

7.3.6.1. Presence/absence of invasive fungal infections

The result of presence or absence of invasive fungal infections during the observation period will be recorded.

If the administration with this product is continued at the completion of study period, the onset of invasive fungal infections until the completion of study period will be judged.

(1) Presence/absence of onset

- Without onset
- With onset → Proven diagnosis* / probable diagnosis** / Possible case*** and reason for judgment
- Underminable (reason for undeterminable)

The diagnostic criteria of the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) will be followed.

[redacted]

*Proven diagnosis: Patients who have clinical symptoms and findings of inflammation caused by mycosis and the causative fungi are proved from the histological diagnosis of the focus of infection or mycological diagnosis from the originally sterile site, etc.
**Probable diagnosis: At least one host factor + one clinical criterion + one mycological criterion
***Possible case: At least one host factor + meeting one clinical criterion but no mycological criterion

(2) Date of onset in case of onset
(3) Name of fungal type in case of onset, sensitivity to this product

7.3.7. Adverse events

Confirm the status of adverse events from the initiation of administration of 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.

(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

7.3.8. 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 be continuously administered this product and patients who must be discontinued administration of 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 be

[redacted]

continuously administered with this product and patients who must be discontinued administration of this product.

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

7.3.8.1.1. 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 GGT increased should be recorded for target patients in this study. If aggravation or new occurrence of hepatic toxicity is observed, the information in detail should be recorded in the adverse event column.

7.3.8.1.2. 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 detail should be recorded in the adverse event column.

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

200 patients (100 patients each for children and adults)

7.5.2. Rationale for sample size

It was considered that the following evaluations were possible if the target sample size was set to be 200 patients in total; 100 patients each for children and adults.

Safety perspectives:

In the phase 3 study of prophylactic administration of Vfend in foreign patients with HSCT (study A1501073), the incidence of adverse reactions classified into the SOC of hepatobiliary disorders was 20.2% (47/233 patients). Of those, one patient was led to discontinuation of administration of this product. In the phase 3 study of secondary prophylactic administration of Vfend in foreign patients with HSCT (study A1501038), the incidence of adverse reactions classified into the SOC of hepatobiliary disorders was 24.4% (11/45 patients). Of those, two patients were led to discontinuation of this product. Also, in the clinical study of Vfend conducted in Japanese children (from 2 years old to under 15 years old) (study A1501096), the incidence of adverse reactions related to hepatic toxicity including abnormal hepatic function test values was 19.0% (4/21 patients). Of those, two patients were led to discontinuation of this product. Based on the above, the incidence of hepatic toxicity in patients administered this product for prophylaxis of invasive fungal infections was similar between Japanese and foreign patients and it was considered that such incidence was also similar between adults and children.

[redacted]

In the case where the number of patients to be collected for the special investigation for prophylactic administration of Vfend for invasive fungal infections is set to be 200 patients and the incidence of hepatic toxicity is presumed to be 20%, it is estimated that at least 31 patients with hepatic toxicity will be accumulated at a probability of about 95%. With the cumulation of this sample size, it was considered possible to compare and review the proportion of patients who discontinued the administration of this product with the clinical studies.

Although the incidence of visual events varies among different studies (study A1501073: 12.0%, study A1501038: 4.4%, and study A1501096: 42.9%), if it is presumed that there is the incidence of 5% or higher, the expected value of the incidence to be observed in 200 patients will be at least 10 patients. While it is possible that there may be no patient who discontinues the administration of this product due to visual events based on the results of clinical studies, if any patient who discontinues the administration of this product is observed, how it happened will be examined.

Effectiveness perspectives:

The successful rate of prophylaxis at Day 100 in the phase 3 study of prophylactic administration (study A1501073) was 54.3% (121/223 patients) and the successful rate of prophylaxis at Day 180 was 48.9% (109/223 patients). Presuming that the 50% prophylactic effect can be obtained at Day 180 by referring to the above results, the 95% CI will be 40 - 60% if the target sample size is set to be 100 patients and 43-57% if the target sample size is set to be 200 patients. The prophylactic effect can be confirmed at the estimate accuracy of about ±10% if 100 patients for whom this product is administered for prophylaxis of invasive fungal infections are accumulated and that of about ±7% if 200 patients are accumulated.

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 Sponsor. Investigator will complete promptly after 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 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 administration of this product with the start date of administration as Day 1.

1) Registration criteria

- Patients who have not developed invasive fungal infection at the initiation of administration with this product

- Patients who received hematopoietic stem cell transplantation or patients who plan to receive hematopoietic stem cell transplantation

2) Registration data

[redacted]

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

[Patient Registration Center]

FAX No.: 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 and the safety has been evaluated.

The effectiveness analysis set shall include patients for whom the presence/absence of invasive fungal infections has been evaluated among the safety analysis set.

2) Analysis method

(1) Safety analysis

[redacted]

The number of patients who developed each adverse reaction and the proportions will be tabulated. Also, for patients who developed major investigation items of hepatic toxicity and visual events, differences between patients who can continuously receive this product and patients who must discontinue the administration of this product will be analyzed experimentally.

(2) Effectiveness analysis

The proportion of patients who developed invasive fungal infections (the number of patients with proven diagnosis + the number of patients with probable diagnosis/number of patients for effectiveness analysis excluding undeterminable patients × 100), proportion of patients with successful prophylaxis of invasive fungal infections (the number of patients without onset of invasive fungal infections/the number of patients for effectiveness analysis excluding undeterminable patients × 100), and each 95% CI will be calculated for effectiveness analysis set. Also, the analysis using the survival analysis method (Kaplan-Meier method) will be performed.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the Sponsor. 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.

[redacted]

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, extravasation, 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 AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None

Safety event	Recorded on the case report form	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
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. This information is more detailed than that recorded on the case report form. 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 first dose of this product, 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 a drug under 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 SAE to be related to this product, 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 adverse event. For AEs with a causal

relationship to this 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 this product caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether this 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 this product 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. Serious adverse events

A serious adverse event 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 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.

[redacted]

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 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;

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) this product, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to this product (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 this 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 exposure 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 this 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 this 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).

[redacted]

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 (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 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 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 :

・ 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 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.

[redacted]

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 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.

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 Department
Address	Shinjuku Bunka Quint Building 3-22-7 Yoyogi Shibuya-ku, Tokyo 151-8589
E-mail address	VFD-yobouPMS@pfizer.com

17. REFERENCES

None.

18. LIST OF TABLES

・Page11. Table 1. Schedule of observation

19. LIST OF FIGURES

N/A

20. LIST OF STAND ALONE DOCUMENTS

N/A

21. ADDITIONAL INFORMATION

N/A

[redacted]