Non-Interventional Study Protocol
<A1501100>

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

Statistical Analysis Plan

Version:5.0

Author:PPD (Clinical Statistics Department)

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[redacted]

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1. AMENDMENTS FROM THE PREVIOUS VERSION

Version/ Date/ Author(s)	Summary of Changes/Comments
1.0 28-Nov-2014 PPD	Initial version
2.0 28-Mar-2017 PPD	Status of investigation: Ongoing 5.4. Subgroups - 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 13-Jun-2018 PPD	Status of investigation: Ongoing 5.1. Safety Analysis Set - Modifications were made in association with the amendment of "Guidance for Criteria for Inclusion in Analysis Sets and Data Handling in Drug Use Investigations" Version 2.0. 5.4. Subgroups - Subgroups that serve as the reference level were underlined. - Tabulations of severity, presence or absence of fever unresponsive to antibacterial agents, presence or absence of concomitant medications requiring precautions for coadministration, presence or absence of concomitant antifungal agents, presence or absence of prior medications (antifungal agents), treatment period, dose on the first day, and mean maintenance dose were added. The tabulation of contraindicated concomitant medications was deleted because of the small number of patients concomitantly using contraindicated medications. - Mycological response was deleted because of the small number of patients evaluable for eradication rate. 6.1. Safety Endpoints - The definition of adverse drug reactions was changed to adverse events determined to be related to Vfend by the physician. - The definition of serious adverse events or adverse drug reactions was added. 6.2. Effectiveness Endpoints - Eradication of causative fungi was added as an effectiveness endpoint. 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

Version/ Date/ Author(s)	Summary of Changes/Comments
	- 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. - Descriptions of test were deleted because no test will be performed in this investigation. 8.2.1. Overview of Patients - Patients excluded from the analysis of effectiveness in the disposition of patients were divided into patients excluded from the analysis of clinical response and patients excluded from mycological analysis for clarification. - The number of patients for whom the case report form was not collected was deleted because these patients cannot be confirmed from the case report form data. - In the tabulation of listing of discontinuations and dropouts, it was clarified that discontinued patients have to be those observed for ≤16 weeks and a description on categories of timing was added. Tabulations of hepatic toxicity and visual events were moved to Section 8.2.3.1 Adverse Drug Reactions/Major Investigation Items. 8.2.2. Patient Background and Treatment History of Vfend - The presence or absence of past or present history of visual disturbance was deleted because it can be confirmed by SOC based on the detailed results of tabulation of concurrent illness and past medical history. In addition, the presence or absence of past or present history of hepatic dysfunction was deleted because it can be confirmed based on data on the presence or absence of hepatic dysfunction. - Tabulations of diagnostic name and diagnostic name [definitive diagnosis] were added. ・ Status of treatment of Vfend - The tabulation of dose per body weight was added to the status of treatment of Vfend because the target patients are children. In addition, it was additionally specified that the dose will be tabulated separately for patients aged <12 years and ≥12 years whose body weight is less than 50 kg and those aged ≥12 years whose body weight is 50 kg or more. - Tabulations of the number of doses, dosage form on the first day, and changes, etc. in dosage form were deleted. 8.2.3. Safety Analysis - The period of tabulation and analysis of adverse events and adverse drug reactions was provided. - The tabulation by known/unknown was added to tabulations of serious adverse drug reactions. - The section of safety specifications was deleted because it overlaps with 6.1 Safety Endpoints/Safety Specifications, and tabulations by intervention (change in Vfend treatment) and outcome were added. - The section of major investigation items was deleted because it overlaps with 6.1 Safety Endpoints/Major Investigation Items, and tabulations by intervention (change in Vfend treatment) and outcome were added. - The logistic regression analysis of major investigation items was deleted because of the

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	small number of accumulable patients. - The category of "≥8 to ≤16 weeks" in the tabulation of the timing of onset of adverse drug reactions was divided into 2 categories. 8.2.3.3. Other Endpoints - Time plots of each laboratory parameter were changed to the tabulation in patients experiencing adverse reactions of hepatic toxicity. 8.2.3.4. Subgroup Analysis - Analyses of major investigation items and adverse drug reactions with an incidence of ≥10% were deleted because of the small number of accumulable patients. 8.2.4.1. Clinical Response - The analysis by definitive diagnosis (name of infection) was added. 8.2.4.2. Mycological Response - The analysis by definitive diagnosis (name of infection) was added. - The tabulation by causative fungus was deleted because of the small number of accumulable patients. 8.2.4.3. Mycological response by Causative Fungus - The section of analysis by causative fungus was added, and the tabulation method was described. - The tabulation by susceptibility by causative fungus was deleted because of the small number of accumulable patients. 8.2.4.4. Subgroup Analysis - The tabulation by causative fungus was deleted because of the small number of accumulable patients. 8.2.4.5. Exploratory Analysis - The logistic regression analysis was deleted because of the small number of accumulable patients. 9. LISTINGS - Listings that can be substituted for by the listing of patients were deleted. - Listings of major investigation items that can be substituted for by safety endpoints were deleted. - The record of administration of Vfend and the list of plasma voriconazole concentration were combined into 1 table. - The listing of others for reasons for discontinuation was added. - Serological test and imaging test were summarized into 1 table. - The listing of concomitant medications by patient and the listing of deaths were added. - 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 Appendix Form 12 was added. 10.1. Appendix 1: Details of Data Extraction - A1.1 Definition of Visit Timing was added.

Version/ Date/ Author(s)	Summary of Changes/Comments
	Other description adjustments were made.
4.0 11-Sep-2018 PPD	Status of investigation: Ongoing 5.4. Subgroups - The classification of dose on the first day and mean maintenance dose in safety and effectiveness analyses was changed. - As for the presence or absence of dose escalation and overdose, dose escalation was deleted from the analysis because of difficulty in judgment, and the definition of overdose was added as a footnote. 8.2.1. Overview of Patients - A description of 'cured' was added in parentheses in the descriptions of listing of discontinuations and dropouts so that it is clarified that completion means cured. 8.2.2. Patient Background and Treatment History of Vfend (Status of Treatment of Vfend) - Twelve weeks was added to categories of treatment period. - The classification of dose on the first day and mean maintenance dose was changed. - Changes were made to analyze dose on the first day and mean maintenance dose in the following 3 patterns: summary statistics, classification of dose, and classification of dose per body weight. - A description that the mean maintenance dose will be analyzed separately for intravenous injection and oral preparations (tablet and dry syrup) was added. - A description on imputation of the number of days of treatment in the case where treatment with Vfend is continued at the end of the observation period was added. 8.2.3.1. Adverse Drug Reactions (Relationship between Concomitant Medications and Development of Adverse Drug Reactions) - The definition of concomitant medications was changed so that medications concomitantly used after the last day of onset of corresponding major investigation items will be excluded from tabulation. - An analysis to evaluate the relationship between the development of overall adverse reactions and concomitant medications was added. 8.2.3.5. Exploratory Analysis - It was specified to analyze plasma voriconazole concentrations using a listing and delete tabulation. - 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. 10.3. Formulas to Calculate Estimated Creatinine Clearance and eGFR - Formulas to calculate estimated creatinine clearance and eGFR, which are added to patient listings, were added. Other description adjustments were made.
5.0 20-Sep-2018 PPD	Status of investigation: Ongoing 8.2.3.1. Adverse Drug Reactions - The definition of censoring in the analysis of period data was changed because of

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	inconsistency with the tabulation period specified in Section 8.2.3.

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 single cohort observational study, and patients will be enrolled with central registration system. Patients under the age of 15 years with severe or intractable fungal infection at the initiation of treatment with this product are subjects of this study. The observation period will start on the day the treatment with this product begins and end on the day the treatment is completed; provided that it will be cut off at Week 16 of treatment (Day 112 counting from Day 1 as the day the treatment begins) if the treatment prolongs. Safety specifications in this study are hepatic toxicity, QT prolongation, ventricular tachycardia, ventricular fibrillation, arrhythmia, complete atrioventricular block, visual events, phototoxicity, peripheral neuropathy such as Guillain-Barre syndrome, renal disorder, hematologic disorder, interstitial pneumonia, cardiac failure, consciousness disorder, and safety after administration to children. Of these, hepatic toxicity and visual events are major investigation items. These events were frequently observed in a previously conducted clinical study. If they occur, differences in patient background and dose between patients who were able to continue treatment with Vfend and those who discontinued treatment will be examined. The target sample size was set out to 100 as the number of patients with which these differences can be detected. The rationale for sample size is shown below.

<Rationale for sample size>

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

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

Because Vfend is metabolized by liver metabolic enzymes CYP2C19, 2C9, and 3A4 and has inhibitory effects against CYP2C19, 2C9, and 3A4, contraindicated concomitant medications and concomitant medications requiring caution are specified in the section of interactions in the package insert of Vfend.

2.2. Study Objectives

This study of Vfend is intended to assess information on unknown adverse drug reactions, the occurrence of adverse reactions under actual clinical settings, and factors considered to affect the safety and effectiveness concerning the safety and effectiveness of Vfend 200 mg for Intravenous Use, Vfend Tablet 50 mg, Vfend Tablet 200 mg, and Vfend Dry Syrup 2800 mg in daily clinical practice in children and review the necessity for further special investigation and post-marketing clinical study.

If hepatic toxicity and visual events, which are major investigation items, occur, differences in patient background and dose between who can continuously receive treatment with this product and patients who must discontinue treatment with this product will be examined based on descriptive statistics.

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”)
Aged ≥15 years at the initiation of treatment

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 Sets

Effectiveness analysis sets are the clinical response analysis set and the mycological analysis set.

5.2.1. Clinical Response Analysis Set

The clinical response analysis set is defined as the population of patients in the safety analysis set for whom data for clinical response evaluation (clinical response at the end of the observation period) were collected. The clinical response 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. Clinical response is not reported at all (description in the report, “no information on clinical response”)

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

5.2.2. Mycological Analysis Set

The mycological analysis set is defined as the population of patients in the safety analysis set for whom the final diagnosis is invasive fungal infections or invasive fungal infections

suspected and data for mycological response evaluation (mycological response at the end of the observation period) were collected. The mycological 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:

i. Disease other than the target diseases of the study (final diagnosis is "others"; description in the report, "non-target disease")

j. Mycological response is not reported at all (description in the report, "no information on mycological response")

5.3. Other Analysis Sets

Not applicable

5.4. Subgroups

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

- Hepatic dysfunction [absent, present]
- Renal dysfunction [absent, present]
- 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 years]
- Diagnostic name (name of infection) [invasive aspergillosis, pulmonary aspergilloma, chronic necrotic pulmonary aspergillosis, candidemia, esophageal candidiasis, candida peritonitis, bronchopulmonary candidiasis, cryptococcal meningitis, pulmonary cryptococcosis, fusariosis, scedosporiosis, other invasive fungal infections, others]
- Severity [mild, moderate, severe]
- Fever unresponsive to antibacterial agents [absent, present]
- Use of concomitant medications requiring precautions for coadministration [absent, present]
- Concomitant antifungal agents [absent, present]
- Prior medications (antifungal agents) [absent, present]
- Treatment period [<1 week, ≥1 to <2 weeks, ≥2 to <4 weeks, ≥4 to <8 weeks, ≥8 to <12 weeks, ≥12 to ≤16 weeks]
- Long-term treatment [≤12 weeks, >12 weeks]
- Dose on the first day (mg/kg) [<6, ≥6 to <7, ≥7 to <8, ≥8 to <9, ≥9 to <10, ≥10, unknown]
- Mean maintenance dose (mg/kg) [<6, ≥6 to <7, ≥7 to <8, ≥8 to <9, ≥9 to <10, ≥10, unknown]

Subgroup analyses of safety will be performed for the following:

- Pregnant and parturient women (pregnancy confirmed)
- Presence or absence of overdose[a]

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.

Subgroup analyses of efficacy (clinical response) will be performed for the following patient background factors. Levels in parentheses are levels of subgroups, and underlined levels are the reference for calculation of risk ratio and risk difference.

- Hepatic dysfunction [absent, present]
- Renal dysfunction [absent, present]
- 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 years]
- Diagnostic name (name of infection) [invasive aspergillosis, pulmonary aspergilloma, chronic necrotic pulmonary aspergillosis, candidemia, esophageal candidiasis, candida peritonitis, bronchopulmonary candidiasis, cryptococcal meningitis, pulmonary cryptococcosis, fusariosis, scedosporiosis, other invasive fungal infections, others]
- Severity [mild, moderate, severe]
- Fever unresponsive to antibacterial agents [absent, present]
- Use of concomitant medications requiring precautions for coadministration [absent, present]
- Concomitant antifungal agents [absent, present]
- Prior medications (antifungal agents) [absent, present]
- Treatment period [<1 week, ≥1 to <2 weeks, ≥2 to <4 weeks, ≥4 to <8 weeks, ≥8 to <12 weeks, ≥12 to ≤16 weeks]
- Long-term treatment [≤12 weeks, >12 weeks]
- Dose on the first day (mg/kg) [<6, ≥6 to <7, ≥7 to <8, ≥8 to <9, ≥9 to <10, ≥10, unknown]
- Mean maintenance dose (mg/kg) [<6, ≥6 to <7, ≥7 to <8, ≥8 to <9, ≥9 to <10, ≥10, unknown]

[a] : Because the upper limit of the dose of oral preparations (tablet and dry syrup) is 350 mg according to the dosage and administration of Vfend in children (aged ≥2 to <12 years and ≥12 years and weighing <50 kg), patients receiving oral preparations at a dose of >350 mg are defined as overdosed. Although there is no upper limit for injection, patients receiving injection at a dose of >350 mg and ≥10 mg/kg are defined as overdosed.

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.
- Important identified risks determined to be safety specifications are listed below.
  - Hepatic toxicity
  - QT prolongation, ventricular tachycardia, ventricular fibrillation, arrhythmia, complete atrioventricular block
  - Visual events
  - Phototoxicity
  - Peripheral neuropathy such as Guillain-Barre syndrome
  - Renal disorder
  - Hematologic disorder
  - Interstitial pneumonia
  - Cardiac failure
  - Consciousness disorder

Specific event terms to be handled as safety specifications will be specified separately.

- Events to be handled as major investigation items are listed below.
  - Hepatic toxicity
  - Visual events

6.2. Effectiveness Endpoints

- Clinical response: Clinical response will be assessed based on clinical course excluding mycological response.
  - Effective
  - Not effective
  - Indeterminate
- Mycological response
  - Eradication: The causative fungi detected from the focus before treatment with this product has become negative

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

• Eradication of causative fungi

The eradication of causative fungi will be assessed by causative fungi based on the eradication of causative fungi obtained at or before the initiation of treatment after administration of Vfend using the results of mycological testing such as culture, microscopy, histopathological test, and genetic diagnosis in the safety analysis set.

- Eradication: The volume of the causative fungi after treatment with Vfend is “-” or a specimen cannot be collected.
- Persistence: The volume of the causative fungi after treatment with Vfend is “+” or higher.
- Indeterminate: All mycological tests after treatment with Vfend are “not performed” or the volume of the causative fungi is “unknown.”

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/outcome of adverse events and action taken with Vfend for the 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.

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 (number of patients) and proportion of each category will be calculated.

8.1.3. Analysis of Binary Data

The number of patients 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 each subgroup 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, the number of patients included in the analysis of clinical response, and the number of patients included in the analysis of mycological response will be tabulated. In addition, the number of patients excluded from the analysis of safety, clinical response, and mycological response 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 discontinued or completed (cured) treatment by Week 16 will be tabulated by timing [<1 week, ≥1 to <2 weeks, ≥2 to <4 weeks, ≥4 to <8 weeks, ≥8 to <12 weeks, ≥12 to ≤16 weeks]. In addition, the number and proportion of patients by reason for discontinuation will be tabulated by timing.

- **Listing of excluded patients**

The listing of patients excluded from the analysis of safety, clinical response, and mycological response and reasons for exclusion will be prepared.

8.2.2. Patient Background and Treatment History of Vfend

- **Patient background**

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

- Sex [male, female]
- Age (continuous; 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 years]
- Body weight (continuous; kg)
- Hospitalized Status [inpatient, outpatient]
- Presence or absence of fever unresponsive to antibacterial agents [absent, present]

- Objective of treatment [treatment of mycosis, others]
- Severity [mild, moderate, severe]
- Presence or absence of prior treatment with antifungal agents [absent, present]
- Presence or absence of hepatic dysfunction [absent, present, unknown]
- Severity of hepatic dysfunction [mild, moderate, severe, unknown]
- Presence or absence of renal dysfunction [absent, present, unknown]
- Severity of renal dysfunction [mild, moderate, severe, unknown]
- Presence or absence of past medical history [absent, present]
- Presence or absence of concurrent illness [absent, present]
- Diagnostic name (name of infection) [invasive aspergillosis, pulmonary aspergilloma, chronic necrotic pulmonary aspergillosis, candidemia, esophageal candidiasis, candida peritonitis, bronchopulmonary candidiasis, cryptococcal meningitis, pulmonary cryptococcosis, fusariosis, scedosporiosis, other invasive fungal infections, others*]
- Diagnostic name (definitive diagnosis)** [invasive aspergillosis, pulmonary aspergilloma, chronic necrotic pulmonary aspergillosis, candidemia, esophageal candidiasis, candida peritonitis, bronchopulmonary candidiasis, cryptococcal meningitis, pulmonary cryptococcosis, fusariosis, scedosporiosis, other invasive fungal infections]

*: Patients will basically be classified based on the name of infection, but patients for whom the diagnostic name is others will be classified as "others."
**: Definitive diagnosis: When the final diagnosis by the physician is invasive fungal infection

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

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

- Concomitant medications
- Contraindicated concomitant medications
- Concomitant medications requiring precautions for coadministration
- Prior treatment (antifungal agents) for infection for which Vfend is administered
- Reasons for discontinuation of prior treatment for infection for which Vfend is administered

- **Status of treatment of Vfend**

In the safety analysis set, the following status of treatment of Vfend will be tabulated: Furthermore, dose will be tabulated separately for patients aged <12 years and ≥12 years

whose body weight is less than 50 kg and those aged ≥12 years whose body weight is 50 kg or more.

- Treatment period [<1 week, ≥1 to <2 weeks, ≥2 to <4 weeks, ≥4 to <8 weeks, ≥8 to <12 weeks, ≥12 to ≤16 weeks, >16 weeks]
- Treatment period (long-term treatment) [≤12 weeks, >12 weeks]
- Treatment period (days) (continuous)
- Dose on the first day (mg) (continuous)
- Dose on the first day (mg) [<50, ≥50 to <100, ≥100 to <150, ≥150 to <200, ≥200 to <250, ≥250 to <300, ≥300 to <350, ≥350, unknown]
- Dose on the first day (mg/kg) (continuous)
- Dose on the first day (mg/kg) [<6, ≥6 to <7, ≥7 to <8, ≥8 to <9, ≥9 to <10, ≥10, unknown]
- Mean maintenance dose (mg) (continuous)
- Mean maintenance dose (mg) [<50, ≥50 to <100, ≥100 to <150, ≥150 to <200, ≥200 to <250, ≥250 to <300, ≥300 to <350, ≥350, unknown]
- Mean maintenance dose (mg/kg) (continuous)
- Mean maintenance dose (mg/kg) [<6, ≥6 to <7, ≥7 to <8, ≥8 to <9, ≥9 to <10, ≥10, unknown]
- Mean maintenance dose of injection alone (mg) (continuous)
- Mean maintenance dose of injection alone (mg) [<50, ≥50 to <100, ≥100 to <150, ≥150 to <200, ≥200 to <250, ≥250 to <300, ≥300 to <350, ≥350, unknown]
- Mean maintenance dose of injection alone (mg/kg) (continuous)
- Mean maintenance dose of injection alone (mg/kg) [<6, ≥6 to <7, ≥7 to <8, ≥8 to <9, ≥9 to <10, ≥10, unknown]
- Mean maintenance dose of oral preparations (tablet + dry syrup) alone (mg) (continuous)
- Mean maintenance dose of oral preparations (tablet + dry syrup) alone (mg) [<50, ≥50 to <100, ≥100 to <150, ≥150 to <200, ≥200 to <250, ≥250 to <300, ≥300 to <350, ≥350, unknown]
- Mean maintenance dose of oral preparations (tablet + dry syrup) alone (mg/kg) (continuous)
- Mean maintenance dose of oral preparations (tablet + dry syrup) alone (mg/kg) [<6, ≥6 to <7, ≥7 to <8, ≥8 to <9, ≥9 to <10, ≥10, unknown]

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.

If treatment with Vfend is continued at the end of the observation period, the treatment period will be considered as 113 days because Vfend is administered for >16 weeks (Week 16 is up to Day 112 with the day of initiation of treatment considered as Day 1).

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*) or if the treatment prolongs, during the period from the initiation of treatment to Week 16 (Day 112 counting from Day 1 as the day the treatment begins) will be tabulated. If the duration of the observation period + follow-up period exceeds 112 days, events observed by Day 112 will be tabulated. All events reported in this study will be included in listings.

*: The duration of the follow-up period in this investigation was set at 28 days because a 30-day follow-up period was provided in a clinical study (Study A1501096) and the period of collection of adverse events using NIS AE Report Form in this investigation 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. Also by diagnostic name (name of infection), the number and proportion of patients with adverse drug reactions will be tabulated by SOC and PT.

- **Serious adverse drug reactions**

The number and proportion of patients with serious adverse drug reactions will be tabulated by SOC and PT. In addition, the number and proportion of patients by known/unknown 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.

- Seriousness [serious, non-serious]
- Known/unknown [known, unknown]
- Intervention [discontinuation, temporarily discontinued, dose reduction]
- Outcome [not recovered, recovered with sequela, recovering, resolved/recovered, unknown]

In addition, the number and proportion of patients with adverse drug reactions meeting all of the following conditions will be tabulated by SOC and PT.

- Seriousness is “non-serious”
- Intervention is “discontinuation,” “temporarily discontinued,” or “dose reduction”
- Outcome is “not recovered” or “recovered with sequela”

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.
- Known/unknown: If both known and unknown events are reported, “unknown” will be adopted.
- Number of days to onset: The number of days to the first event will be adopted.
- Intervention: If multiple types of action taken with Vfend for the adverse events are reported, one of discontinuation, temporarily discontinued, dose reduction, or none, 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 intervention 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. The number and proportion of patients with major investigation items by intervention (change in treatment with Vfend) and outcome will be tabulated by SOC and PT.

The number and proportion of patients with adverse drug reactions considered as major investigation items will be calculated by intervention (change in treatment with Vfend) to assess whether treatment with Vfend was discontinued because of the onset of the adverse drug reaction after its onset.

The listing of patient background and concomitant medications will be prepared in patients with major investigation items with high incidence to evaluate factors common to patients with major investigation items.

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

The number of patients with major investigation items and adverse drug reactions observed in ≥10% of patients will be tabulated by SOC and PT by timing of initial onset [<1 week, ≥1 to <2 weeks, ≥2 to <4 weeks, ≥4 to <8 weeks, ≥8 to <12 weeks, ≥12 to ≤16 weeks].

For major investigation items and adverse drug reactions observed in ≥10% of patients, time to event onset will be summarized in accordance with Section 8.1.4 with the initial onset of the adverse drug reaction considered as an event. Patients without adverse drug reactions will be censored after the observation period + follow-up period (28 days). Patients for whom the duration of the observation period + follow-up period exceeds 112 days will be censored at Day 112.

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

The number of patients with hepatic toxicity and visual events will be tabulated overall and by PT by presence or absence of actually used concomitant medications to evaluate the relationship of contraindicated concomitant medications and concomitant medications requiring precautions for coadministration 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 + 28 days will be excluded from tabulation.

In addition, the number of patients with adverse drug reactions will be tabulated by SOC and PT by presence or absence of actually used concomitant medications to evaluate the relationship of contraindicated concomitant medications and concomitant medications requiring precautions for coadministration with adverse drug reactions. However, medications started to be used after the day of the last onset of the adverse drug reaction during the observation 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 intervention (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. The same analysis will be performed for serious adverse drug reactions.

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.

- 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.

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. Clinical Response

In the clinical response analysis set, the number and proportion (clinical response rate) of patients for whom clinical response was determined as effective and the 95% confidence interval will be calculated. The formula to calculate the clinical response rate is shown below.

$$\text{Clinical response rate (\%)} = \frac{\text{the number of responders}}{\text{the number of patients in the clinical response analysis set excluding indeterminate patients}} \times 100$$

The clinical response rate will be calculated also by diagnostic name (name of infection) (definitive diagnosis + suspected cases) and by diagnostic name [definitive diagnosis] (name of infection).

8.2.4.2. Mycological Response

In the mycological analysis set, the number and proportion (eradication rate) of patients for whom mycological response was determined as eradication or presumed eradication and the

95% confidence interval will be calculated. The formula to calculate the eradication rate is shown below.

$$\text{Eradication rate (\%)} = \frac{\text{the number of patients with mycological eradication + presumed eradication}}{\text{the number of patients in the mycological analysis set excluding indeterminate patients}} \times 100$$

The eradication rate will be calculated also by diagnostic name (name of infection) (definitive diagnosis + suspected cases) and by diagnostic name [definitive diagnosis] (name of infection).

8.2.4.3. Mycological response by Causative Fungus

The number and proportion (eradication rate) of fungus for which eradication after treatment with Vfend was determined as eradication and the 95% confidence interval will be calculated by causative fungus identified at the initiation of treatment. The formula to calculate the eradication rate is shown below.

$$\text{Eradication rate by causative fungi (\%)} = \frac{\text{the number of eradicated fungi}}{\text{the number of (eradicated + persistent) fungi}} \times 100$$

8.2.4.4. Subgroup Analysis

For each factor specified in Section 5.4, subgroup analyses of clinical response will be performed.

8.2.4.5. Exploratory Analysis

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 without change.

- Listing of patients[a]

[a] : Estimated creatinine clearance in the listing will be calculated from serum creatinine before the initiation of Vfend treatment using the Cockcroft-Gault Ccr calculation formula. eGFR will also be calculated because the CDK guideline for children recommends calculation of eGFR. A quintic equation will be used for calculation of

- Listing of patients with adverse events (including events observed after the observation period and follow-up period)
- Listing of patients with adverse drug reactions
- Listing of patients with adverse drug reactions among patients excluded from the safety analysis set
- Listing of patients with serious adverse drug reactions [Intext]
- List of events corresponding to safety specifications including major investigation items
- List of adverse drug reactions falling under safety specifications including major investigation items [Intext]
- Listing of other reasons for discontinuation [Intext]
- Listing of mycological test
- Listing of laboratory values
- Listing of serological test and imaging test
- Listing of the record of administration of Vfend and plasma voriconazole concentration
- Listing of prior medications (antifungal agents) by patient
- Listing of concomitant medications by patient [Intext]
- Listing of deaths [Intext]

Furthermore, the following tables corresponding to appendix tables for periodic safety report (PSUR) will be prepared:

- Appendix Form 16 (Overview of patients in post-marketing surveillance)
- Appendix Form 15 (List of development of adverse drug reactions and infections)
- Appendix Form 12 (Development of adverse drug reactions and infections in additional pharmacovigilance plan)

eGFR for children. (See Attachment 10.3) The quintic equation is for patients aged 2 to 19 years but will be used also in patients aged <2 years.

10. APPENDICES

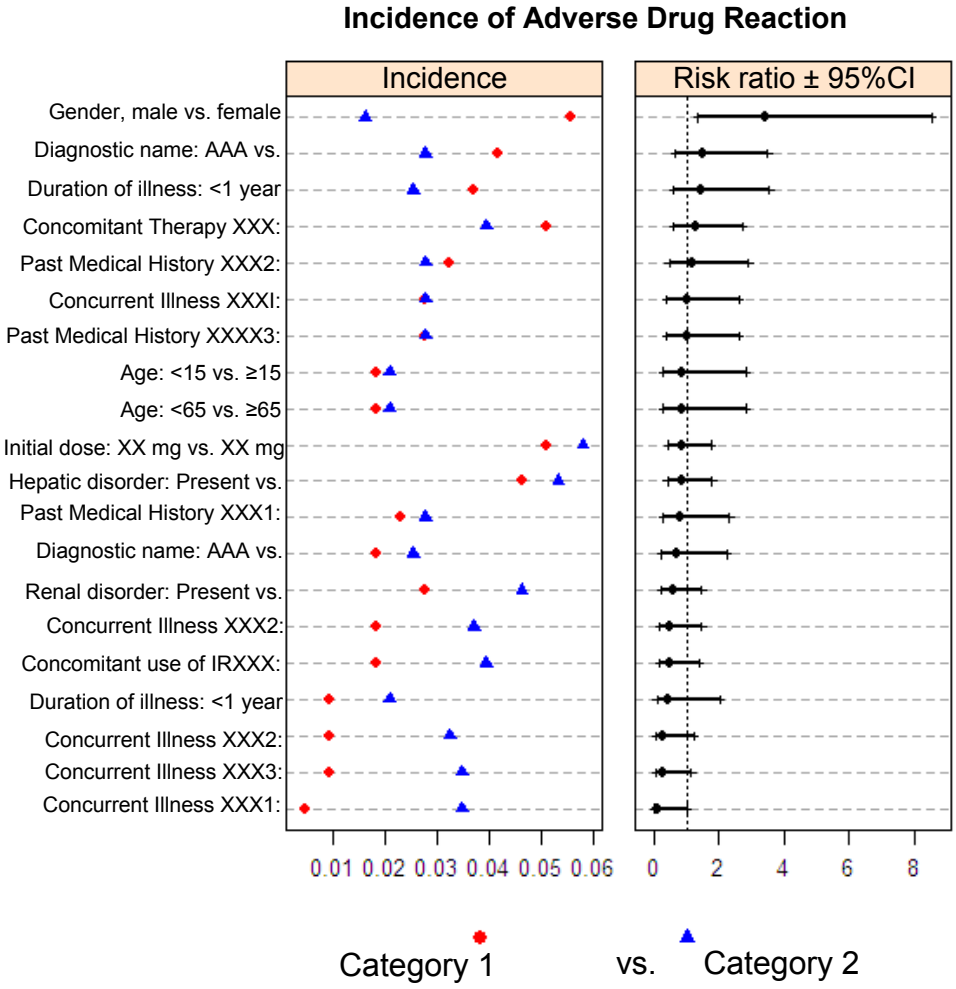
10.1. Appendix 1: Details of Data Extraction

A1.1 Definition of Visit Timing

Visit timing	Endpoint	Definition [acceptable range]
At initiation of treatment	Laboratory test	Day of initiation of Vfend treatment [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	Day of completion of Vfend treatment (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)}

- Quintic equation

See Page 13 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.

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

<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: $-4.536\,Ht^5 + 27.16\,Ht^4 - 63.47\,Ht^3 + 72.43\,Ht^2 - 40.06\,Ht + 8.778$

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[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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