Non-Interventional Study Protocol

A1501106

VFEND SPECIAL INVESTIGATION

-For prophylaxis of invasive fungal infections in pediatric and adult-

Statistical Analysis Plan

Version: 4.0

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1. AMENDMENTS FROM THE PREVIOUS VERSION

Version/ Date/ Author(s)	Summary of Changes/Comments
1.0 21-DEC-2015 PPD	Initial version
2.0 28-MAR-2017 PPD	Status of investigation: Ongoing 5.4. Subgroup Analysis - Risk difference was added to the text. - A description on patients who may meet contraindications in the package insert of Vfend was added. 8.1.3. Analysis of Binary Data - Risk difference and 95% confidence interval were added. 8.2.3.4. Subgroup Analysis - A description on an analysis in patients who meet contraindications was added. Other description adjustments were made.
3.0 26-NOV-2018 PPD	Status of investigation: Ongoing 5.4. Subgroup Analysis - Age was divided into 2 factors. - Indication for transplantation and duration of treatment with Vfend were added to factors. 6.1. Safety Endpoints - It was specified not to use the company's judgment in the definitions of causal relationship and seriousness of adverse events. 6.4. Covariates - Information up to approval was reexamined and descriptions were changed. 7. HANDLING OF MISSING DATA - Handling of missing data related to adverse events was changed. 8.1.3. Analysis of Binary Data - It was specified that risk ratio, etc. will not be calculated if the number of patients in each subgroup compared is ≤5 when the proportion is compared between subgroups based on risk ratio, etc. 8.2. Statistical Analysis - All analyses were planned to be performed overall as well as in adults and children. However, it was specified to perform only some analyses in children, and relevant descriptions were deleted. 8.2.1. Overview of Patients - It was specified to tabulate the number of patients in patients who completed the study in dispositions of patients, and patients for whom the case report form was not collected were deleted.

Version/ Date/ Author(s)	Summary of Changes/Comments
	- The analysis of discontinuation was changed to tabulate not only discontinued patients but also completed patients by timing. The listing of other reasons for discontinuation was added. 8.2.2. Patient Background and Treatment History of Vfend - Indication for transplantation was added to patient background. - The presence or absence of concurrent visual disturbance and the breakdown of visual disturbance were deleted because they can be confirmed based on the tabulation of complications by SOC and PT. - The tabulation of hepatic dysfunction and renal dysfunction by disease name was deleted because it is included in the tabulation of complications and overlaps with it. - It was specified to tabulate concomitant medications separately for contraindicated concomitant medications, concomitant medications requiring precautions for coadministration, immunosuppressants, and other antifungal agents. - The tabulation of reasons for discontinuation of prior treatment by drug (antifungal agent) was added. - The tabulation by pregnancy status was added. - The tabulation of administration status by dosage form was deleted, and the tabulation of the initial dose and mean maintenance dose and the tabulation per body weight were added. Furthermore, a subgroup analysis of subjects aged < 15 years and those aged ≥ 15 years was added because the doses in children and adults differ. - The analysis of overdose was added. 8.2.3. Safety Analysis - The period of tabulation and analysis of adverse events and adverse drug reactions was provided. It was added that all adverse events should be output in the listing of adverse events. 8.2.3.1. Adverse Drug Reactions - Tabulations by age (1), age (2), hepatic dysfunction, renal dysfunction, and long-term treatment were added to details of adverse drug reactions. - The description was changed from "intervention (for adverse events)" to "change in treatment with Vfend," and the category was further subdivided. - The handling of change in treatment with Vfend when the same adverse drug reaction occurs more than once in the same patient was changed. - Tabulations by Expected/unexpected , age (1), age (2), hepatic dysfunction, renal dysfunction, change in treatment with Vfend, and long-term treatment were added to tabulations of serious adverse drug reactions. - The tabulation by change in treatment with Vfend was added to the analysis of major investigation items. - The tabulation of adverse drug reactions by timing of onset was changed to tabulations of adverse reactions and major investigation items. - For the relationship between concomitant medications and the onset of adverse drug

Version/ Date/ Author(s)	Summary of Changes/Comments
	reactions, the existing analysis method was changed to be more clarified, and the tabulation by SOC and PT by presence/absence of concomitant medications actually used was added. 8.2.3.3. Other Endpoints - It was changed to calculate summary statistics by timing of onset of adverse drug reactions of hepatic toxicity in patients who experienced adverse drug reactions of hepatic toxicity from the time plots of each laboratory parameter. 8.2.3.4. Subgroup Analysis - Analyses of major investigation items, adverse drug reactions with an incidence of ≥10%, and serious adverse drug reactions were deleted because of the small number of accumulable patients. 8.2.3.5. Exploratory Analysis - The tabulation of the number and proportion of patients with adverse drug reactions by timing of onset by SOC and PT in patients who received treatment for ≥180 days was added. - A description that the number and proportion of patients with adverse drug reactions will be tabulated by SOC and PT by factor with a risk ratio of ≥2 or ≤0.5 was added. - It was specified to analyze plasma voriconazole concentrations using a listing and delete tabulation. 8.2.4.1. Proportion of Patients Who Developed Invasive Fungal Infections - Analyses by objective of treatment, indication for transplantation, age, hepatic dysfunction, renal dysfunction, and long-term treatment were added. 8.2.4.2. Proportion of Patients with Successful Prophylaxis of Invasive Fungal Infections - Analyses by indication for transplantation, age, hepatic dysfunction, renal dysfunction, objective of treatment, and long-term treatment were added. 8.2.4.3. Analysis of Period Data - The description was changed because there was an omission in the definition of right censoring. 8.2.4.5. Exploratory Analysis A description that a listing will be prepared by factor with a risk ratio of ≥2 or ≤0.5 was added. 9. LISTINGS - It was changed to add [Intext] to listings to be used in the text of the report. - Listings that can be substituted for by the listing of patients were deleted. - Listing of deaths, listing of contraindicated patients, listing of concomitant medications by patient, and other reasons for discontinuation were added. - The record of administration of Vfend and the list of plasma voriconazole concentration were combined into 1 table. - In accordance with PSEHB/PED Notification No. 1128-2, Appendix Form 2 was changed to Appendix Form 15, Appendix Form 3 was changed to Appendix Form 16, and

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	Appendix Form 12 was added. 10. APPENDICES - Appendix 1 and Appendix 3 were added. Other description adjustments were made.
4.0 10-JUN-2019 PPD	Status of investigation: Ongoing 5.4. Subgroup Analysis - Concurrent visual disturbance was deleted from the factors, and concomitant use of immunosuppressants (other than steroids) and concomitant use of steroids were added. 8.2.1. Overview of Patients - Overall period was added to the tabulation of the status of discontinuation/dropout by timing. 8.2.2. Patient Background and Treatment History of Vfend - Concomitant use of immunosuppressants (other than steroids) and concomitant use of steroids were added. - The definition of overdose in status of treatment of Vfend was changed. 8.2.3.1. Adverse Drug Reactions - For major investigation items, the tabulation of the occurrence of adverse drug reactions by SOC and PT by age (<15 years and ≥15 years) was added. - Regarding the relationship between concomitant medications and the onset of adverse drug reactions, similar analyses were added not only for major investigation items but also for adverse drug reactions, and the text was clarified. 8.2.3.4. Subgroup Analysis - It was described that risk ratio and risk difference will not be calculated for concomitant use of steroids or immunosuppressants other than steroids. 8.2.3.5. Exploratory Analysis - Patients with leukemia, an indication for transplantation, were classified into overall patients, those with acute lymphocytic leukemia, those with acute myeloid leukemia, and others (including chronic leukemia), and the tabulation of the occurrence of adverse drug reactions by SOC and PT was added. 8.2.4.4. Subgroup Analysis - It was described that risk ratio and risk difference will not be calculated for concomitant use of steroids or immunosuppressants other than steroids. 9. LISTINGS - Listings of the occurrence of adverse drug reactions in children, elderly, patients with hepatic dysfunction, and patients with renal dysfunction were added. Other description adjustments were made.

2. INTRODUCTION

This statistical analysis plan describes the statistical analysis plan for the special investigation of Vfend. In this plan, sentences cited from the Protocol are shown in *Italics*.

2.1. Study Design

This study is a prospective multicenter cohort study conducted in patients receiving this product. Pediatric and adult patients who were treated with this product for the purpose of prophylactic administration of this product for invasive fungal infections (IFI) at the commencement of treatment with this product will be included in the study. The observation period shall start on the day of initiation of Vfend treatment and end on the day of completion of treatment; provided that the patients will be followed until the last day of the study period as long as possible if the treatment prolongs. The target sample size is set to be 200 patients in total, 100 patients each for children and adults. The rationale for target sample size is shown below. With hepatic toxicity and visual events considered as major investigation items, tally the occurrence status for patients who developed events related to major investigation items and evaluate 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.

Rationale for sample size

The sample size is 100 patients each for children and adults, 200 patients in total.

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 treatment with 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 treatment with 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 hepatotoxicity including abnormal hepatic function test values was 19.0% (4/21 patients). Of those, two patients were led to discontinuation of treatment with this product. Based on the above, the incidence of hepatotoxicity in patients treated with this product for prophylaxis of mycosis was similar between the Japanese and foreign patients and it was considered that such incidence is also similar between adults and children.

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 hepatotoxicity is presumed to be 20%, it was estimated that at least 31 patients with hepatotoxicity 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 discontinue the treatment with this product with other 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 treatment with this product due to visual events based on the results of clinical studies, if any patient who discontinues the treatment with 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 are accumulated and that of about ±7% if 200 patients are accumulated.

2.2. Study Objectives

This surveillance is intended to grasp the following items, etc. for the safety and effectiveness of this product in daily clinical practice for prophylactic administration of this product for invasive fungal infections in pediatric and adults and review the necessity for further special investigation and post-marketing clinical study.

- *Unknown adverse reactions including the time of long-term use*
- *Occurrence of adverse reactions under actual clinical settings*
- *Factors considered to affect the safety and effectiveness of this product*

3. INTERIM AND FINAL ANALYSES

In this study, interim analyses for periodic safety report will be performed periodically. At the time of interim analyses, only the analyses of items necessary for periodic safety update report among the statistical analyses specified in this plan will be performed. In addition, the final analysis for the application for reexamination will be performed. At the time of the final analysis, all analyses specified in this plan will be performed.

4. HYPOTHESIS AND DECISION RULES

4.1. Statistical Hypothesis

Because this study is not a confirmatory investigation, the tests are considered as exploratory tests. The P value of test results will be evaluated as descriptive statistics. The significance level is not provided, but a threshold may be set afterwards for the purpose of screening.

4.2. Statistical Decision Rules

Not applicable

5. ANALYSIS SETS

5.1. Safety Analysis Set

The safety analysis set is defined as the full analysis set that is as close as possible to all patients treated with Vfend. More specifically, the safety analysis set is defined as the population of patients registered or reported, excluding patients who meet at least one of the following conditions:

a. The case report form could not be collected at all (description in the report, “case report form not collected”)

b. There was a violation or deficiency in the contract (description in the report, “contract violation/deficiency”)

c. There was a violation of registration (description in the report, “registration violation”)

d. Administration of the drug under investigation is not reported at all (description in the report, “no administration information”)

e. Information on adverse events is not reported at all - no visits after the first prescription day (description in the report “no adverse event information - no revisits”)

f. Information on adverse events is not reported at all - there is a visit after the first prescription day but no description of safety information (description in the report, “no adverse event information - no description”)

“Guidance for Criteria for Inclusion in Analysis Sets and Data Handling in Drug Use Investigations” will be followed for the details of each criterion.

5.2. Effectiveness Analysis Set

The effectiveness analysis set is defined as the population of patients in the safety analysis set, excluding patients who meet at least one of the following conditions:

g. Effectiveness assessment is not reported at all (description in the report, “no information on effectiveness”)

h. Disease other than the target diseases of the study (description in the report, “non-target disease”)

5.3. Other Analysis Sets

Not applicable

5.4. Subgroup Analysis

Subgroup analyses of safety and effectiveness will be performed for the following patient background factors and other factors. Levels in parentheses are levels of subgroups, and underlined levels are the reference for calculation of risk ratio and risk difference.

- Sex [male, female]
- Age (1) [<15 years, ≥15 years]
- Age (2) [≤65 years, ≥65 years)
- Age (children 1) [newborns (<1 month after birth), infants (≥1 month to <1 year), younger children (≥1 to <7 years), children (≥7 to <15 years)]
- Age (children 2) [<2 years, ≥2 to <15 years]
- Hospitalized Status [inpatient, outpatient]
- Objective of treatment [primary prophylaxis (patients without history of fungal infection), secondary prophylaxis (patients with history of fungal infection), others]
- Type of transplantation [autograft, allogeneic full transplantation, allogeneic mini-transplantation]
- Source of transplantation [bone marrow, cord blood, peripheral stem cell]
- Occurrence of GVHD (graft versus host disease) [absent, present]
- Indication for transplantation[1] [leukemia, myelodysplastic syndrome, malignant lymphoma, myeloma, others]
- Severity of indication for transplantation [mild, moderate, severe]
- Hepatic dysfunction [absent, present]
- Severity of hepatic dysfunction [mild, moderate, severe]
- Renal dysfunction [absent, present]
- Severity of renal dysfunction [mild, moderate, severe]
- Past medical history [absent, present]
- Concurrent illness [absent, present]
- Congenital severe immunodeficiency[2] [absent, present]
- White blood cell count before administration [<3000/μL, ≥3000/μL]
- Neutrophil count before administration [<500/μL, ≥500/μL]
- Concomitant use of broad-spectrum antibiotics [absent, present]
- Use of contraindicated concomitant medications [absent, present]
- Use of concomitant medications requiring precautions for coadministration [absent, present]
- Concomitant use of immunosuppressants (other than steroids) [absent, present]
- Concomitant use of steroids [absent, present]
- Concomitant use of steroids or immunosuppressants other than steroids [absent, present]
- Concomitant use of other antifungal agents [absent, present]
- Prior treatment (antifungal agents administered for prophylaxis of invasive fungal infections) [absent, present]
- Long-term treatment [≤180 days, ≥180 days]
- Duration of treatment with Vfend (<30 days, ≥30 to <60 days, ≥60 to <90 days, ≥90 to <120 days, ≥120 to <150 days, ≥150 to <180 days, ≥180 days)

[1]: Indication will be classified in reference to the Japanese Society of Hematology Guideline for Hematological Malignancies (http://www.jshem.or.jp/gui-hemali/table.html).

[2]: Congenital severe immunodeficiency is defined as a complication included in MedDRA HLGT "congenital immune system disorders" and "immunodeficiency syndrome" (primary and secondary).

Patients who may meet contraindications in the package insert of Vfend (hereinafter referred to as contraindicated patients) will be extracted based on separately specified criteria, and subgroup analyses of safety will be performed.

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

- Adverse drug reactions: Adverse events determined to be related to Vfend by the physician
- Adverse events: All-causality adverse events
- Serious adverse events or adverse drug reactions: Adverse events or adverse drug reactions determined to be serious by the physician
- Safety specifications
  - Hepatic toxicity
  - QT prolongation, ventricular tachycardia, ventricular fibrillation, arrhythmia, atrioventricular block complete
  - Visual events
  - Phototoxicity
  - Peripheral neuropathy such as Guillain-Barre syndrome
  - Renal failure
  - Hematologic disorder
  - Interstitial pneumonia
  - Hart failure
  - Consciousnessdistubed
- Major investigation items: Events to be handled as major investigation items among safety specifications are listed below.
  - Hepatic toxicity
  - Visual events
- Laboratory test

White blood cell count, neutrophil count, platelet count, total bilirubin, AST (GOT), ALT (GPT), Al-P, GGT, CRP, BUN, and serum creatinine before the start of treatment with Vfend and by the end date of the observation period in this study

6.2. Effectiveness Endpoints

- Presence or absence of invasive fungal infections: The onset of invasive fungal infections during the observation period will be judged. If the treatment 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.

- Without onset
- With onset
- Indeterminate

- In case of "with onset" of invasive fungal infections, it will be classified as follows according to the diagnostic criteria of the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG).

  - Proven diagnosis*
  - Probable diagnosis**
  - Possible case***

*: 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 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

6.3. Other Endpoints

Not applicable

6.4. Covariates

As for the safety and effectiveness of Vfend, there are no covariates identified from clinical study data thus far obtained.

7. HANDLING OF MISSING DATA

When the seriousness of adverse events, change in treatment with Vfend, and outcome of adverse events are missing, these data are handled as "unknown" for counting. Because information on causal relationship will be collected by dosage form in this study, causal relationship will be handled as "missing" only when it is missing for all of injection, tablet, and dry syrup and will be handled as "related" for counting. If data on effectiveness endpoints are missing, they will be handled as "missing."

The strategy for handling data with uncompleted cleaning is described below.

- Items of missing data: The items will be handled as missing (category of categorical variable is "unknown") for both tabulation and listing.

- Items of inconsistent data: The items will be handled as missing for both tabulation and listing. However, the list of data handling will be separately prepared.

- No signature: Descriptions in the case report form without the signature of the contracted physician (including the case report form with the signature of an uncontracted physician only) will be handled as missing for both tabulation and listing. If there is a field for the date of signature but there is no date of signature or if there is inconsistency in the date entered (e.g. before the day of initiation of treatment, future date), descriptions in the case report form will be regarded as not signed.

8. STATISTICAL METHODS AND STATISTICAL ANALYSIS

8.1. Statistical Methods

8.1.1. Analysis of Continuous Data

Summary statistics (number of patients, mean, standard deviation, median, maximum, and minimum) will be calculated.

8.1.2. Analysis of Categorical Data

The frequency (e.g., number of patients) and proportion of each category will be calculated.

8.1.3. Analysis of Binary Data

The frequency and proportion will be calculated. If the confidence interval of proportion is calculated, two-sided 95% confidence interval (exact method) will be calculated.

If the proportion is compared between subgroups, risk ratio and its 95% confidence interval, and risk difference and its 95% confidence interval will be calculated. In addition, risk ratio and its 95% confidence interval will be graphically presented (see Appendix 2). If the number of patients in at least one category compared is ≤5, the number of patients and proportion will be calculated but risk ratio and its 95% confidence interval, and risk difference and its 95% confidence interval will not be calculated.

8.1.4. Analysis of Period Data (Time to Event Onset)

The median, first quartile, and third quartile by Kaplan-Meier method will be calculated. In addition, Kaplan-Meier plots will be prepared.

8.2. Statistical Analysis

8.2.1. Overview of Patients

- **Number of sites by establisher and number of patients**

In patients for whom the case report form was collected, the number and proportion of sites by establisher shown below and the number and proportion of patients will be calculated.

- University hospitals
- National hospitals established by the Ministry of Health, Labour and Welfare
- Prefectural and municipal hospitals

- Public organizations
- Hospitals other than the above four established by corporations and individuals
- General practitioners/clinics

In addition, the mean, minimum, and maximum will be calculated for the number of patients per site.

- **Dispositions of patients**

In patients who completed the study, the number of patients included in the analysis of safety and the number of patients included in the analysis of effectiveness will be tabulated. In addition, the number of patients excluded from the analysis of safety and effectiveness and the number of patients by reason for exclusion will be tabulated.

- **Listing of discontinuations and dropouts**

In the safety analysis set, the number and proportion of patients who completed or discontinued treatment will be tabulated by timing (<30 days, ≥30 to <60 days, ≥60 to <90 days, ≥90 to <120 days, ≥120 to <150 days, ≥150 to <180 days, ≥180 days, overall). In addition, the number and proportion of patients by reason for completion and discontinuation will be tabulated. The listing of other reasons for discontinuation will be prepared.

- **Listing of excluded patients**

The listing of patients excluded from the analysis of safety and effectiveness and reasons for exclusion will be prepared.

8.2.2. Patient Background and Treatment History of Vfend

- **Patient background**

In the safety analysis set and effectiveness analysis set, the following patient background factors will be tabulated in accordance with Section 8.1.

- Sex [male, female]
- Age (years; continuous)
- Age [<15 years, ≥15 to <65 years, ≥65 years]
- Age (children 1) [newborns (<1 month after birth), infants (≥1 month to <1 year), younger children (≥1 to <7 years), children (≥7 to <15 years)]
- Age (children 2) [<2 years, ≥2 to <15 years]
- Age (adults) [≥15 to <20 years, ≥20 to <40 years, ≥40 to <65 years, ≥65 to <70 years, ≥70 to <75 years, ≥75 years]
- Hospitalized status [inpatient, outpatient]
- Body weight (kg; continuous)
- Objective of treatment [primary prophylaxis (patients without history of fungal infection), secondary prophylaxis (patients with history of fungal infection), others]
- Details of other objectives of treatment

- Type of transplantation [autograft, allogeneic full transplantation, allogeneic mini-transplantation]
- Source of transplantation [bone marrow, cord blood, peripheral stem cell]
- Occurrence of GVHD (graft versus host disease) [absent, present]
- Indication for transplantation [leukemia, myelodysplastic syndrome, malignant lymphoma, myeloma, others]
- Severity of indication for transplantation [mild, moderate, severe]
- Hepatic dysfunction [absent, present, unknown]
- Severity of hepatic dysfunction [mild, moderate, severe, unknown]
- Renal dysfunction [absent, present, unknown]
- Severity of renal dysfunction [mild, moderate, severe, unknown]
- Past medical history [absent, present]
- Concurrent illness [absent, present]
- Concurrent congenital severe immunodeficiency [absent, present]
- White blood cell count before administration [<3000/μL, ≥3000/μL]
- Neutrophil count before administration [<500/μL, ≥500/μL]
- Concomitant use of immunosuppressants (other than steroids) [absent, present]
- Concomitant use of steroids [absent, present]
- Concomitant use of steroids or immunosuppressants other than steroids [absent, present]
- Use of contraindicated concomitant medications [absent, present]
- Use of concomitant medications requiring precautions for coadministration [absent, present]
- Concomitant use of other antifungal agents [absent, present]
- Concomitant use of broad-spectrum antibiotics [absent, present]
- Prior treatment (antifungal agents administered for prophylaxis of invasive fungal infections) [absent, present]

In the safety analysis set, the number and proportion of the following patients will be tabulated by System Organ Class (SOC) and Preferred Term (PT) of MedDRA.

- Past medical history
- Concurrent illness
- Concurrent congenital severe immunodeficiency

In the safety analysis set and effectiveness analysis set, the number and proportion of the following patients will be tabulated.

- Contraindicated concomitant medications
- Concomitant medications requiring precautions for coadministration
- Concomitant immunosuppressants
- Concomitantly used other antifungal agents
- Prior treatment (antifungal agents for prophylaxis of invasive fungal infections)
- Reasons for discontinuation of prior treatment (antifungal agents for prophylaxis of invasive fungal infections)

- **Presence/absence of pregnancy**

In the safety analysis set (women), the number of patients by pregnancy status will be calculated.

- **Status of treatment of Vfend**

In the safety analysis set, the following status of treatment of Vfend will be tabulated.

- Treatment period [≥1 to <30 days, ≥30 to <60 days, ≥60 to <90 days, ≥90 to <120 days, ≥120 to <150 days, ≥150 to <180 days, ≥180 days]
- Long-term treatment [<180 days, ≥180 days]
- Treatment period (days; continuous)
- Dose on the first day (mg; continuous)
- Mean maintenance dose (mg; continuous)
- Dose on the first day (mg/kg; continuous)
- Mean maintenance dose (mg/kg; continuous)
- Overdose[3] [absent, present]

The treatment period is from the initial day of administration in this study to the last confirmed day of administration, including the period during which Vfend is suspended.

Tabulation by age (1) [<15 years, ≥15 years] will be performed in the same manner as above.

8.2.3. Safety Analysis

Adverse drug reactions and adverse events observed during the observation period (from the day of initiation of Vfend treatment to the day of completion of treatment) + follow-up period (28 days*) will be tabulated. If the duration of the observation period + follow-up period is beyond October 31, 2018, events observed by October 31, 2018 will be tabulated. All events reported in this study will be included in listings.

*: The duration of the follow-up period in this study was set at 28 days because a 30-day follow-up period was provided in a clinical study and the period of collection of adverse events using NIS AE Report Form in this study is up to 28 days after the day of completion of treatment.

8.2.3.1. Adverse Drug Reactions

- **All adverse drug reactions**

The number and proportion of patients with adverse drug reactions will be tabulated by SOC and PT.

- **Serious adverse drug reactions**

[3]: The initial dose and the mean dose (mean maintenance dose) for each of injection and oral agent on and after Day 2 will be calculated for each patient, and administration at doses exceeding the upper limit of the dosage regimen of Vfend or the maximum dose will be considered as overdose.

The number and proportion of patients with serious adverse drug reactions will be tabulated by SOC and PT.

- **Details of adverse drug reactions**

The number and proportion of patients with adverse drug reactions will be tabulated by SOC and PT for each of the following items and factors.

- Age (1) [<15 years, ≥15 years]
- Age (2) [<65 years, ≥65 years]
- Hepatic dysfunction [absent, present, unknown]
- Renal dysfunction [absent, present, unknown]
- Long-term treatment [<180 days, ≥180 days]
- Seriousness [serious, non-serious]
- Expected/unexpected [Expected, unexpected]
- Change in treatment with Vfend [discontinuation, temporarily discontinued, dose reduction, dose increase, no change]
- Outcome [not recovered, recovered with sequela, recovering, resolved/recovered, unknown]

In addition, the number and proportion of patients with serious adverse drug reactions will be tabulated by SOC and PT for each of the following items and factors.

- Age (1) [<15 years, ≥15 years]
- Age (2) [<65 years, ≥65 years]
- Hepatic dysfunction [absent, present, unknown]
- Renal dysfunction [absent, present, unknown]
- Long-term treatment [<180 days, ≥180 days]
- Expected/unexpected [Expected, unexpected]
- Change in treatment with Vfend [discontinuation, temporarily discontinued, dose reduction, dose increase, no change]
- Outcome [not recovered, recovered with sequela, recovering, resolved/recovered, unknown]

If the same adverse event (the same PT) occurs more than once in the same patient, it will be handled as follows in the tabulation of the number of patients with events:

- Seriousness: If both serious and non-serious events are reported, “serious” will be adopted.
- Expected/unexpected: : If both expected and unexpected events are reported, “unexpected” will be adopted.
- Number of days to onset: The number of days to the first event will be adopted.
- Change in treatment with Vfend: If multiple types of change in treatment with Vfend are reported, one of discontinuation, temporarily discontinued, dose reduction, dose increase or no change, in descending order of precedence, will be adopted.
- Outcome: The outcome of the last occurring event will be used.

- **Safety specifications**

The number and proportion of patients with events will be tabulated. In addition, the number and proportion of patients with safety specifications by change in treatment with Vfend and outcome will be tabulated by SOC and PT.

- **Major investigation items**

The number and proportion of patients with major investigation items will be tabulated by SOC and PT. In addition, the number and proportion of patients with major investigation items will be tabulated by SOC and PT for each of the following items.

  - Change in treatment with Vfend [discontinuation, temporarily discontinued, dose reduction, dose increase, no change]
  - Outcome [not recovered, recovered with sequela, recovering, resolved/recovered, unknown]
  - Age (1) [<15 years, ≥15 years]

Furthermore, in order to examine the difference between patients who discontinued treatment and those who did not by major investigation item, patients with major investigation items will be tabulated by patient background factor, status of discontinuation/completion, concomitant medication, and status of administration.

- **Timing of onset of adverse drug reactions**

The number of patients with adverse drug reactions will be tabulated by SOC and PT by timing of initial onset of adverse drug reactions. Categories of timing of onset will be every 30 days. However, if there are many adverse drug reactions that occur at an early stage, the analysis will be performed by subdividing the category of the first 30 days as necessary. Major investigation items will be analyzed in the same manner.

For major investigation items, time to event onset will be summarized for each patient in accordance with Section 8.1.4 with the initial onset of the major investigation item considered as an event. Patients without adverse drug reactions will be right-censored after the observation period + follow-up period (28 days) of this study.

- **Relationship between concomitant medications and development of adverse drug reactions**

The number and proportion of patients with adverse drug reactions and major investigation items will be tabulated overall and by PT by presence or absence of actually used concomitant medications for each adverse drug reaction and major investigation item to evaluate the relationship of contraindicated concomitant medications, concomitant medications requiring precautions for coadministration, concomitantly used other antifungal agents, and concomitant immunosuppressants with adverse drug reactions considered as major investigation items. However, medications started to be used after the day of the last onset of the event during the observation period + follow-up period (28 days) will be excluded from tabulation.

In addition, the number and proportion of patients with adverse drug reactions and major investigation items will be tabulated by PT by presence or absence of each actually used concomitant medication for

each adverse drug reaction and major investigation item to evaluate the relationship of contraindicated concomitant medications, concomitant medications requiring precautions for coadministration, concomitantly used other antifungal agents, and concomitant immunosuppressants with adverse drug reactions considered as major investigation items. However, medications started to be used after the day of the last onset of the event during the observation period + follow-up period (28 days) will be excluded from tabulation.

- **The adverse drug reactions by patients of included/excluded in the safety analysis set**

In patients for whom the case report form was collected, the listing of adverse drug reactions in patients excluded from the safety analysis set will be prepared. The number of patients with events will be tabulated by SOC and PT.

8.2.3.2. Adverse Events

- **All adverse events**

The number and proportion of patients with adverse events will be tabulated by SOC and PT.

- **Adverse events by serious/non-serious**

The number and proportion of patients with serious adverse events will be tabulated by SOC and PT. The same tabulation will be performed for non-serious adverse events.

8.2.3.3. Other Endpoints

- **Laboratory test values**

In patients with hepatic toxicity, an adverse drug reaction considered as a major investigation item, summary statistics of the values of laboratory parameters related to hepatic function (AST, ALT, Al-P, and γ-GTP) at the initiation of treatment, the onset of the adverse drug reaction, and the completion of treatment will be calculated by change in treatment with Vfend. A1.1 Definition of Visit Timing of Appendix 10.1 will be followed for values at the initiation and completion of treatment. The value immediately before the day of onset of adverse drug reaction after the day of initiation of Vfend treatment will be used as the value at onset.

8.2.3.4. Subgroup Analysis

The number and proportion of patients who experienced at least one adverse drug reaction will be tabulated for each factor specified in Section 5.4. To evaluate the relationship between patient background factors and the development of adverse drug reactions, the analysis specified in Section 8.1.3 will be performed. Risk ratio and risk difference will not be calculated for concomitant use of steroids or immunosuppressants other than steroids.

The listing of adverse drug reactions will be prepared for contraindicated patients. The number and proportion of patients with adverse drug reactions will be tabulated by SOC and PT as necessary.

8.2.3.5. Exploratory Analysis

The following exploratory analysis will be performed for factors affecting safety.

- In patients treated for ≥180 days in the safety analysis set, the number and proportion of patients with adverse drug reactions by timing of onset of initial event (<180 days, ≥180 days) will be calculated by SOC and PT.
- The number and proportion of patients with adverse drug reactions will be tabulated by SOC and PT by factor with a risk ratio of ≥2 or ≤0.5.
- In patients determined to have leukemia as an indication for transplantation, the number and proportion of patients with adverse drug reactions will be calculated by SOC and PT for each of acute lymphocytic leukemia, acute myeloid leukemia, and others (including chronic leukemia).

An additional analysis may be performed as necessary. The exploratory analysis will be reported only when results giving important interpretation are obtained.

8.2.4. Effectiveness Analysis

8.2.4.1. Proportion of Patients Who Developed Invasive Fungal Infections (IFI rate)

In the effectiveness analysis set, the proportion of patients who developed invasive fungal infections (%) and its 95% confidence interval will be calculated. The calculation formula is shown below.

Proportion of patients who developed invasive fungal infections (%) = [(number of patients with proven diagnosis + number of patients with probable diagnosis)/number of patients for effectiveness analysis excluding undeterminable patients] × 100

For each of the following factors specified in Section 5.4, the same subgroup analyses will be performed.

- Indication for transplantation
- Objective of treatment [primary prophylaxis, secondary prophylaxis]
- Age (1) [<15 years, ≥15 years]
- Age (2) [<65 years, ≥65 years]
- Hepatic dysfunction [absent, present, unknown]
- Renal dysfunction [absent, present, unknown]
- Long-term treatment [<180 days, ≥180 days]

8.2.4.2. Proportion of Patients with Successful Prophylaxis of Invasive Fungal Infections (Success rate)

In the effectiveness analysis set, the proportion of patients with successful prophylaxis of invasive fungal infections (%) and its 95% confidence interval will be calculated. The calculation formula is shown below.

Proportion of patients with successful prophylaxis of invasive fungal infections (%) = (number of patients without onset of invasive fungal infections/number of patients for effectiveness analysis excluding undeterminable patients) × 100

For each of the following factors specified in Section 5.4, the same subgroup analyses will be performed.

- Indication for transplantation
- Objective of treatment [primary prophylaxis, secondary prophylaxis]
- Age (1) [<15 years, ≥15 years]
- Age (2) [<65 years, ≥65 years]
- Hepatic dysfunction [absent, present, unknown]
- Renal dysfunction [absent, present, unknown]
- Long-term treatment [<180 days, ≥180 days]

8.2.4.3. Analysis of Period Data

In the effectiveness analysis set, time to event onset will be summarized in accordance with Section 8.1.4 with the onset of invasive fungal infections (patients with proven diagnosis + patients with probable diagnosis) considered as an event. Similarly, time to event onset will be summarized in accordance with Section 8.1.4 with the onset of invasive fungal infections considered as an event. Patients without onset will be right-censored at the end of treatment.

8.2.4.4. Subgroup Analysis

To evaluate the relationship between patient background factors and effectiveness, subgroup analyses of the proportion of patients who developed invasive fungal infections and the proportion of patients with successful prophylaxis of invasive fungal infections will be performed in accordance with Section 8.1.3 for each of the factors specified in Section 5.4. Risk ratio and risk difference will not be calculated for concomitant use of steroids or immunosuppressants other than steroids.

8.2.4.5. Exploratory Analysis

The following exploratory analysis will be performed for factors affecting effectiveness.

- Listings by presence/absence of onset of invasive fungal infections and presence/absence of successful prophylaxis of invasive fungal infections will be prepared by factor with a risk ratio of ≥2 or ≤0.5.

An additional analysis may be performed as necessary. The exploratory analysis will be reported only when results giving important interpretation are obtained.

9. LISTINGS

The following listings will be prepared. Listings with [Intext] specified after the table name are in a format which allows attachment to the report.

- Listing of patients[4]

[4]: Estimated creatinine clearance and eGFR before administration will be added to the patient listing. Refer to Appendix 10.3 for calculation method.

- Listing of patients with adverse events
- Listing of patients with adverse drug reactions
- Listing of patients with adverse drug reactions among pediatric patients
- Listing of patients with adverse drug reactions among elderly patients
- Listing of patients with adverse drug reactions among patients with hepatic dysfunction
- Listing of patients with adverse drug reactions among patients with renal dysfunction
- Listing of patients with adverse drug reactions among patients excluded from the safety analysis set
- Listing of patients with serious adverse drug reactions [Intext]
- Listing of deaths [Intext]
- List of events corresponding to safety specifications
- List of adverse drug reactions falling under safety specifications [Intext]
- Listing of laboratory values
- Listing of patients evaluated for effectiveness
- Listing of the status of treatment of Vfend and plasma voriconazole concentration
- List of contraindicated patients
- Listing of prior treatment (antifungal agents administered for prophylaxis of invasive fungal infections)
- Listing of other reasons for discontinuation [Intext]
- Listing of concomitant medications by patient [Intext]

Furthermore, tables corresponding to appendix tables for periodic safety report (PSUR) and application for reexamination will be prepared in accordance with the notification.

10. APPENDICES

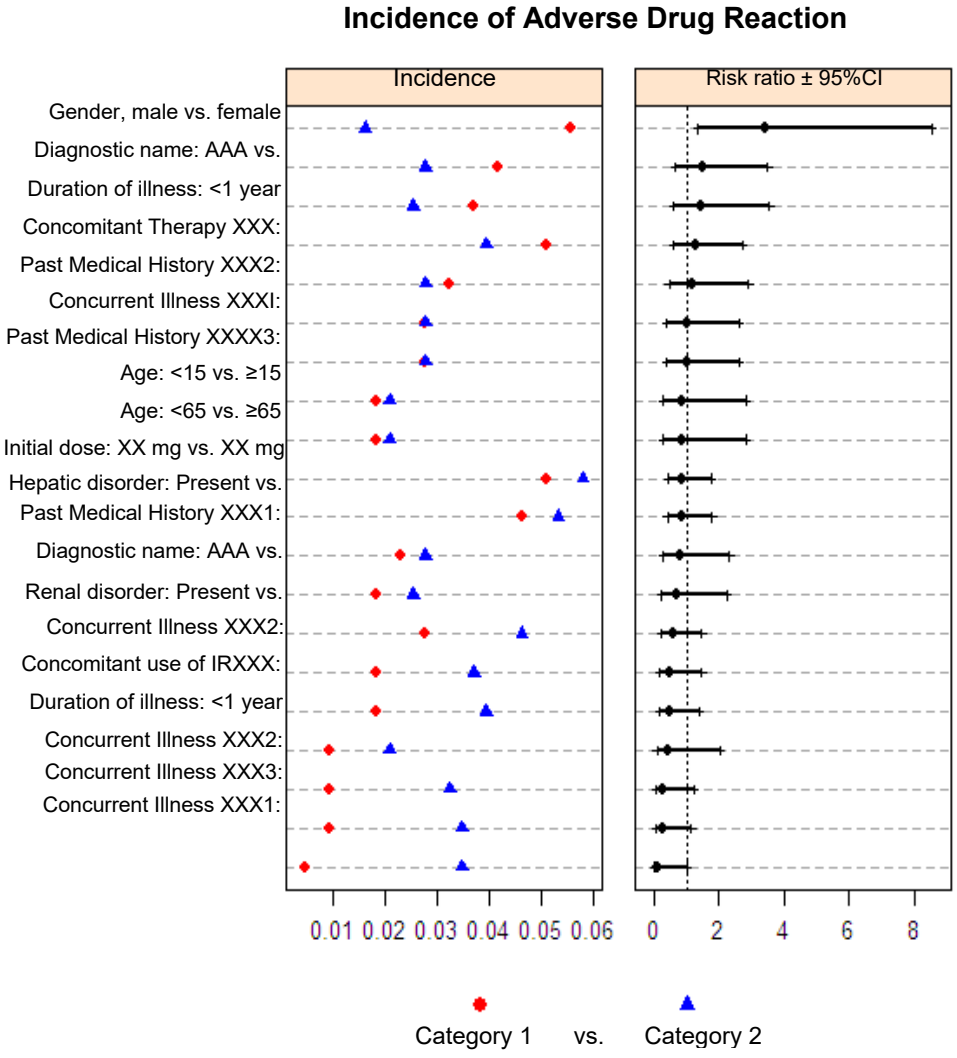
10.1. Appendix 1: Details of Data Extraction

A1.1 Definition of Visit Timing

Visit timing	Endpoint	Definition [acceptable range]
Before initiation of treatment	Laboratory test	From 30 days before the day of initial dose in this study (day of initiation of treatment)] to the day of initiation of treatment. If there are multiple days, the date closer to the day of initial dose will be adopted.
At completion of treatment	Laboratory test	On or after the day of last dose in this study. If there are multiple days, the date closer to the day of last dose will be adopted.

10.2. Appendix 2: Examples of Risk Ratio of Incidence of Adverse Drug Reactions by Subgroups

Event name: XXX increased	Category 1		Category 2		Risk ratio (RR)	
	Number of patients/N	(%)	Number of patients/N	(%)	RR	95 %CI
Gender (male vs. female)	18/2220	(0.8)	3/1099	(0.3)	2.97	(0.88-10.06)
≥65 years vs. <65 years	19/2788	(0.7)	2/531	(0.4)	1.81	(0.42-7.74)
Diagnosis (Disease A vs. Disease B)	3/221	(1.4)	18/3098	(0.6)	2.34	(0.69-7.87)
Duration of illness (<1 year vs. ≥1 year)	9/771	(1.2)	7/866	(0.8)	1.44	(0.54 -3.86)
Drug A Concomitant use (present vs. absent)	9/798	(1.1)	12/2521	(0.5)	2.37	(1.00-5.60)
Drug A Prior treatment (present vs. absent)	1/148	(0.7)	20/3171	(0.6)	1.07	(0.14-7.93)
Disease B Complications (present vs. absent)	16/1614	(1.0)	5/1703	(0.3)	3.38	(1.24-9.20)
Disease B Past medical history (present vs. absent)	7/674	(1.0)	14/2643	(0.5)	1.96	(0.79-4.84)
Hepatic dysfunction (present vs. absent)	0/80		18/2056	(0.9)		
Renal dysfunction (present vs. absent)	1/140	(0.7)	17/2004	(0.8)	0.84	(0.11-6.28)



10.3. Appendix 3: Formulas to Calculate Estimated Creatinine Clearance and eGFR

Cockcroft-Gault Ccr calculation formula

Male: Ccr = {(140 - age) × weight (kg)} / {72 × serum creatinine (mg/dL)}
Female: Ccr = 0.85 × {(140 - age) × weight (kg)} / {72 × serum creatinine (mg/dL)}

- eGFR calculation formula

Male: eGFR (mL/min/1.73 m^2) = 194 × serum Cr (mg/dL) - 1.094 × age - 0.287
Female: eGFR (mL/min/1.73 m^2) = 0.739 × {194 × serum Cr (mg/dL) - 1.094 × age - 0.287}

Reference: Evidence-based Clinical Practice Guideline for CKD 2018 - Japanese Society of Nephrology

https://cdn.jsn.or.jp/data/CKD2018.pdf

- Quintic equation

See Page 22 of Guidance for Evaluation of Renal Function at Diagnosis of Pediatric Chronic Kidney Disease (Pediatric CKD)

1. **Quintic equation (≥2 to <19 years)**
   With height presented as Ht (m), the reference value of serum Cr will be calculated, and eGFR will be calculated based on the reference value.

$$\textbf{eGFR(mL/min/1.73m}^2\textbf{)= 110.2 x } \frac{\textbf{Reference value of serum Cr (mg/dL)}}{\textbf{Observed value of serum Cr (mg/dL)}} \textbf{ + 2.93}$$

<Reference value of serum Cr (mg/dL)>
Male:-1.259 Ht^5 + 7.815 Ht^4 - 18.57 Ht^3 + 21.39 Ht^2 - 11.71 Ht + 2.628
Female: -4.536 Ht^5 + 27.16 Ht^4 - 63.47 Ht^3 + 72.43 Ht^2 - 40.06 Ht + 8.778

Uemura O, et al.Clin Exp Nephrol 2013 : Epub ahead of print

Guidance for Evaluation of Renal Function at Diagnosis of Pediatric Chronic Kidney Disease (Pediatric CKD)

[Edition] 2013 Health Labour Sciences Research Grant for Refractory Disease Research Project (Refractory Disease Research Project)
Group to Elucidate the Natural History of Pediatric Chronic Kidney Disease Including Congenital Anomalies of the Kidney and Urinary Tract and Establish Treatment Methods for Early Diagnosis and Inhibition of Progression of Renal Failure (Japanese Pediatric CKD Research Group)
[Cooperation] Japan Pediatric Society, Japanese Society of Pediatric Urology, The Japanese Society for Pediatric Nephrology
https://cdn.jsn.or.jp/academicinfo/report/201402.pdf

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