# CLINICAL REVIEW

<table>
<tr><td>Application Type</td><td>sNDA 21-266 (S-039), 21-267 (S-050), 21-630 (S-029)</td></tr>
<tr><td>Application Number(s)</td><td>NDA 21-266 (oral tablets); NDA 21-267 (IV for injection); NDA 21-630 (oral suspension)</td></tr>
<tr><td>Priority or Standard</td><td>Priority</td></tr>
<tr><td>Submit Date(s)</td><td>June 1, 2017</td></tr>
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<tr><td>PDUFA Goal Date</td><td>December 1, 2017</td></tr>
<tr><td>Division/Office</td><td>Division of Anti-Infective Products (DAIP)<br>Office of Antimicrobial Products (OAP)</td></tr>
<tr><td>Reviewer Name(s)</td><td>Caroline J. Jjingo, MD, MPH</td></tr>
<tr><td>Review Completion Date</td><td>November 8, 2017</td></tr>
<tr><td>Established/Proper Name</td><td>Voriconazole</td></tr>
<tr><td>(Proposed) Trade Name</td><td>VFEND®</td></tr>
<tr><td>Applicant</td><td>Pfizer</td></tr>
<tr><td>Dosage Form(s)</td><td>VFEND® IV for injection; VFEND® oral tablets; VFEND® oral suspension</td></tr>
<tr><td>Applicant Proposed Dosing Regimen(s)</td><td>
<table>
<tr><th rowspan="2">Infection</th><th>Loading Dose</th><th colspan="2">Maintenance Dose</th></tr>
<tr><th>Intravenous infusion</th><th>Intravenous infusion</th><th>Oral</th></tr>
<tr><td>Invasive Aspergillosis</td><td rowspan="3">9 mg/kg every12 hours for the first 24 hours</td><td rowspan="3">8 mg/kg every 12 hours after the first 24 hours</td><td rowspan="3">9 mg/kg every 12 hours (maximum dose of 350 mg every 12 hours)</td></tr>
<tr><td>Candidemia in nonneutropenics and otherdeep tissue Candida infections</td></tr>
<tr><td>Scedosporiosis and Fusariosis</td></tr>
<tr><td>Esophageal Candidiasis</td><td>Not Evaluated</td><td>4 mg/kg every 12 hours</td><td>9 mg/kg every 12 hours (maximum dose of 350 mg every 12 hours)</td></tr>
</table>
</td></tr>
<tr><td>Applicant Proposed Indication(s)/Population(s)</td><td>Pediatric patients aged 2 to < 18 years old with:<ul><li>Invasive Aspergillosis (IA)</li><li>Candidemia in Non-neutropenic (b) (4) and (b) (4) Candida Infections (b) (4)</li><li>Esophageal Candidiasis (EC)</li></ul></td></tr>
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| | |
|---|---|
| | • Serious Fungal Infections Caused by *Scedosporium apiospermum* and *Fusarium solani*, in Patients Intolerant of, or Refractory to, Other Therapy |
| **Recommendation on Regulatory Action** | Complete Response |
| **Recommended Indication(s)/Population(s)** | Pediatric patients aged 2 to < 18 years old with:<br>• Invasive Aspergillosis (IA)<br>• Candidemia in Non-neutropenic (b) (4) and (b) (4) *Candida* Infections (b) (4)<br>• Esophageal Candidiasis (EC)<br>• Serious Fungal Infections Caused by *Scedosporium apiospermum* and *Fusarium solani*, in Patients Intolerant of, or Refractory to, Other Therapy |

# Table of Contents

# Table of Tables

# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

The evidence provided in these supplemental NDAs (sNDA) indicates that the safety profile of pediatric patients ages 2 to <12 years old is comparable to that in adults and pediatric patients ages 12 and older. The Phase 3 pediatric studies were not powered to establish efficacy in pediatric patients 2 to <18 years old, since efficacy was to be extrapolated from adults. Global response rates in patients 2 to <18 years old were similar to those observed in the adults. Therefore, this reviewer concludes that the Applicant has provided adequate information to support the safety and efficacy of voriconazole in pediatric patients 2 to < 12 years old.

On November 28, 2017, the Applicant notified the Agency that they will not be submitting revised labeling during this review cycle. A complete response for these NDAs is therefore recommended as the Applicant did not come to an agreement with the Agency on labeling.

## 1.2 Risk Benefit Assessment

Safety data from 105 patients enrolled in two uncontrolled Phase 3 pediatric studies in patients 2 to <18 years of age as well as previously collected safety information from patients 12 to <18 years of age enrolled in the original registrational trials were evaluated. The absence of an active comparator combined with a critically ill patient population made attribution of causality for treatment emergent adverse events and differentiation of events from the underlying medical condition particularly challenging. However, the most frequently observed treatment emergent adverse events in patients ages 2 to <18 years old were as follows: visual disturbances (26%) (i.e. vision blurred, visual brightness, visual impairment); pyrexia (25%); vomiting (20%); epistaxis (16%); nausea (13%); rash (13%); abdominal pain (12%); diarrhea (11%); hypertension (11%); hypokalemia (11%); cough (10%); headache (10%); thrombocytopenia (10%); alanine aminotransferase (ALT) abnormal (9%); hypotension (9%); peripheral edema (9%); hyperglycemia (7%); tachycardia (7%); dyspnea (6%); hypocalcemia (6%); liver function test (LFT) abnormal (6%); mucosal inflammation (6%); photophobia (6%); abdominal distension (5%); constipation (5%); dizziness (5%); hallucinations (5%); hemoptysis (5%); hypoalbuminemia (5%); hypomagnesemia (5%); renal impairment (5%); and upper respiratory infection (5). While the evidence showed that the safety profile of pediatric patients ages 2 to <18 years old was comparable to that of adults, a higher incidence of hepatic toxicity events (including elevations in liver enzymes) (26.7% vs 24.1%), and photophobia (5.7% vs 2.6%) were observed in this age group relative to adults. Visual disturbances were nearly equivalent between pediatric and adult patients enrolled in the Applicant's VFEND studies, at 25.7% and 27.3%. Although, photosensitivity reactions and squamous cell carcinoma (SCC) have been frequently reported in pediatric patients, there were no such events found in the pooled safety analysis population. In addition, QTc prolongation, another azole specific adverse event (AE), was not observed.

Efficacy, for all approved indications, was extrapolated from adults due to similarities in the clinical course of invasive fungal infections in adults and children, as well as evidence from adequate and well-controlled studies in adults and pediatric patients (ages 12 to <18) and

pharmacokinetic (PK) studies. Despite limitations in study size, non-comparative pediatric studies demonstrated response rates comparable to those seen in adults for all treatment indications. Global response rates for pediatric patients with IA compared with adults were 64% and 52%, respectively. In ICC, the global response rate was considerably higher in pediatric patients than in adults, 86% compared with 43%; whereas, EC response rates in pediatric and adult patients were 70% vs 87.5%, respectively.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There is no recommendation for postmarket risk evaluation and mitigations strategies.

### 1.4 Recommendation for Postmarket Requirement and Commitments

There is no recommendation for postmarket requirements and/or commitments.

## 2 Introduction and Regulatory Background

### 2.1 Product Introduction

VFEND (voriconazole) is an azole class antifungal agent indicated for treatment, in patients ages 12 years and older, with the following fungal infections:

- Invasive Aspergillosis (IA)
- Candidemia in non-neutropenic patients and disseminated *Candida* skin infections as well as *Candida* infections of the abdomen, kidney, bladder wall and wounds
- Esophageal candidiasis (EC)
- Serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium solani*, in patients intolerant of, or refractory to, other therapy

VFEND is available in three dosage formulations: an injection for intravenous (IV) use (200-mg); tablets for oral use (50-mg and 200-mg); and an oral suspension (45-mg). VFEND tablets and injection were originally approved on 24 May 2002 and VFEND oral suspension was approved on 19 December 2003. Current VFEND dosing recommendations apply to patients aged 12 years and older and are as follows:

**Table 1: Current VFEND® Dosage Recommendations in Patients Aged 12 Years and Older**

| Infection | Loading Dose | Maintenance Dose | |
|---|---|---|---|
| | IV | IV | Oral |
| **Invasive Aspergillosis** | 6-mg/kg every 12 hours, x first 24 hours | 4-mg/kg every 12 hours | 200-mg every 12 hours |

| Infection | Loading Dose | Maintenance Dose | |
|---|---|---|---|
| | IV | IV | Oral |
| **Candidemia in non-neutropenic patients and other deep tissue *Candida* infections** | 6-mg/kg every 12 hours, x first 24 hours | 3-4-mg/kg every 12 hours | 200-mg every 12 hours |
| **Esophageal Candidiasis** | IV formulation not evaluated in patients with EC | IV formulation not evaluated in patients with EC | 200-mg every 12 hours |
| **Scedosporiosis and Fusariosis** | 6-mg/kg every 12 hours, x first 24 hours | 4-mg/kg every 12 hours | 200-mg every 12 hours |
| **Source:** VFEND label<br>**Note:** Adult patients weighing less than 40-kg should receive only half of the oral maintenance dose. | | | |

The United States prescribing information (USPI), currently recommends that in the treatment of IA, VFEND should be administered for a minimum of 7 days, and can be switched to oral tablets or oral suspension once patients can demonstrate clinical improvement and can tolerate oral medications. An oral maintenance dose of 200-mg achieves a voriconazole exposure similar to 3-mg/kg IV and a 300-mg oral dose achieves an exposure the equivalent of 4-mg/kg IV. For adult patients with candidemia and deep tissue *Candida* infections, treatment duration is currently recommended for a minimum of 14 days after the resolution of symptoms or following the last positive fungal culture whichever is longer. EC patients 12 years of age and older should be treated for a minimum of 14 days and for at least 7 days following resolution of symptoms.

Under the Pediatric Research Equity Act (PREA), all Applicants of new drugs or biologic agents are mandated to evaluate the safety and efficacy of a drug in all relevant pediatric subpopulations. These supplements fulfill the Applicant's post-marketing requirement, in accordance with PREA, to establish the safety, efficacy and PK of VFEND in pediatric patients ages 2 to <12 years old. The proposed VFEND dosing for pediatric subjects evaluated in these supplements is summarized in **Table 2** below.

**Table 2: Proposed VFEND® Pediatric Dosing**

| Infection | Loading Dose | Maintenance Dose | |
|---|---|---|---|
| | Intravenous infusion | Intravenous infusion | Oral |
| **Invasive Aspergillosis** | 9 mg/kg every12 hours for the first 24 hours | 8 mg/kg every 12 hours after the first 24 hours | 9 mg/kg every 12 hours (maximum dose of 350 mg every 12 hours) |
| **Candidemia in nonneutropenics and other deep tissue *Candida* infections** | | | |
| **Scedosporiosis and Fusariosis** | | | |
| **Esophageal Candidiasis** | Not Evaluated | 4 mg/kg every 12 hours | 9 mg/kg every 12 hours (maximum dose of 350 mg every 12 hours) |

VFEND safety and efficacy has not been established in patients younger than two years of age, as children in this subgroup were not studied.

## 2.2 Analysis of Current Treatment Options

**Table 3: Current FDA Approved Treatment Options for Invasive Fungal Infections**

| Drug | Route of Administration | Pediatric Dosing Age Cohorts | Indications | Pediatric Dosing |
|---|---|---|---|---|
| **Abelcet** | Intravenous | Yes | Invasive fungal infections in patients refractory to or intolerant of conventional amphotericin B therapy | **Neonates:** 2.5-5-mg/kg/dose IV every 24-hours, duration at least 3 weeks |
| | | | | **Pediatric**: 5-mg/kg/dose IV every 24-hours |
| **Ambisome (Liposomal)** | Intravenous | Yes | Invasive fungal infections in patients refractory to or intolerant of conventional amphotericin B therapy | **Pediatric**: 3-5-mg/kg/dose IV every 24-hours |
| **Amphotericin B** | Intravenous | Yes | Invasive fungal infections | **Candidemia:**<br>**Loading:** 0.25-0.30-mg/kg slow IV daily<br>**Maintenance:** 1-mg/kg IV daily<br><br>**Systemic Fungal Infection:**<br>**Loading:** 1-mg IV over 30 min<br>**Maintenance:** 0.25 to 1 mg/kg slow IV daily (maximum dose: 1.5-mg/kg total daily dose) |
| **Caspofungin** | Intravenous | 3 months to 17 years of age | Treatment of candidemia and the following *Candida* infections: intraabdominal abscesses, peritonitis, and pleural space infections | Dosing should be based on the patient's body surface area. For all indications |
| | | | Treatment of Esophageal Candidiasis | **Loading:** For all indications, administer a single 70-mg/m$^2$ loading dose |
| | | | Treatment of Invasive Aspergillosis in patients who are refractory to or intolerant of other therapies | **Maintenance:** 50-mg/m$^2$, not to exceed 70-mg |
| | | | Empirical therapy for presumed fungal infections in febrile neutropenic patients | |
| **Fluconazole** | Oral tablets<br>Oral suspension | 6 months and older | • Vaginal candidiasis<br>• Oropharyngeal and esophageal candidiasis<br>• Prophylaxis for candidiasis in patients undergoing bone marrow transplant who receive cytotoxic chemotherapy and/or radiation therapy | • **Oropharyngeal/Esophageal candidiasis:** 200-mg, followed by 100-mg once daily<br>• **Systemic *Candida* infections:** Optimal therapeutic dosage and duration of therapy have not been established |

| Drug | Route of Administration | Pediatric Dosing Age Cohorts | Indications | Pediatric Dosing |
|---|---|---|---|---|
| **Isavuconazonium** | Oral capsules Intravenous | 18 years of age and older | • Invasive Aspergillosis<br>• Invasive Mucormycosis | No dosing approved for children <18 years old |
| **Itraconazole** | Oral suspension | 6 months and older | • Oropharyngeal and esophageal Candidiasis | 5-mg/kg by mouth daily |
| **Micafungin** | Intravenous | 4 months and older | • Treatment of Candidemia, Acute Disseminated Candidiasis, Peritonitis and Abscesses | 2- mg/kg/day, (maximum 100-mg daily) |
| | | | • Treatment of Esophageal Candidiasis | • **≤30 kg:** 3-mg/kg/day<br>• **> 30 kg:** 2.5 mg/kg/day (maximum 150-mg daily) |
| **Posaconazole** | Oral suspension Oral Tablets | 13 years and older (Delayed-release tablets and oral suspension) | Prophylaxis of Invasive *Aspergillus* and *Candida* Infections | **Oral Suspension:** 200-mg (5mL) three times a day.<br>Note: Duration of therapy is based on recovery from neutropenia or immunosuppression |
| | | | Oropharyngeal Candidiasis | **Delayed-Release Tablets:**<br>**Loading dose:** 300-mg (three 100-mg tablets) twice a day on Day 1<br>**Maintenance dose:** 300-mg (three 100-mg tablets) once a day, beginning on Day 2 |
| | | | Oropharyngeal Candidiasis Refractory to Itraconazole and/or Fluconazole | |
| **Sources:** Individual product prescribing information and IDSA guidelines | | | | |

## 2.3 Important Safety Issues with Consideration to Related Drugs

Azoles, including VFEND, are associated with several serious adverse reactions described in **Section 5 Warnings and Precautions** of the currently approved VFEND labeling:

- Drug Interactions
- Hepatic Toxicity
- Visual Disturbances
- Arrhythmias and QT Prolongation
- Infusion Related Reactions
- Laboratory Tests (i.e. electrolyte disturbances such as hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to initiation of and during VFEND therapy)
- Serious Exfoliative Cutaneous Reactions
- Photosensitivity
- Skeletal Adverse Reactions

## 2.4 Summary of Presubmission Regulatory Activity Related to Submission

**Key** elements of VFEND's US regulatory history, particularly as it pertains to the pediatric clinical development history are summarized below.

**17 November 2000:** VFEND NDA was submitted to Division for the treatment of invasive aspergillosis; serious *Candida* infections, including esophageal and systemic infections; serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp.; treatment of other serious fungal infections in patients intolerant of or refractory to other therapy; and empirical treatment of presumed fungal infections in febrile immunocompromised patients. VFEND was to have two dosage formulations, intravenous (IV) and oral. VFEND was not recommended for children less than 2 years of age. Adolescents (12 to 16 years of age) were to be dosed as adults.

**21 December 2001:** FDA issued the Applicant an initial pediatric written request (PWR) to conduct two pediatric studies: (Study 1) an open label, multiple dose, IV-to-oral switch study evaluating the PK in pediatric patients aged 2 to 17 years old with febrile neutropenia and a second study (Study 2) to provide "comparative safety adverse event data for voriconazole and a comparator in pediatric patients aged 2 to 17 years old with an anticipated due date of 31 December 2005."

**31 January 2002:** The Applicant requested an extension of the deferral date for submission of pediatric oral formulation of VFEND. Due to stability problems with the pediatric oral formulation, the Division agreed to the Applicant's extension request.

**24 May 2002:** NDA 21-266, for VFEND tablets, and NDA 21-267, VFEND for Injection, were approved with deferral of post marketing requirement (PMR) # 5 to conduct a study evaluating the "safety and tolerability of voriconazole in the treatment of children with invasive aspergillosis and serious mold infections caused by *Scedosporium* and *Fusarium* in patients refractory to or intolerant of other therapies."

**4 February 2003:** Applicant proposed a 50 patient non-comparative study for the treatment of invasive fungal infections including invasive aspergillosis, scedosporiosis and fusariosis, where the remaining patients would most likely have invasive candidiasis.

**23 September 2003:** Applicant submitted an amended Written Review including a 60 patient comparative study with at least 10 subjects with IA administered VFEND and 5 subjects with IA administered a comparator. It was understood that the remaining patients would most likely have invasive candidiasis. Subjects with candidiasis were included implicitly in the study "for the treatment of patients with invasive fungal infections including aspergillosis, scedosporiosis and fusariosis."

**16 June 2005:** Applicant granted approval for revised pediatric written request for: **Study 1:** an open, multi-center study to investigate the pharmacokinetics, safety and tolerability of an intravenous to oral switch of voriconazole in immunocompromised pediatric patients at high risk for invasive fungal infection; **Study 2:** an open, multi-center study to investigate the pharmacokinetics, safety and toleration of an intravenous to oral switchover regimen of voriconazole in immunocompromised adolescent patients (ages 12 to <17 years) who are at high risk of developing systemic fungal infection; **Study 3:** a prospective, randomized, double-blind, comparator-controlled trial for the indication of invasive aspergillosis and treatment of molds

such as *Scedosporium* or *Fusarium* species, once a dose has been established based on the clinical pharmacology studies (for children 2 to 16 years of age). This was to be a descriptive study with no formal sample size calculations, and an enrollment target of approximately 75 patients (50 in voriconazole and 25 in comparator arm).

**29 June 2005:** Applicant submitted prior approval labeling supplements for NDA 21-266; 21-267 and NDA 21-630 to provide dosing regimens in pediatric patients ages 2 to <12 years old based on population PK analyses (modeling). However, the Agency disagreed with the Applicant's PK model and accompanying pediatric dosing regimens, which prompted the Agency to request that the Applicant complete three additional PK studies (A1501081, A1501088 and A1501092). In addition, the Applicant conducted an integrated population PK analysis with pooled concentration data (children, adolescents and adults) from studies A1501007, A1501037, A1501088, A1501081, and A1501092 to derive the appropriate pediatric dosing regimens across the continuum of patients from 2 to <17 years old.

**20 June 2007:** Agency met with Applicant to amend the VFEND Written Request and to amend the candidemia post-approval commitment.

**13 April 2009:** Applicant submitted a revised Written Request for Protocols A1501080 and A1501085 and supportive PK studies A1501088, -1081.

**19 April 2010:** Type C meeting held and in subsequent correspondence both the Applicant and the Agency agreed on the appropriate dosing regimens for evaluation in pediatric patients ages 2 to <12 years old to be enrolled in Studies A1501080 and A1501085.

**23 June 2010:** Agency agrees with Applicant's request to revise 16 June 2005 Written Request (WR) for pediatric studies for voriconazole. This WR reduces the number of subjects required for evaluation in **Study 1** and amends primary study objective so that the appropriate dosing regimens for pediatric patients 2 to <12 years old be evaluated and states that a minimum of 30 patients be studied. **Study 2** revised to no longer require "comparative safety adverse event data between voriconazole and a comparator drug." Required a minimum of 36 evaluable patients, with at least 15 evaluable patients with proven or probable IA. **Study 3** was revised to evaluate a minimum of 36 patients ages 2 to <17 years with IA and other mold infections. **Study 4** was to have a minimum of 30 patients with serious *Candida* infections between the ages of 2 to <17 years old.

**23 September 2011:** Revised pediatric WR issued **(**Amendment 6)

**30 November 2015:** Applicant submitted a prior approval labeling supplemental application to submit proposed draft labeling and justification in support of revisions to the VFEND package insert including updated pediatric dosing recommendations to prescribers and pharmacokinetic information following the completion of the prospective Phase 3 pediatric studies A1501080 and A1501085.

**18 December 2015:** The Applicant provided the final study report for Studies A1501080 and A1501085.

**31 August 2016:** The Applicant submitted an amended Clinical Study Report (CSR) for Study A1501085.

The European Medicines Agency, the European Union counterpart to the FDA, approved VFEND for pediatric patients 2 and older in 23 April 2015.

# 3 Ethics and Good Clinical Practices

## 3.1 Submission Quality and Integrity

The Applicant collected patient level data and incorporated this information onto case report forms (CRF). Independent quality assurance (QA) audits were conducted by the Applicant's independent QA group, a contract research organization (CRO), and/or by individual contract personnel. The Applicant conducted audits in accordance with their procedures and Good Clinical Practice (GCP) guidelines.

## 3.2 Compliance with Good Clinical Practices

The Applicant states that Studies A1501080 and A1501085 were conducted in compliance with the International Conference on Harmonization (ICH) and GCP Guidelines.

## 3.3 Financial Disclosures

The Applicant submitted Form FDA 3455 for clinical investigator disclosure of financial disclosures, and a debarment certification for all investigators involved in the conducted studies. Study A1501080 had one Principal Investigator, (b) (6), who disclosed $27,584.61 worth of payments in the form of honoraria and speaking engagements. There were no Principal Investigators or Sub-Investigators in Study A1501085 who reported any disclosable financial arrangements.

# 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

## 4.1 Product Quality

No new product quality information was submitted with this application.

## 4.2 Nonclinical Pharmacology/Toxicology

Dr. Owen McMaster was the Pharmacology/Toxicology reviewer for this application. Based on five week juvenile studies of 21-day old rats, Dr. McMaster concluded that there were new toxicity findings in juvenile rates when compared with adult rats. As with adult rats, serious hepatic reactions, namely abnormal elevations in liver enzymes, were reported in juvenile rats.

### 4.3 Clinical Pharmacology

Drs. Grace Yan and Fang Li were the clinical pharmacology and pharmacometrics reviewers, respectively, for this application. They noted the following:

- VFEND dosing in pediatric patients was based on a population PK analysis of data obtained from 112 immunocompromised patients ages 2 to <12 years old and 26 immunocompromised patients ages 12 to <17 years old.
- Data indicated that predicted total exposure ($AUC_{12}$) in pediatric patients ages 2 to < 12 years old following a 9 mg/kg IV loading dose was comparable to an adult IV loading dose of 6 mg/kg.
- VFEND's predicted total exposures in pediatric patients ages 2 to <12 years old following IV maintenance doses of 4 and 8 mg/kg twice daily were comparable to adult dosing following 3 and 4 mg/kg IV twice daily, respectively.
- The predicted total exposure in pediatric patients ages 2 to <12 years old following an oral maintenance dose of 9 mg/kg twice daily was comparable to adult oral dosing of 200 mg twice daily.
- It was determined that IV VFEND 8 mg/kg would provide exposures that are approximately 2-fold higher than a 9 mg/kg oral dose in pediatric patients ages 2 to <12 years old.
- VFEND exposures in the majority of pediatric patients ages 12 to <17 years old were comparable to those in adults receiving the same dosing regimens. However, lower VFEND exposures were observed in pediatric patients ages 12 to <17 years old with lower body weights.
- Trough samples were collected on 11 patients ages 2 to <12 years old and those ages 12 to 14 years old weighing <50 kgs who were administered VFEND 9mg/kg IV every 12 hours, followed by maintenance dosing of 8 mg/kg IV, with mean trough concentrations of 3.6 micrograms/mL (range 0.3 to 10.7 micrograms/mL). Four patients ages 2 to <12 years old and those ages 12 to 14 years old weighing <50 kgs who received VFEND 4 mg/kg IV every 12 hours, had mean trough concentrations of 0.9-micrograms/mL (range: 0.3 to 1.6 micrograms/mL).

## 5 Sources of Clinical Data and Review Strategy

### 5.1 Table of Clinical Studies

**Table 4** provides a summary overview of the Applicant's two non-comparative, open-label Phase 3 studies, Study 1501080 and Study 1501085. A table summarizing the original registrational trials, upon which pediatric safety was additionally established among pediatric patients ages 12 to <18 years old can be found in **Section 13 Appendix**.

**Table 4: Clinical Studies for Invasive Aspergillosis, Invasive Candidiasis with Candidemia, and Esophageal Candidiasis in Pediatric Patients**

| Trial | Phase | Trial Design | Regimen/Schedule/ Route | Treatment Duration/ Follow-Up | Study Endpoints | Number of Patients Enrolled | Study Population | Number of Centers and Countries |
|---|---|---|---|---|---|---|---|---|
| **Study 1501080** (26 May 2009 thru 15 May 2013) | Phase 3b | Prospective, Open-Label, Non-Randomized, Multicenter | **24-hour IV- loading dose:** 2 to <12 years/adolescents 12 to 14 years (weighing <50-kg): 9-mg/kg every 12-hours IV x 24 Adolescents 12 to <18 years (weighing ≥ 50 kg) 6-mg/kg every 12 hours<br><br>**Maintenance dose:** 2 to <12 years/adolescents 12 to 14 years (weighing <50-kg) : 8-mg/kg IV every 12-hours; Adolescents 12 to <18 years (weighing ≥ 50 kg): 4-mg/kg IV every 12 hours and/or an oral maintenance dose of 200-mg every 12 hours (up to 300-mg) | At least 6 weeks up to a maximum of 12 weeks | **Primary End Point:** Assess safety and tolerability throughout follow-up (FU) visit<br><br>**Secondary End Point:** Rate of global response at 6 weeks and EOT; All cause and attributable mortality at 6 weeks and EOT; Time to death | 31 patients enrolled; Safety population: 30 subjects | Pediatric Patients: age 2 to <18 years with Invasive Aspergillosis | **42 sites** participated **15 sites enrolled** subjects 5 countries: United Studies (5 sites) Thailand (3) Singapore (2) Spain (2) Poland (1) Netherlands (1) Czech Republic (1) |
| **Study 1501085** (28 October 2010 thru 30 May 2013) | Phase 3 | Prospective, Open-Label, Non-Randomized, Multicenter | **24-hour IV- loading dose:** 2 to <12 years/adolescents 12 to 14 years (weighing <50-kg): 9-mg/kg every 12-hours IV x 24 Adolescents 12 to <18 years (weighing ≥ 50 kg) 6-mg/kg every 12 hours **Maintenance dose:** | **ICC** (primary or salvage): At least 14 days. A maximum of 42 days of treatment **EC** (primary or salvage): At least 7 | **Primary End Point:** Assess safety and tolerability of voriconazole for the treatment of invasive candidiasis, candidemia (ICC) and esophageal candidiasis (EC) **Secondary End Point:** To assess the efficacy of | 22 patients enrolled; Safety population: 22 subjects | Pediatric Patients: age 2 to <18 years with Invasive candidiasis, candidemia (ICC) and Esophageal candidiasis (EC) | **11 sites** enrolled subjects 8 countries: China (2 sites) Czech Republic (1) Hong Kong (2 sites) Hungary (2) Mexico (1) Philippines (1) Poland (1) |

| Trial | Phase | Trial Design | Regimen/Schedule/ Route | Treatment Duration/ Follow-Up | Study Endpoints | Number of Patients Enrolled | Study Population | Number of Centers and Countries |
|---|---|---|---|---|---|---|---|---|
| | | | 2 to <12 years/adolescents 12 to 14 years (weighing <50-kg) : 8-mg/kg IV every 12-hours; Adolescents 12 to <18 years (weighing ≥ 50 kg): 4-mg/kg IV every 12 hours and/or an oral maintenance dose of 200-mg every 12 hours (up to 300-mg) | days after the resolution of clinical signs and symptoms. A maximum of 42 days of treatment | voriconazole for the treatment of ICC and EC; To assess time to death and all-cause mortality during study therapy, at Day 28, and at the 1-month follow-up visit. | | | Slovakia (1) |

### 5.2 Review Strategy

This review of safety in pediatric patients is based upon the evaluation of safety data from two Phase 3 non-comparative, multi-center, open-label studies in pediatric patients ages 2 to <18 years old (Studies A1501080 and A1501085). Additionally, the Applicant provided safety data in patients ages 12 to <18 years old enrolled in eight of the original registrational trials (Trials 303, 304, 307-602, 309, 603, 604, and 608). The pooled data from these trials formed the basis of the Integrated Summary of Safety (ISS). The reviewer initially conducted safety analyses stratified by two separate age cohorts, patients ages 2 to <12 years old and those ages 12 to < 18 years old. However, upon finding no significant discrepancies in safety between these two age cohorts, safety events were combined. The combined safety population of 105 patients was used to compare the frequency of pediatric safety events against those observed in adults.

Efficacy is only briefly discussed in this review as the Phase 3 trials were not powered to make efficacy determinations. Efficacy was to be extrapolated from adults because the pathophysiology of invasive fungal infections is similar in both populations. Nonetheless, the endpoint of global response is briefly addressed in this review. Drs. Grace Yan and Fang Li, the clinical pharmacology reviewers, discuss pediatric dosing and PK parameters relative to adult dosing.

## 6 Review of Relevant Individual Trials Used to Support Efficacy

### 6.1 Study A1501080

#### 6.1.1 Study Design

*Trial Overview and Objectives*
Study A1501080 entitled **"**A Prospective, Open-Label, Non-Randomized, Multicenter Study to Investigate the Safety and Tolerability of Voriconazole as Primary Therapy for Treatment of Invasive Aspergillosis (IA) and Molds Such as *Scedosporium* or *Fusarium* Species in Pediatric Patients" was a Phase 3b study conducted to evaluate the safety, tolerability, and efficacy of voriconazole as primary treatment in pediatric subjects ages 2 and <18 years old.

**Primary Objective:**

- To evaluate the safety and tolerability of VFEND (voriconazole) as primary treatment of IA and rare molds such as *Scedosporium* or *Fusarium* species in immunocompromised pediatric subjects from 2 to <18 years of age.

**Secondary Objective:**

- To describe the response to therapy with VFEND (voriconazole) as treatment of IA and rare molds such as *Scedosporium* or *Fusarium* species in immunocompromised pediatric subjects from 2 to <18 years of age.

This multi-center, multi-national open-label study commenced on 29 May 2009 and was completed on 15 May 2013. It was terminated prematurely due to slow enrollment and not due to safety. Subjects were enrolled from 15 of a total of 42 participating global sites.

*Study Population and Eligibility Criteria*
Enrollment was targeted at approximately 36 eligible subjects, with a minimum of 15 subjects diagnosed with proven or probable IA as defined by the European Organisation for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG).

**Key** eligibility criteria included:

*Inclusion Criteria*

- Immunocompromised subjects "with a clinically compatible illness" between the specified age ranges (2 and <18 years old) with proven, probable or possible IA.
    - However, subjects with possible IA were required to be re-evaluated within a week of enrollment to determine if they had proven or probable IA. Those determined to neither have proven or probable IA were discontinued from the study; whereas, those without a prevailing alternative diagnosis could continue in the study at investigator discretion.

*Exclusion Criteria*

- Excluded subjects included those with liver dysfunction (defined as total bilirubin >5 x upper limit of normal [ULN] or aspartate aminotransferase [AST], alanine aminotransaminase [ALT], or alkaline phosphatase >5 x ULN); those with moderate or severe renal impairment (calculated creatinine clearance <50 mL/min); and subjects concomitantly receiving drugs with clinically relevant interactions with voriconazole unless closely monitored or dosage adjusted.

*Study Treatments*
All subjects meeting eligibility criteria received *at least* 6 weeks and up to a maximum of 12 weeks of VFEND, based on the investigator's clinical discretion. During the first 7 days of treatment, subjects were administered IV voriconazole and had the option to switch to oral VFEND therapy based on the investigator's determination of clinical improvement. VFEND dosing was as follows:

- **Patients 2 < 12 years of age** (and ages 12 to 14 weighing < 50-kg):
  A loading dose of 9-mg/kg every 12 hours was given for the first 24-hours. This was followed by a maintenance dose of 8-mg/kg IV every 12 hours.
- **Patients ages 12 to 14 weighing ≥ 50-kg** (and adolescents ≥15 years irrespective of weight): received an IV loading dose of 6-mg/kg every 12 hours for the first 24-hours followed by a maintenance dose of 4-mg/kg IV every 12 hours or an oral maintenance dose of 200-mg every 12 hours (up to 350-mg), at the investigator's discretion.
- **Dose adjustments** based on clinical response, intolerance to treatment and/or voriconazole plasma trough concentrations were made upon subsequent dosing.

**Medical Reviewer's Comments:**
*The study design and eligibility criteria of Study A1501080 were acceptable.*

*Safety Assessments*
Adverse events (AE) were assessed at baseline (Day 1) and throughout the study, including a one month follow-up visit. Safety assessments included: the collection of clinical laboratories (i.e. hematology and chemistries [including liver function tests]) at screening and at all post-baseline visits; clinical assessments of signs and symptoms; physical examinations (a complete exam at screening and a targeted exam at pre-specified time points); radiologic assessments; and assessment for visual disturbances, a known side effect of VFEND (voriconazole) in adults (at baseline Weeks 1, 2, 4, 6, 12 and at the end of treatment).

**Medical Reviewer's Comments:**
*Safety assessments were appropriate and collected at adequate time points. Given the well-characterized side effect profile of VFEND, including hepatic toxicity and visual disturbances, the Applicant performed an extensive evaluation of visual events and frequent monitoring of liver tests, see* ***Section 8.3.3 Routine Clinical Tests*** *for further details. Protocol thresholds for re-evaluation of hepatic lab abnormalities were pre-specified. In light of azole-associated QTc prolongation, electrocardiograms (ECGs) were collected at pre-specified time points (Screening, end of treatment [EOT], and at the one month follow-up visit).*

*Assessment of Treatment Response*
**Global response** to treatment, a secondary endpoint, was assessed at Study Week 6 and at the EOT visit. It was defined as follows:

- ***Success***: "A complete response (resolution of all clinical signs and symptoms and resolution of ≥90% of baseline lesions visible on radiological studies attributed to IA) or a partial response (clinical improvement and 50 to 90% resolution of radiological lesions attributed to IA at baseline)."
- ***Failure:***
    - **Stable disease** (no improvement and no worsening of the clinical course and/or <50% resolution of radiological lesions attributed to IA at baseline),
    - **Failure to respond** (clinical worsening or no improvement or worsening of radiological findings attributed to IA at baseline), or
    - **Indeterminate response** (not enough information was available to determine the clinical or radiologic response)."

**Medical Reviewer's Comments:**
*Efficacy was a secondary endpoint in this study. This reviewer finds the Applicant's definitions of treatment success and failure acceptable. The modified intent-to-treat analysis (MITT) population, defined as all subjects diagnosed with proven or probable IA who received at least one dose of study drug, was the main efficacy analysis population. The reviewer finds the Applicant's use and definition of the MITT analysis population to be acceptable.*

### 6.1.2 Study Results

*Patient Disposition*

In all, 31 of a total 32 screened patients enrolled into Study A1501080. There was a single screen failure (Subject (b) (6) who was deemed ineligible for study participation due to being on mechanical v

All 31 patients comprised the Safety Population. Fourteen (45.2%) of the 31 patients were included in the MITT population: 5 patients 2 to <12 years old and 9 patients 12 to <18 years old. Of the 17 (54.8%) patients excluded from the MITT population, the most common reason for exclusion was a patient failing to demonstrate proven/probable IA infection (16 of 17 patients; 88.9%). One (5.9%) patient was excluded after it was agreed that he did not meet criteria for proven IA based on radiologic findings.

Twenty-six patients (83.9%) of 31 were documented as having a present medical condition coded under the Neoplasms SOC, with the most frequently reported diagnoses as follows: 15 (48.4%) patients with acute lymphocytic leukemia; 5 (19.2%) patients with lymphoma; and 4 (15.4%) with acute myeloid leukemia. In all, 29 patients had medical conditions coded under the Blood and Lymphatic Tissue SOC and were documented as having the following: anemia [N=16]; thrombocytopenia [N=14]; febrile neutropenia [N=12]; neutropenia [N=10]; and pancytopenia [N=7]. The most commonly administered classes of concomitant medications included: analgesics; systemic antibacterials, systemic antihistamines, antineoplastic agents, and systemic corticosteroids.

Twenty-five patients (80.7%) completed the study and 16 (51.6%) patients completed treatment with VFEND. Nearly half of all patients (15 patients) (48.4%) discontinued treatment, with the most commonly cited reasons being: death (5 patients) and "Other" (7 patients), with "other" including, for example, failure to demonstrate proven or probable IA (5 patients). One patient each discontinued treatment due to either a lack of efficacy, an adverse event (Subject (b) (6) (b) (6) or an unwillingness to participate further in the study.

**Medical Reviewer's Assessment**

*The Applicant was successful in enrolling 31 of an originally planned 36 patients into Study A1501080. Most patients had hematologic malignancies, for which 4 patients (13.0%) either received an allogeneic stem cell transplant prior to or during study participation. Over half of all patients completed VFEND treatment. Likewise, nearly half of all patients failed to complete VFEND (48.4%), with death factoring prominently into treatment discontinuations, a further indication of how critically ill most patients were. A more detailed discussion of patient demographics is found in* ***Section 8.2.2 Relevant Characteristics of the Safety Population****.*

## 6.2 Study A1501085

### 6.2.1 Study Design

*Trial Overview and Objectives*
Study A1501085 entitled "A Prospective, Open-Label, Non-Comparative Study to Assess the Safety, Tolerability and Efficacy of Voriconazole for the Primary and Salvage Treatment of Invasive Candidiasis, Candidemia, and Esophageal Candidiasis in Pediatric Subjects" was an open-label, non-comparative study of pediatric patients ages 2 to <18 years old with invasive candidiasis and candidemia (ICC) or esophageal candidiasis (EC). VFEND could be administered as either primary therapy for ICC or EC or as salvage therapy in individuals with ICC or EC refractory to at least one other previous therapy. VFEND could not be used as an adjunct to an existing antifungal salvage regimen.

As efficacy in children with ICC or EC can be extrapolated from adults, the purpose of this non-comparative, descriptive trial was to bridge VFEND dosing levels with those used in adults. As such, no statistical comparisons or statistical testing were conducted for this study.

The Applicant reports that they were unable to achieve their target enrollment of 30 subjects and therefore terminated the study early for reasons unrelated to safety, but rather due to slow enrollment. A total of 22 subjects had enrolled into the study at the time of termination.

**Primary Objective**
- To assess the safety and tolerability of voriconazole for the treatment of ICC and EC in pediatric subjects 2 to <18 years of age.

**Secondary Objective**
- To assess the efficacy of voriconazole for the treatment of ICC and EC in pediatric subjects 2 to <18 years of age.
- To assess time to death and all-cause mortality during study therapy, at Day 28, and at the 1-month follow-up visit.

**Medical Reviewer's Comments:**
*Slow patient recruitment resulted in a reduction in the targeted patient enrollment from an initial 30 patients to 22 patients as well as early termination of the study for reasons unrelated to safety. This study was not powered for efficacy, but was intended to further characterize* VFEND*'s safety profile in pediatric patients 2 to <18 years as well as to establish adequate dosing regimens. The study was neither subject to patient or investigator blinding and was absent of an active comparator.*

*Study Population and Eligibility Criteria*
Subjects were eligible for study inclusion if they demonstrated any one of several pre-specified vital signs and symptoms, in addition to any of the following additional criteria (within 7 days prior to the receipt of VFEND): (a) at least one positive culture (either a blood culture or other normally sterile site for *Candida*); (b) histopathologic/microscopic evidence suggestive of

*Candida* spp. from at least one specimen obtained from a normally sterile site; (c) at least one positive culture for yeast or *Candida* spp. from a drain; and/or (d) a new radiologic finding in the presence of disseminated disease after a positive culture for *Candida* spp. from a normally sterile site within 14 days prior to enrollment.

EC eligibility required meeting 3 of the following criteria within 7 days prior to enrollment: (a) clinical symptoms consistent with EC (i.e. dysphagia, odynophagia, and retrosternal pain, with or without concomitant oropharyngeal candidiasis); (b) lesions characteristic of EC visualized by esophagoscopy; and (c) positive microscopy and/or mycological culture for yeast (later confirmed as *Candida* spp.) or *Candida* spp. from a brush biopsy or tissue biopsy of esophageal lesions.

**Medical Reviewer's Comments:**
*Eligibility criteria for Study A1501085 were appropriate for both disease indications.*

*Study Treatment*
Both primary and salvage therapy for ICC or EC were as follows:

- **Patients 2 < 12 years of age** (and ages 12 to 14 years old weighing < 50-kg):
  A 24-hour loading dose of 9-mg/kg every 12 hours was given for the first 24-hours. This was followed by a maintenance dose of 8-mg/kg IV every 12 hours or 9-mg/kg by mouth every 12 hours for a maximum dose of 350-mg.
- **Patients ages 12 to 14 years old weighing ≥ 50 kg** (and adolescents ≥15 years old irrespective of weight): received an IV loading dose of 6-mg/kg every 12 hours for the first 24-hours followed by a maintenance dose of 4-mg/kg IV every 12 hours or an oral maintenance dose of 200-mg to 300-mg by mouth every 12 hours, to be administered at the investigator's discretion.
- **Dose adjustments:** Initial VFEND dosing was both age and weight based; whereas, subsequent dosing was adjusted based on clinical response, the emergence of drug toxicity, and/or VFEND plasma levels.
- **ICC patients**, treated for either primary or salvage, were administered a minimum of 14 days of VFEND following the last positive *candida* culture and were permitted to receive a maximum of 42 days of treatment.
- **EC patients,** treated for either primary or salvage therapy of EC, were administered a minimum of 7 days of VFEND *after* resolution of clinical signs and symptoms up to a maximum of 42 days of therapy.

*Safety Analysis*
The primary endpoint for this study was the evaluation of safety. Safety and tolerability of VFEND was determined by the incidence of both serious and non-serious AEs as well as TEAEs resulting in discontinuation of the study drug. Safety assessments were pre-specified and similar to those conducted in Study A1501085 (i.e. clinical monitoring, safety laboratory testing, ECG and visual monitoring). AE monitoring began upon initiation of treatment and continued through the 1-month follow-up visit.

***Medical Reviewer's Comments:***
*All subjects were monitored for azole specific AEs, including cardiac and hepatic related AEs. In addition, subjects were assessed for visual disturbances (i.e. altered vision, photophobia, and blurred vision), a well characterized VFEND (voriconazole) specific AE. Please refer to* ***Section 8.3.3 Routine Clinical Tests*** *for more details on the extent and timing of safety assessments.*

*Efficacy Analysis*
Efficacy was considered a secondary endpoint and was assessed as a global response to EOT, with global frequencies and percentages used to determine treatment response. Treatment failures were similarly defined as in Study A1501085. All efficacy analyses were conducted using the MITT population, which was defined as "all subjects who received at least one dose of study drug and who had microbiologically confirmed ICC or EC." Additional, analyses included time to death and determination of all-cause mortality rates at Day 28 and at the 1-month follow-up visit.

**Medical Reviewer's Comment:**
*Study A1501085, like the previous study, was intended to establish both dosing and safety in patients 2 to <18 years and secondarily to describe voriconazole efficacy outcomes in this population. Reviewer finds efficacy endpoints as well as the use of the MITT population as the primary efficacy analysis population acceptable. Reviewer also finds the description of treatment failures and treatment successes acceptable.*

### 6.2.2 Study Results

A total of 24 patients were screened for Study A1501085. Two patients, (Subjects (b) (6) (b) (6) were deemed screen failures after deciding they no longer wanted to participate in the study. Otherwise, 22 patients enrolled in the study. These 22 patients comprised the safety analysis population. Seventeen (77.3%) patients out of the 22 comprised the MITT population. Five patients were excluded from the MITT population due to a lack of microbiologic confirmation of *Candida* infection. A total of 14 (63.6%) patients ages 2 to <12 years and 8 (36.4%) patients ages 12 to <18 years received VFEND. Among patients in the 2 to <12 age cohort, 11 were treated for invasive candidiasis and candidemia (ICC), two of whom received VFEND for salvage therapy; whereas, three patients had a primary diagnosis of esophageal candidiasis (EC) and received VFEND as primary therapy. All patients ages 12 to <18 years had a primary diagnosis of EC, two of whom received salvage therapy while the remaining six patients received VFEND primary therapy for EC. No subjects in the 12 to <18 age cohort had ICC.

In all, 21 (95.5%) of 22 patients completed the study. The single patient (Subject (b) (6) (b) (6) who discontinued the study early was a 2 year old female with a primary diagnosis of ICC. The Applicant reports that she was in the study a total of 8 days, however, she failed to return for all subsequent visits beyond the EOT visit. Furthermore, her *Candida* status remained unconfirmed. Thirteen (59.1%) of 22 patients completed treatment and nine failed to complete treatment (including the 2 year old female who discontinued the study early). The reasons for

premature discontinuation for the remaining eight patients were as follows: two patients sustained treatment emergent adverse events (Subject (b) (6) [PT: liver disorder] and Subject (b) (6) PT: hyperbilirubinemia]), one patient experienced a progression of suspected splenic candidiasis (Subject (b) (6) and another patient developed pulmonary aspergillosis; two patients had unconfirmed *Candida* infection. One patient each discontinued treatment due to a medication error without an associated AE and another patient sustained a protocol violation (failure to comply with inclusion criterion 3), respectively.

All 22 subjects had underlying hematologic malignancies, with the most frequently identified malignancies being: acute lymphocytic (including one patient in remission) (6 patients, 27.3%), acute myeloid leukemia (4 patients; 18.2%), one patient each with Burkitt's lymphoma, non-Hodgkins lymphoma, and medulloblastoma, respectively. Several patients were reported to have neoplasm (not otherwise specified). A single patient had a previous autologous bone marrow transplant. Glucocorticoids, antibacterials and antivirals were the most commonly administered classes of concomitant medications.

***Medical Reviewer's Comments:***
*While most all patients completed the study, 9 patients (41%) discontinued VFEND prematurely. Two treatment discontinuations were due to hepatic related TEAEs and will be discussed in greater detail in* ***Section 8 Review of Safety****. All patients were quite ill as demonstrated by all of them having a history of malignancy. It is also noted that all patients with ICC were ages 2 to <12 years. A more detailed discussion of patient demographics and TEAEs resulting in treatment discontinuations is found in* ***Section 8 Review of Safety.***

## 7 Integrated Review of Efficacy

### 7.1 Assessment of Efficacy Across Studies

#### 7.1.1 Primary Endpoints

The primary endpoint for both Studies A1501080 and A1501085 pertained to the safety and tolerability of VFEND among pediatric patients aged 2 to <18 years old and is discussed in **Section 8 Review of Safety** of this review. Efficacy was a secondary endpoint, for both studies, and is discussed in greater detail below in **Section 7.1.2 Secondary Endpoints**.

For a discussion of efficacy in the previously conducted registrational trials, from which 52 of the pediatric subjects included in this safety review were originally enrolled, the reader is referred to the original VFEND NDA review.

#### 7.1.2 Secondary Endpoints

Of the three secondary efficacy endpoints proposed by the Applicant (a. rate of global response at 6 weeks and EOT, b. all-cause and attributable mortality at 6 weeks and EOT, and c. time to death), only the rate of global response at 6 weeks and EOT will be briefly discussed in this

review. For a greater discussion of efficacy endpoints, the reader is referred to the statistical review authored by Dr. Cheryl Dixon, the biostatistical reviewer.

**Study A1501080**

Overall, 14 (45.2%) of the 31 subjects who enrolled in Study A1501080 were included in the modified intent-to-treat (MITT) population: 5 subjects in the age 2 to <12 years old age cohort and 9 subjects in the 12 to <18 years old age cohort. Seventeen subjects (54.8%) were excluded from the MITT population. Among the reasons cited by the Applicant for subject exclusion from the MITT, failure to demonstrate a proven/probable case of IA (16 of 17 subjects; 88.9%) was the most commonly cited reason. Table 5 summarizes global response rates to treatment at Week 6 and at the EOT visit for the 14 IA patients who comprised the MITT population.

**Table 5: Study A1501080 Global Response[a] to Treatment at Week 6 and EOT, Modified Intent-to-Treat (MITT)[b] Population, N=14**

| Parameter | Global Response at Week 6 | | | Global Response at EOT | | |
|---|---|---|---|---|---|---|
| | Voriconazole N=14 | | | Voriconazole N=14 | | |
| | Ages 2-<12 years N=5 | Ages 12-<18 years N=9 | Overall N=14 | Ages 2-<12 years N=5 | Ages 12-<18 years N=9 | Overall N=14 |
| **Global Response** | | | | | | |
| Number of successes, n (%) | 2 (40.0%) | 7 (77.8%) | **9 (64.3%)** | 2 (40.0%) | 7 (77.8%) | **9 (64.3%)** |
| Number of failures, n (%) | 3 (60.0%) | 2 (22.2%) | **5 (35.7%)** | 3 (60.0%) | 2 (22.2%) | **5 (35.7%)** |
| **Successes** | | | | | | |
| | **N=2** | **N=7** | **N=9** | **N=2** | **N=7** | **N=9** |
| Complete Response, n (%) | 1 (50.0%) | 5 (71.4%) | **7 (50.0%)** | 2 (40.0%) | 5 (71.4%) | **7 (50.0%)** |
| Partial Response, n (%) | 1 (50.0%) | 2 (28.6%) | **2 (14.3%)** | 0 (0.0%) | 2 (28.6%) | **2 (14.3%)** |
| **Failures** | | | | | | |
| | **N=3** | **N=2** | **N=5** | **N=3** | **N=2** | **N=5** |
| Failed Response, n (%) | 0 (0.0%) | 0 (0.0%) | **0 (0.0%)** | 1 (20.0%) | 0 (0.0%) | **1 (7.1%)** |
| Stable Responses, n (%) | 0 (0.0%) | 0 (0.0%) | **0 (0.0%)** | 0 (0.0%) | 0 (0.0%) | **0 (0.0%)** |
| Indeterminate Responses, n (%) | 0 (0.0%) | 1 (50.0%) | **1 (7.1%)** | 0 (0.0%) | 1 (50.0%) | **1 (7.1%)** |
| Missing, n (%) | 2 (100.0%) | 1 (50.0%) | **3 (21.4%)** | 2 (40.0%) | 1 (50.0%) | **3 (21.4%)** |
| **Success rate (%)** | **2 (40.0%)** | **7 (77.8%)** | **9 (64.3%)** | **2 (40.0%)** | **7 (77.8%)** | **9 (64.3%)** |

**Source: ADSL and ADICR (AdAM) data sets** and confirmed against Tables 17 and 18 of Trial A1501080 Clinical Study Report (pages 75 and 76).

[a] Global response rate was defined as the number of subjects with a successful response (complete or partial) as a percentage of all subjects (including subjects with an indeterminate or missing response) at 6 weeks and end-of-treatment (EOT) in the MITT population.

[b]The Modified Intent-to-Treat (MITT) population was defined as all subjects who received at least 1 dose of study drug and who were diagnosed with proven or probable aspergillosis as defined by the modified EORTC/MSG criteria. Patients with a category of "indeterminate" were treated as "failure." Patients with missing data were considered treatment "failures" as well.

**Medical Reviewer's Comments:**

*Small numbers of enrolled patients (31 subjects) in Study A1501080 were further compounded by even fewer numbers of patients comprising the MITT population (14 patients). Less than 40% of patients ages 2 to <12 years old demonstrated an overall global response at EOT; however, only 5 patients were available for the efficacy analysis. In contrast, among the nine patients in the 12 to <18 years old age group, the response rate at EOT was higher at 77.8%. Such limited numbers make it challenging to draw any meaningful conclusions from the presented data in this immunocompromised and critically ill population of patients with underlying malignancy (in most cases) and an aggressive fungal infection.*

*In spite of the aforementioned limitations of this study, overall global response rates in this pediatric cohort with IA were comparable to those in adults, 64% vs 53% (76/144) (Trial 307/602) and 52% (26/50) (Trial 304). Patients in the registrational trials were also seriously ill, with most patients having underlying hematologic malignancies including bone marrow transplantation. In Trial 307/602 a satisfactory response was assessed at 12 weeks and included either a complete or partial resolution of all attributable symptoms, signs, radiographic/bronchoscopic abnormalities present at baseline. The imbalance in success rates between pediatric and adult studies can, in part, be explained by smaller numbers of pediatric patients.*

**Study A1501085**

Similar to Study A1501080, Study A1501085 was not designed to demonstrate efficacy among pediatric patients who, in this case, were diagnosed with either ICC or EC. As with IA, efficacy was to be extrapolated from adults. As mentioned above in **Section 6.2 Study A1501085**, the outcome assessment was based on the "global response at the EOT," in the MITT population. The global response rate was assessed as a patient either being a treatment "success" or a treatment "failure."

The MITT population was comprised of 17 (77%) of the 22 subjects enrolled in Study A1501085: 10 subjects with EC and 7 subjects with ICC (all aged 2 to <12 years old). The five subjects excluded from the MITT analysis population were excluded due to a "lack of microbiologic confirmation of a *Candida* infection." Table 6 below provides a tabular summary of global response rates, subdivided by EC and ICC and by age cohort (patients 2 to <12 and 12 to <18).

**Table 6: Study A1501085 Global Response to Treatment in Subjects with ICC and EC, Modified Intent-to-Treat (MITT) Population, N=17**

| | **EC N=10** | | | **ICC N=7** | | |
|---|---|---|---|---|---|---|
| **Global Response** | **Ages 2-<12** | **Ages 12-<18** | **Overall** | **Ages 2-<12** | **Ages 12-<18** | **Overall** |
| | N=2 | N=8 | N=10 | N=7 | N=0 | N=7 |
| Number of successes, n (%) | 2 (100.0%) | 5 (62.5%) | 7 (70.0%) | 6 (85.7%) | 0 (0.0%) | 6 (85.7%) |
| Number of failures, n (%) | 0 (0.0%) | 3 (37.5%) | 3 (30.0%) | 1 (14.3%) | 0 (0.0%) | 1 (14.3%) |

| **Failures** | | | | | | |
|---|---|---|---|---|---|---|
| Failed Response, n (%) | 0 (0.0%) | 1 (33.3%) | 1 (10.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Indeterminate Response, n (%) | 0 (0.0%) | 2 (66.7%) | 2 (20.0%) | 1 (100.0%) | 0 (0.0%) | 1 (100.0%) |
| Missing, n (%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| **Success rate (%)** | **2 (100.0%)** | **5 (62.5%)** | **7 (70.0%)** | **6 (85.7%)** | **Not applicable** | **6 (85.7%)** |

**Source: ADSL and ADICR (AdAM) data sets.** Table created by clinical reviewer and confirmed against Table 21 of **Trial A1501085** Clinical Study Report (page 69).
**Note:** Subjects with a category of "indeterminate" were treated as "failure." Patients with missing data were to be considered treatment "failures" as well. These efficacy analyses were assessed in the Modified Intent-to-Treat (MITT) population, which was defined as all subjects who received at least 1 dose of study drug and who had microbiologically confirmed ICC or EC.

**Medical Reviewer's Comments:**
*Few patients comprised the MITT analysis population in Study A1501085. Overall global success rates were 70% and 85.7% for EC and ICC, respectively; however, this was based on 7 of 10 patients with EC and 6 of 7 patients with ICC, all of whom were 2 to <12 years old. In comparison, in the original registrational trials comparing VFEND (n=283) against amphotericin B (followed by fluconazole) (n=139) in non-neutropenic patients with candidemia and other deep tissue Candida infections, the primary efficacy analysis endpoint was determined by an independent Data Review Committee's (DRC) assessment of treatment success at 12 weeks post-therapy. In this trial (Trial 150-608, an open-label, comparative, multicenter trial study), VFEND response rates were 41%, similar to the comparator drug. In all, the higher observed success rates in the pediatric population were most likely attributable to the small numbers of pediatric subjects comprising the MITT in this non-powered trial. No definitive efficacy conclusions in pediatric patients can be made based on the presented data.*

The efficacy of oral VFEND in adults with EC was determined from Trial 150-305, a double blind, comparative trial evaluating VFEND (n=200) against fluconazole (n=191) in immunocompromised patients with endoscopically-proven EC. The outcome was assessed, in the intent-to-treat (ITT) population, by repeat endoscopy at the end of treatment (EOT), with a successful response defined as symptomatic cure or improvement at EOT when compared to baseline. Overall, efficacy of subjects in the VFEND arm (175/200) was comparable to its comparator (87.5%. vs 89.5%). VFEND efficacy in the treatment of patients with EC in the dedicated pediatric study, Study A1501085, compared with Trial 150-305 in adults is similarly comparable (85.7% vs 87.5%).

For a discussion of additional efficacy endpoints for this study, please refer to Dr. Cheryl Dixon's biostatistics review.

### 7.1.4 Dose and Dose Response

Due to limited PK sampling, it was difficult to evaluate any discernible dose response patterns with VFEND dosing, particularly with the correlation of VFEND toxicity with trough concentrations.

### 7.3 Integrated Assessment of Efficacy

VFEND efficacy in pediatric patients aged 2 to <18 years old was extrapolated from adults. Moreover, efficacy was a secondary endpoint for both Studies A1501080 and A1501085. Neither study was designed to draw inferential conclusions on overall efficacy in pediatric patients**.** Small patient sizes were observed in the IA, ICC and EC MITT analysis populations, with 14, 10 and 7 patients included in outcome assessments, respectively. Such limited numbers made it difficult to draw any definitive conclusions on VFEND efficacy in pediatric patients with these fungal infections. In spite of limited numbers and a non-comparative study design, it was noted that pediatric global response rates were higher than rates observed in adults with IA (64% *vs* 53% and 52% in two adult trials) and ICC (70.0 *vs* 41%). Efficacy rates among pediatric patients with EC were comparable to those in adults (85.7% *vs* 87.5%). This difference may have resulted from smaller numbers of pediatric patients since adult and pediatric patients enrolled in these studies were equally ill.

# 8 Review of Safety

## 8.1 Safety Review Approach

The VFEND pediatric safety database was comprised of a total of 105 pediatric patients: 53 patients ages 2 to <18 years old, who enrolled in the Applicant's two Phase 3 pediatric open-label, non-comparative trials (Studies A1501080 and A1501085) and 52 pediatric patients aged 12 to <18 years old (including a single 11 year old patient) who were enrolled in the initial registrational trials.

By definition, the safety analysis population consisted of all enrolled subjects who received at least one dose of study drug. Case report forms (where applicable) and the ADAE data sets for each trial were reviewed. This safety review separately describes all deaths, SAEs, TEAEs resulting in treatment withdrawal and/or treatment reductions for each of the Phase 3 studies as well as the combined pediatric legacy data (where applicable). However, the Applicant did not supply full details for legacy patients; therefore, additional clarifications on legacy data were obtained by the reviewer by issuing informational requests (IR) to the Applicant. Treatment emergent adverse events (TEAEs) are discussed for both Phase 3 studies. Patients in both Phase 3 studies were pooled and grouped according to two age cohorts (ages 2 to <12 and 12 to <18). Safety data from all 105 patients was pooled and comprised the ISS population. TEAEs occurring at higher rates than adults, as well as all adverse events of special interest (AESI) were assessed. The Applicant identified eight AESIs, for example hepatic toxicity, visual events, phototoxicity, that are frequently associated with VFEND administration. For evaluation of all PTs pertinent to an identified AESI, this reviewer generated customized MedDRA queries (CMQ) based on select, clinically relevant PT terms as well as PT terms included in clinically

related standardized MedDRA queries (SMQs). In addition, all TEAEs included in the Applicant's incidence table of adult and pediatric TEAEs, irrespective of causality, were reviewed and compared.

Available hepatic and renal specific clinical laboratory data (i.e. ALT, AST, total bilirubin, alkaline phosphatase and creatinine) were analyzed according to DAIDs or NCI toxicity grading scales for the Phase 3 trials only, as data for these studies and not the legacy trials were made available for the reviewer to evaluate. **Section 8.4.6 Laboratory Findings** discusses laboratory analyses in greater detail. Likewise, vital sign and ECG data for the Phase 3 studies alone were evaluated and are discussed briefly in **Sections 8.4.7 Vital Signs** and **8.4.8 Electrocardiograms**, respectively. Such data were unavailable for the 52 subjects contained in the legacy trials, as they would have been reviewed in the original NDA application.

***Medical Reviewer's Comments:***
*Noting that there were no overall safety differences between age cohorts or disease indications, this reviewer pooled data from the Phase 3 studies with the legacy data to have an expanded safety database. All pediatric safety data were compared against the adult VFEND safety profile in the label and in the registrational trials. Several features of the Phase 3 study designs made ascertainment of causality for commonly identified TEAEs particularly challenging, since these studies were open-label, non-comparative studies with limited numbers of critically ill, immunocompromised patients on multiple medications and with disease conditions that could have equally contributed to the observed events. The purpose of this safety review was to confirm whether or not the proposed pediatric dosing resulted in increased (or worsened) safety signals than safety findings observed in adults.*

## 8.2 Review of the Safety Database

### 8.2.1 Overall Exposure

Table 7 below summarizes the numbers of pediatric subjects comprising the Applicant's Phase 3 and legacy trials.

**Table 7 Pediatric Trials, Safety Population, Size and Denominators**

| Trial Number | Voriconazole Pediatric Subjects (n) | Comments |
|---|---|---|
| **Phase 3 Studies** | | |
| A1501080 | 31 | Subject (b) (6) received study drug but did not report an AE (17 year old female) |
| A1501085 | 22 | Subject (b) (6) received study drug but did not report an AE (16 year old male)<br>• 11 patients with EC<br>• 11 patients with ICC |
| **Legacy Trials** | | |
| **Study 303** | 2 | n/a |
| **Study 304** | 4 | Subject (b) (6) eceived study drug but did not report an AE (17 year old female). |
| **Study 305** | 0 | No pediatric data contained in this study |
| **Study 3076** | 3 | Hybrid of Studies 307 and 602 |

| Trial Number | Voriconazole Pediatric Subjects (n) | Comments |
|---|---|---|
| **Study 309** | 12 | n/a |
| **Study 603** | 13 | n/a |
| **Study 604** | 13 | n/a |
| **Study 608** | 5 | n/a |
| **Subject Totals:** | **105** | |

### Study A1501080 Treatment Exposure and Duration

**Table 8** summarizes duration of IV, PO, and combined IV and PO exposures, by age cohort, for IA patients.

**Table 8: Study A1501080 Intravenous (IV) and Oral (PO) Treatment Exposures, Pediatric Subjects with IA Ages 2 to <18 years old**

| Treatment Duration (days) | 2 to <12 years old | 12 to <18 years old | Overall |
|---|---|---|---|
| | IA | IA | |
| **Duration of IV treatment** | | | |
| | **n=11** | **n=20** | **n=31** |
| Mean (SD) | 13.6 (10.3) | 10.2 (4.7) | 11.4 (7.2) |
| Median | 8.0 | 8.5 | 8.0 |
| Range | 3-33 | 5-22 | 3-33 |
| **Duration of PO treatment** | | | |
| | **n=8** | **n=14** | **n=22** |
| Mean (SD) | 45 (34.3) | 52.6 (24.7) | 49.9 (28.0) |
| Median | 55 | 59.5 | 59.5 |
| Range | 2-78 | 8-81 | 2-81 |
| **Duration of IV + PO treatment** | | | |
| | **n=8** | **n=14** | **n=22** |
| Mean (SD) | 59.4 (27.7) | 62.4 (25.2) | 61.3 (25.5) |
| Median | 68.5 | 68.5 | 68.5 |
| Range | 18-85 | 19-90 | 18-90 |

**Source:** Trial A1501080. ADSL (AdAM) data set. Table was created by the Clinical Reviewer using JMP software.

**Medical Reviewer's Comments:**

*The median duration of VFEND exposure for patients enrolled in Study A1501080, across both age cohorts, was 8.0 and 59.5 days, respectively, for IV and oral therapy. Overall treatment duration ranged from 2 to 81 days. In Study A1501085, the median duration of IV therapy was comparable to that of Study A1501080 with all 22 subjects in the safety population receiving a median of 7 days of IV therapy, as proposed in the original study design. However, when compared with Study A1501080, the duration of oral therapy received among the 13 patients (59%; 13/22) in Study A1501085 administered oral VFEND, irrespective of age and infection type, was considerably shorter, with these 13 patients receiving a median of 9.0 days (range: 2-37 days) of oral therapy. Not all patients receiving IV therapy in Study A1501085 transitioned onto oral therapy (9/22; 41%), 5 and 4 patients with ICC and EC, respectively, only received IV*

*VFEND*. **Table 8** and **Table 9** *provide a summary overview of the duration of study treatment exposure for patients in each individual Phase 3 pediatric study.*

**Study A1501085 Treatment Exposure and Duration**

**Table 9** below provides an overview of treatment exposure (in days) of patients in Study A1501085.

**Table 9: Study A1501085 Intravenous (IV) and Oral (PO) Treatment Exposures, Pediatric Subjects with EC and ICC, Ages 2 to <18 years old**

| Treatment Duration (days) | 2 to <12 years old | | 12 to <18 years old | | Overall | |
|---|---|---|---|---|---|---|
| | EC | ICC | EC | ICC | EC | ICC |
| **Duration of IV treatment** | | | | | | |
| | **n=3** | **n=11** | **n=8** | **n=0** | **n=11** | **n=11** |
| Mean | 6 (0) | 10.9 (7.7) | 9.5 (4.3) | n/a | 8.6 (4.0) | 10.9 (7.7) |
| Median | 6.0 | 8.0 | 8.0 | n/a | 6.0 | 8.0 |
| Range | 6 | 2-24 | 5-17 | n/a | 5-17 | 2-24 |
| **Duration of PO treatment** | | | | | | |
| | **n=2** | **n=6** | **n=5** | **n=0** | **n=7** | **n=6** |
| Mean | 13 (5.7) | 19.3 (13.8) | 4.8 (2.4) | n/a | 7.1 (5.0) | 19.3 (13.8) |
| Median | 13 | 15.5 | 5 | n/a | 6 | 15.5 |
| Range | 9-17 | 3-37 | 2-8 | n/a | 2-17 | 3-37 |
| **Duration of IV + PO treatment** | | | | | | |
| | **n=2** | **n=6** | **n=5** | **n=0** | **n=7** | **n=6** |
| Mean | 18.5 (6.4) | 31.2 (14.3) | 12.4 (2.6) | n/a | 14.1 (4.5) | 31.2 (14.3) |
| Median | 18.5 | 38 | 14 | n/a | 14 | 38 |
| Range | 14-23 | 8-42 | 8-14 | n/a | 8-23 | 8-42 |

**Source:** Trial A1501085. ADSL (AdAM) Data Set. Table was created by the Clinical Reviewer using JMP software.

**Medical Reviewer's Comments:**
*Overall treatment exposures (in days) were somewhat higher, by approximately 2 weeks, in patients with ICC versus those with EC. This is not unexpected given the more severe nature of ICC when compared with EC.*

## 8.2.2 Relevant Characteristics of the Safety Population

**Table 10** summarizes the demographic characteristics of patients in the ISS (53 subjects in the Phase 3 studies and 52 patients from the adult therapeutic trials).

**Table 10: Demographic Characteristics, Safety Analysis Set**

| Parameter | Trial A1501080 | Trial A1501085 | Pooled Legacy | All Trials |
|---|---|---|---|---|
| | Voriconazole N=31 | Voriconazole N=22 | Voriconazole N=52 | Overall |

| | **Ages 2-<12 years n=11 (35.5%)** | **Ages 12-<18 years n=20 (64.5%)** | **Total** | **Ages 2-<12 years n=14 (63.6%)** | **Ages 12-<18 years n=8 (36.4%)** | **Total** | | |
|---|---|---|---|---|---|---|---|---|
| **Ages (years)** | | | | | | | | |
| Mean (SD) | 7.9 (2.3) | 14.1 (1.7) | **11 (3.5)** | 6.8 (2.9) | 14.4 (1.7) | **9.6 (4.5)** | 15.2 (1.7) | 13.0 (3.7) |
| Median (min, max) | 8 (3, 11) | 14 (12, 17) | **12 (3, 17)** | 6.5 (2, 11) | 14.5 (12, 16) | **9.5 (2, 16)** | 16.0 (11.0, 17.0) | 14.0 (2, 17) |
| **Sex, n (%)** | | | | | | | | |
| Female | 4 (36.5%) | 11 (55.0%) | **15 (48.4%)** | 8 (57.1%) | 6 (75.0%) | **14 (63.6%)** | 21 (42.0%) | 51 (48.6%) |
| Male | 7 (63.6%) | 9 (45.0%) | **16 (51.6%)** | 6 (42.9%) | 2 (25.0%) | **8 (36.4%)** | 29 (58.0%) | 54 (51.4%) |
| **Race, n (%)** | | | | | | | | |
| Asian | 8 (72.7%) | 10 (50.0%) | **18 (58.1%)** | 5 (35.7%) | 1 (12.5%) | **6 (27.3%)** | 5 (10.0%) | 30 (28.6%) |
| White | 3 (27.3%) | 8 (40.0%) | **11 (35.1%)** | 5 (35.7%) | 5 (62.5%) | **10 (45.5%)** | 35 (70.0%) | 57 (54.3%) |
| Other/Black or African American | 0 (0.0%) | 2 (10.0%) | **2 (6.5%)** | 4 (28.6%) | 2 (25.0%) | **6 (27.3%)** | 10 (20%) | 18 (17.1%) |
| **Weight, (kg)** | | | | | | | | |
| Mean (SD) | 26.7 (9.7) | 50.1 (15.3) | **41.8 (17.5)** | 23.9 (11.1) | 54.6 (19.7) | **35.1 (20.8)** | 53.2 (16.1) | 45.9 (18.9) |
| Median (min, max) | 25.6 (15.6,42.0) | 47.2 (31.5,94.0) | **41.5 (15.6, 94.0)** | 22.7 (11, 50) | 53.4 (25.0, 85.0) | **27.4 (11, 85)** | 51.5 (26.0, 108.0) | 45 (11, 108) |
| # subjects aged 12 to 14 years <50 kg | N/A | 8 | **8** | N/A | 2 | **2** | 13 | 24 |
| Median (min, max) | N/A | 35.7 (31.5, 47.0) | **35.7 (31.5, 47.0)** | N/A | 34.5 (25.0, 44.0) | **34.5 (25.0, 44.0)** | 39.5 (26.0, 48.0) | 39.0 (25.0, 48.0) |
| # subjects aged 12 to 14 years ≥ 50 kg | N/A | 4 | **4** | N/A | 2 | **2** | 4 | 10 |
| Median (min, max) | N/A | 54.5 (53,71) | **54.5 (53,71)** | N/A | 61.8 (59.8, 63.7) | **61.8 (59.8, 63.7)** | 56.0 (50.0, 57.5) | 56.0 (50.0, 71.0) |
| **Country, n (%)** | | | | | | | | |
| USA | 3 (27.3%) | 4 (20.0%) | **7 (22.6%)** | 0 (0.0%) | 0 (0.0%) | **0 (0.0%)** | 24 (46.2%) | 31 (29.5%) |
| Non-US site | 8 (72.7%) | 16 (80.0%) | **24 (77.4%)** | 14 (100.0%) | 8 (10.00%) | **22 (100.0%)** | 28 (53.8%) | 74 (70.5%) |

**Source:** Advers data set.

**Medical Reviewer's Comments:** *Demographic features of both Phase 3 and the legacy studies shows that most enrolled patients were male (51.4%), White (54.3%) followed by Asian (28.6%), and from outside of the United States (70.5%).*

### 8.2.3 Adequacy of the Safety Database

Challenges encountered in the recruitment of pediatric patients resulted in the Applicant's early termination of both Phase 3 studies prior to achieving their originally targeted subject enrollment populations. This restricted the numbers of patients available for safety and PK analyses. Even

with the Applicant's inclusion of the 52 pediatric patients enrolled in their original registrational trials, resulting in a total of 105 pediatric patients in the ISS, the overall safety database was limited, but sufficient, for the characterization of VFEND safety.

***Medical Reviewer's Comments:***
*While the safety profile in pediatric patients was fairly comparable to that in adults, the smaller numbers of pediatric patients contributed to higher rates of safety events among pediatric patients. Limited numbers of patients in the ISS, in addition to the open-label, non-comparative design of the Phase 3 studies made ascertainment of causality between observed events and VFEND rather challenging. Limited PK information, particularly for trough concentrations made it more difficult to correlate AE findings (i.e. hepatic elevations, visual disturbances) with VFEND dosing.*

## 8.3 Adequacy of Applicant's Clinical Safety Assessments

### 8.3.1 Issues Regarding Data Integrity and Submission Quality

Notable data integrity and submission issues for this Application included:

- **Missing Data Sets:** The Applicant initially failed to submit an Integrated Summary of Safety data set including adverse events for all subjects with AEs in Studies A1501080 and A1501085 as well as the pediatric legacy data from the original NDA trials. This was addressed to the Applicant in a subsequent information request (IR).

- **Data Sets Containing Incomplete Data:** On more than one occasion, the Applicant presented data sets that had missing subject information for several coded variables. This required the reviewer to send IRs for missing data.

- **Inconsistent Coding of Data:** In addition, to missing information found in the data sets, the reviewer also noted at times that information was coded inconsistently, with the use of both upper and lower caps for data coding (for the same variable), double entries for the same event etc.

### 8.3.2 Categorization of Adverse Events

Adverse event (AE) monitoring and documentation began on Study Day 1 (baseline) and continued through the one month follow-up visit. AEs were reported for all subjects included in the Safety Population, defined as all subjects receiving *at least* one dose of study drug. All Serious Adverse Events (SAEs) adhered to the standard regulatory definition for SAEs: untoward medical occurrence resulting in death, an inpatient hospitalization or prolongation of an existing hospitalization, a congenital anomaly/birth defect, or a life-threatening event. The Applicant, additionally, reported any "significant hazard to the subject population, such as a lack of efficacy of the investigational product," as an SAE.

Study investigators provided their assessments of AE seriousness (non-serious versus serious), severity, relationship to study drug, action taken, and outcome assessment for each reported AE. AEs, for both Phase 3 studies, were recorded and coded according to Medical Dictionary for

Regulatory Activities version 16.0 (MedDRA v 16.0). However, MedDRA v 17.0 was used for the ISS data set. For details of AE categorization in the original NDA registrational trials, please refer to the original 2002 NDA Clinical review.

***Medical Reviewer's Comments***
*AEs were assessed within the appropriate time frames, at Study Day 1 and 1 month post-therapy. The Applicant adhered to standardly recognized regulatory definitions and practices for the documentation and reporting of SAEs. Standard seriousness, severity, causality, action taken, and outcome assessments were conducted.*

### 8.3.3 Routine Clinical Tests

**Section 5 Warnings and Precautions** of the present VFEND USPI cautions against hepatic toxicity and visual disturbances which have been observed in the adult population. To address these concerns, the Applicant conducted the following routine safety assessments:

- **Laboratory evaluation:** The following clinical laboratories were collected at the Screening, Weeks 1, 2, 4, 6, 12 (or EOT), and 1-month follow-up (post-therapy) visits and at Screening , Day 1, every 7 days until the EOT (or Day 42) for Trials A1501080 and A1501085, respectively: hematology (complete blood count with differential), chemistries (including sodium, potassium, calcium, magnesium, chlorine, glucose), renal function, and liver function tests (including aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [Tbili]) and pancreatic function (amylase and lipase).
    - **Hepatic Events:**
        - Trial A1501080:

      Abnormal AST, ALT, and Tbili values, in the absence of other causes of liver injury were further evaluated for drug-induced liver injury (or Hy's Law cases) if the subject met certain prespecified thresholds relative to their baseline AST, ALT and total bilirubin values. Patients meeting Hy's law criteria underwent detailed histories, testing for acute hepatitis A, B, and C and liver imaging (when warranted).

- **Visual Safety Monitoring:** Each Phase 3 study conducted visual safety monitoring: Study A1501080 conducted visual assessments at Baseline (Day 1), Weeks 1, 2, 4, and 6 and EOT (or Week 12), and 1-month post-treatment and for Study A1501085 visual assessments were conducted at Screening, every 7 days, at EOT, and at the 1-month post-therapy visit. The following visual safety assessments were performed:
    - **Visual questionnaire** for children 3 years of age and older (as appropriate)
    - **Color vision testing** with the Hardy-Rand-Rittler (HRR) color vision testing for children 3 years of age and older (as appropriate)
    - **Visual acuity testing, best-corrected distance** (at ≥ 4 meters) with the Early Treatment Diabetic Retinopathy Study (EDTRS). However, for children too

young to undergo visual acuity testing the investigator assessed "whether fixation was central, steady, and maintained in each eye."

- **Dilated Fundoscopy** was conducted by an ophthalmologist for all subjects reporting treatment-emergent visual AEs for Study A1501080. Both normal and abnormal dilated funduscopic reports were documented. In Study A1501085, dilated funduscopic exams were conducted at Screening, at EOT, and at 1-month post-therapy for *all* subjects and additionally for subjects experiencing visual AEs.
- **Additional Visual Testing** In Study A1501085, additional testing was performed at the Screening and EOT visits. This included visual field testing by confrontation and automated visual field testing in children 5 and older.

- **Electrocardiogram (ECG) Assessments:** Azoles, including VFEND (voriconazole), are associated with QT prolongation. Therefore, ECGs were collected at pre-specified time points for each Phase 3 study, including at Screening, EOT, and 1-month post-therapy for Study A1501080 and at Screening, EOT (or Day 42), for Study A1501085.

***Medical Reviewer's Comments***
*The Applicant's safety assessments for such VFEND (voriconazole) (and/or azole) associated adverse reactions as hepatic and visual safety findings was acceptable, particularly with regards to timing of assessments, thoroughness of evaluations, and follow-up measures pursued in instances when a subject sustained either a hepatic and/or visual adverse event (or SAE). While it is noted that dermatologic (i.e. phototoxicity) and psychiatric AEs (i.e. hallucinations) are associated with VFEND in adults, no formal dermatologic and psychiatric assessments were conducted in the pediatric studies. The Applicant considered phototoxicity and suicidal related events as AEs of special interest (AESI) and conducted standardized MedDRA Queries (SMQ) in their evaluation of safety among this pediatric cohort (aged < 18 years).*

*DAIP consulted, Dr. Wiley Chambers, of the Division of Transplant and Ophthalmology Products (DTOP) to evaluate all reported visual events. Upon review of the visual monitoring data which were submitted by the Applicant for both Phase 3 studies, Dr. Wiley Chambers noted that while attempts were made to conduct ocular examinations on pediatric patients treated with VFEND, there was no new information generated from the visual assessments performed in this cohort of pediatric patients; however, the data were limited. No significant findings were observed on fundoscopic exams, color vision assessments, or in visual field testing (in Study A1501085). Although a few patients reported declines in visual acuity, the majority of patients did not. While visual disturbances were observed, with the most common being blurred vision and photophobia, based on the presented data, Dr. Chambers did not believe that any additional clinical trials evaluating VFEND's impact on pediatric patients were warranted. It was Dr. Chambers opinion, as well as this reviewer's opinion upon review of his consult, that there were no additional ocular issues observed in this pediatric population that were not already present in adults. All observed visual disturbances captured in the Phase 3 pediatric studies are already contained in current VFEND labeling.*

# 8.4 Safety Results

## 8.4.1 Deaths

### Overview

In all, there were a total of 21 combined pediatric deaths: 6 deaths in the Phase 3 pediatric studies and 15 deaths in patients ages 12 to <18 in the original registrational trials. All deaths from the Phase 3 studies are summarized in **Table 11** below. In a response to an IR, the Applicant provided a listing of all pediatric deaths from their legacy trials.

### Study A1501080

A total of 5 patient deaths occurred in Study A1501080: 3 deaths among patients ages 2 to <`12 years old and 2 among patients ages 12 to <18 years old. Descriptions of these five deaths are summarized in **Table 11** below. None of these deaths were assessed by either the Applicant or this reviewer as being related to VFEND. In most instances, however, patients' deaths were a consequence of the underlying medical condition or related complications.

### Study A1501085

There were no subject deaths during the safety reporting period for Study A1501085. However, a single subject, Subject (b) (6) died after the safety reporting period. The decedent was a 3-year old male patient with anaplastic medulloblastoma who reportedly died, from complications of his underlying illness, 490 days after the first dose of VFEND.

**Table 11 Summary of Pediatric Patient Deaths in Phase 3 Studies**

| Unique Subject Identifier | Age/Sex | Relationship of Death to Voriconazole Therapy | System Organ Class | Cause of Death by Dictionary Derived Term | Study /Post treatment Day on which Death occurred | Duration of Study Treatment | Description of Death |
|---|---|---|---|---|---|---|---|
| **Study 1501080** | | | | | | | |
| (b) (6) | 8/F | Unrelated | Cardiac Disorders | Cardiac Arrest | (18) | 18 | **Subject** (b) (6) aneurysm ruptured and cardiac arrest): A 21.0-kg 8 year old Thai female with a primary diagnosis of aspergillosis and a prior medical history of acute lymphocytic leukemia and mycotic aneurysm (diagnosed in 2011). She received IV voriconazole from Study Day 1 to Study Day 7, and oral voriconazole from Study Day 8 through Study Day 18, when she sustained a ruptured aneurysm (presenting as pulmonary hemorrhage and hemoptysis). She subsequently sustained a cardiac arrest. She underwent an unsuccessful cardiopulmonary resuscitation and died that same day (Study Day 18). The study investigator deemed that clinical response to voriconazole therapy was indeterminate.<br><br>***Medical Reviewer's Comments:*** *While this reviewer agrees that this case of ruptured mycotic aneurysm resulting in death was unrelated to voriconazole therapy, it appears as though her underlying infection may have been refractory to voriconazole therapy. It is unclear when mycotic aneurysm emerged in relation to start of voriconazole therapy.* |
| (b) (6) | 11/F | Unrelated | Infections and Infestation | Septic Shock | (30) | 30 | **Subject** (b) (6) (lower GI hemorrhage; septic shock; aspergillosis): A 37-kg, 11 year old Thai female with a primary diagnosis of aspergillosis enrolled in Study A1501080 from Study Day 1 through Study Day 30 (final day of VFEND therapy). Relevant medical history included a history of lower gastrointestinal (GI) hemorrhage; aplastic anemia; bronchopulmonary aspergillosis and colon neoplasm. This patient was switched from VFEND IV to VFEND oral suspension on Study Day 29 in the setting of acute kidney failure. Her treatment course was complicated by progression of aspergillosis on Study Day 21 for which she underwent a right lower lobectomy. On Study Day 28, patient developed septic shock from a suspected right thoracotomy surgical wound infection with probable growth of meropenem-resistant *Acinetobacter baumanii*. She died from cardiac |

| Unique Subject Identifier | Age/Sex | Relationship of Death to Voriconazole Therapy | System Organ Class | Cause of Death by Dictionary Derived Term | Study /Post treatment Day on which Death occurred | Duration of Study Treatment | Description of Death |
|---|---|---|---|---|---|---|---|
| | | | | | | | arrest on Study Day 30. Investigator posited cause of death was septic shock and was unrelated to VFEND therapy.<br><br>***Medical Reviewer's Comments:*** *This reviewer agrees that while the patient's underlying IA infection was refractory to VFEND, VFEND therapy was not responsible for her death from septic shock, which appears to have been the result of bacterial superinfection of a surgical wound site in this medically complicated patient. Episodes of GI bleeding were also considered by this reviewer to be unrelated to study treatment.* |
| (b) (6) | 11/F | Unrelated | Infections and Infestation | Septic Shock | (38) | 37 | **Subject** (b) (6) (renal failure, acute [SAE]; neutropenia (SAE]; septic shock [SAE]; hypoglycemia [SAE]): A 41.5-g 11 year old Thai female with a primary diagnosis of aspergillosis was enrolled in Study A1501080 from Study Day 1 through Study Day 37. This patient had a complicated history significant for cerebral aspergillosis; brain abscess; systemic lupus erythematosus (SLE) complicated by lupus nephritis. She received her first dose of IV VFEND on Study Day 1 and her final dose on Study Day 37. She was switched from IV to oral VFEND on Study Day 32. Her treatment course was complicated by onset of acute renal failure (Study Day 34) requiring hemodialysis (HD) (Study Day 34). Renal failure was believed to be related to VFEND treatment in addition to superimposed and newly diagnosed class 4 lupus nephritis for which she was begun on cyclophosphamide. On Study Day 35, patient developed neutropenia (absolute neutrophil count of 0.003 x 109 cells/L) believed to be secondary to active SLE and cyclophosphamide treatment. She subsequently developed septic shock (Study Day 37); respiratory distress requiring mechanical ventilation; hypotension requiring pressors and hypoglycemia all in the setting of septic shock. On Study Day 37, she was again placed on IV VFEND. She eventually sustained and succumbed to a cardiac arrest on Study Day 38. |

| Unique Subject Identifier | Age/Sex | Relationship of Death to Voriconazole Therapy | System Organ Class | Cause of Death by Dictionary Derived Term | Study /Post treatment Day on which Death occurred | Duration of Study Treatment | Description of Death |
|---|---|---|---|---|---|---|---|
| | | | | | | | ***Medical Reviewer's Comments:*** *The above-described case narrative of a critically ill 11 year old girl who died from septic shock in the setting of underlying IA infection refractory to VFEND therapy and further aggravated by neutropenia (unrelated to VFEND therapy), and acute renal failure (related to VFEND and class 4 lupus nephritis). Death from cardiac arrest was due to progression of underlying disease and multi-organ failure in this setting* (respiratory distress, cardiac failure/hypotension, renal failure etc.). |
| (b) (6) | 13/F | Unrelated | Cardiac Disorders | Congestive Heart Failure | (75) | 75 | **Subject** (b) (6) (febrile neutropenia; upper gastrointestinal hemorrhage; septic shock; renal failure, acute; acute lymphocytic leukemia [ALL]): A 31.5-kg 13 year old Thai female with a primary diagnosis of aspergillosis enrolled in Study A1501080 from Study Day 1 through Study Day 37. Patient had a complicated history significant acute lymphocytic leukemia; bronchopulmonary aspergillosis; febrile neutropenia; and cardiomyopathy. First dose of IV VFEND was received on Study Day 1 and the final dose of VFEND was received on Study Day 75. This patient developed febrile neutropenia and septic shock on Study Day 54. She was admitted to hospital with fever, dyspnea, and productive cough the following on Study Day 55 when she was diagnosed with acute lymphocytic leukemia (ALL) complicated by febrile neutropenia; acute renal failure; septic shock and upper GI hemorrhage. All of which resolved within one to five days. On Study Days 72 and 73, she experienced pneumonia and congestive heart failure, respectively. The patient reportedly died from congestive heart failure and ALL on Study Day 75.<br>***Medical Reviewer's Comments:*** *This reviewer agrees that the cause of death in this subject was unrelated to VFEND therapy but rather due to ALL further complicated by congestive heart failure in this 13 year female with multiple co-morbid conditions.* |
| (b) (6) | 16/M | Unrelated | Respiratory, thoracic and | Pulmonary Edema | (20) | 19 | **Subject** (b) (6) pulmonary edema and septic shock): A 46.7-kg 16 year old Thai male with a primary diagnosis of aspergillosis and a prior |

| Unique Subject Identifier | Age/Sex | Relationship of Death to Voriconazole Therapy | System Organ Class | Cause of Death by Dictionary Derived Term | Study /Post treatment Day on which Death occurred | Duration of Study Treatment | Description of Death |
|---|---|---|---|---|---|---|---|
| | | | Mediastinal Disorders | | | | medical history of acute lymphocytic leukemia (ALL) diagnosed in 2007; anxiety; depressed mood; pancytopenia; and febrile neutropenia. The patient enrolled into Study A1501080 on Study Day 1 and received his first dose of IV VFEND that same day. His final dose of VFEND was on Study Day 19. Patient underwent a bone marrow transplant (BMT) on Study Day 2, and was placed on methotrexate and cyclosporine, as per BMT protocol, after which he had a prolonged course of febrile neutropenia complicated by multiple infectious complications, including sinusitis; and suspected aspergillosis pulmonary infiltrates. IV VFEND was switched to oral VFEND therapy on Study Day 12. On Study Day 18, the patient developed pulmonary edema, respiratory arrest and acute renal failure with a decline in urine output and was admitted into the intensive care unit (ICU). The following day, on Study Day 19, he developed bloody emesis, was intubated, and placed on mechanical ventilation. He was begun on continuous renal replacement therapy, for volume overload, on Study Day 20 but died that same day from pulmonary edema, septic shock (likely form underlying infections) and cardiac arrhythmia.<br><br>***Medical Reviewer's Comments:*** *This narrative describes a fatal case of an unfortunate 16-year old immunocompromised male who was status post BMT for ALL. Acute renal failure most likely also related to administration of nephrotoxic medications, (including VFEND, gentamicin, acyclovir, and cyclosporine), septic shock, and multi-organ failure. Despite multiple complications, patient's death from septic shock appears to be related to progression of IA with superimposed pulmonary hemorrhage (given angioinvasive nature of IA) due to disease most likely refractory to VFEND therapy.* |
| | | Unrelated | Infections and Infestation | Septic Shock | | | |
| **Study 1501085** | | | | | | | |
| (b) (6) | 3/M | Unrelated | | | (490) | - | **Subject** (b) (6) died after safety reporting (the one month follow-up visit). This was a 3-year old male patient with anaplastic medulloblastoma |

| Unique Subject Identifier | Age/Sex | Relationship of Death to Voriconazole Therapy | System Organ Class | Cause of Death by Dictionary Derived Term | Study /Post treatment Day on which Death occurred | Duration of Study Treatment | Description of Death |
|---|---|---|---|---|---|---|---|
| | | | | | | | who reportedly died from complications of underlying illness 490 days after the first does of VFEND. |

**Legacy Trials**

Among the 15 (28.9%; 15/52) reported pediatric deaths in the registrational trials, 7 were due either to IA or related complications; 2 were related to graft versus host disease (GVHD), with one patient death complicated by pneumonia and the other by respiratory failure; 1 each was due to astrocytoma; leukemia; cardiopulmonary arrest; multi-organ failure; multi-organ failure in the setting of BMT rejection. A single patient (Subject (b) (6) reportedly died from fungemia, hepatic failure and viral infection. All deaths, with the exception of the latter, were deemed by this reviewer to be unrelated to VFEND. It is unclear whether Subject (b) (6) (b) (6) eath was due to the underlying illness, progression of her underlying infection, and/or VFEND treatment (which may have acted to exacerbate pre-existing conditions).

***Medical Reviewer's Comments***

*There were a total of 21 deaths among the 105 patients comprising the ISS. Most deaths were related to the underlying disease condition and/or underlying fungal infection. Only a single death was considered potentially attributable to VFEND; however, the details of this patient's (Subject (b) (6) death were not available. Please refer to the original NDA application for details on this event.*

**8.4.2 Serious Adverse Events**

**Overall**

The review team noted that there was a discrepancy in the coding of treatment emergent events between the combined ISS dataset and Study A1501085 individual AdAM adae dataset: three subjects in ISS versus 10 subjects in 1085 adae were flagged as having treatment emergent SAEs. Section 13 Appendix Tables 19 and 20 provide a footnote to indicate which SAE were listed as non-treatment emergent in the ISS data set. The rest of this review displays analyses of treatment emergent adverse events for all 105 pediatric patients as flagged in the ISS dataset.

Overall, 48 (45.7%) out of a total of 105 patients in the ISS population experienced at least one treatment emergent SAE (both fatal and non-fatal). However, 15 patients in Study A1501080 sustained a total of 36 treatment emergent SAEs (30 of which were non-fatal); whereas, a total of 3 patients in Study A1501085 sustained a total of 3 non-fatal, treatment emergent SAEs.

Of these subjects, only a single subject, Subject (b) (6) a 14 year old male with a non-fatal SAE coded to the PT term drug-induced liver injury (a potential Hy's law case) was considered by this reviewer, as well the Applicant, as having a VFEND related SAE. Two other SAEs, which occurred in patients (b) (6) (PT term: renal failure acute) and (b) (6) (b) (6) (PT term: splenic candidiasis), were deemed by either the investigator and/or the Applicant as being related to VFEND treatment. However, this reviewer did not consider these events to be definitely related to VFEND therapy. Please also refer to **Section 13 Appendix** for a tabular summary all non-fatal SAEs.

**Study A1501080**

In all, 21 (67.7%) of the 31 subjects comprising the safety analysis population of Study A1501080 experienced *at least* one SAE, 15 of whom had sustained treatment emergent SAEs.

*Non-Fatal SAEs in Subjects 2 to <12 years*

Among subjects aged 2 to <12 years old, 6 of a total 11 patients experienced a total of 13 treatment emergent SAEs (10 of which were non-fatal), with only one patient (Subject (b) (6) (b) (6) in this age group assessed by the investigator as having a treatment related SAE acute renal failure). In addition to VFEND, this patient also received several other nephrotoxic concomitant medications, such as vancomycin (Study Days 28-30, 36), colistin (Study Day 37), and ganciclovir (Study Day 35), late in her treatment course. This subject ultimately succumbed to cardiac arrest secondary to septic shock (Fatal SAE: septic shock). This fatal outcome was, however, deemed by this reviewer as being unrelated to acute renal failure. Subject (b) (6) was discussed above in Section 8.4.1 Deaths.

*Non-Fatal SAEs in Subjects 12 to <18 years*

Fourteen of the 17 subjects ages 12 to <18 years were documented as having at least one SAE, nine of whom experienced 23 treatment emergent SAEs (20 of which were non-fatal). A single SAE, which occurred in Subjec (b) (6) was determined to be related to VFEND therapy (PT: drug induced liver injury). atal, treatment related SAE is briefly summarized below.

**Subject** (b) (6) (PT: drug-induced liver injury): A 14 year old male weighing 55-kg with a history of IA enrolled into Study A1501080 on (Study Day 1). The patient received his first dose of study drug (voriconazole 4-mg/kg) on this same day. His final treatment dose was administered on (Study Day 40). His relevant past medical history included acute lymphocytic leukemia, a history of febrile neutropenia, and hyperbilirubinemia (baseline total bilirubin 2.2 mg/dL). Patient additionally experienced muscular weakness, also reported as an SAE, on Study Day 34. On Study Day 40, he was hospitalized after presenting febrile to 38.5 C, with moderate jaundice, and mild facial edema. His liver span was measured to be 4 cm beneath the costal margin. Liver function tests collected on Study Day 40, ALT, AST, total bilirubin and conjugated bilirubin were measured as 684 IU/L (>3.0 x upper limit of normal) (baseline ALT 22 IU/L), 694 IU/L (>3.0 x upper limit of normal) (baseline AST 9 IU/L), 6.4 mg/dL (>1.5 x ULN) (baseline total bilirubin 2.2 mg/dL) and 5.7 mg/dL, respectively. His alkaline phosphatase was within normal limits at 346 IU/L. VFEND (voriconazole) was initially "temporarily discontinued" on Study Day 40. However, according to the subject narrative, "Since the global response to study drug was determined to be completed, the investigator decided not to reintroduce voriconazole." The investigator assessed the event severity as severe and described it as a case of "drug-induced liver injury." Concomitant medications included calcium carbonate, multivitamin, cefotaxime, potassium, and Tylenol prn. HIV, HAV, HBV, and HCV serologies were all negative. By Study Day 54, ALT and AST were 96 IU/L and 65 IU/L, respectively, and both had returned to normal on Study Day 64. Additional events included development of steroid induced myopathy presenting as muscle weakness (Study Day 34); parainfluenza type 1 bronchitis for which he was begun on oseltamivir on Study Day 41.

**Medical Reviewer's Comments**
*Upon review of the patient narrative and the accompanying subject level data, this reviewer agrees that there appears to be a plausible temporal association between the observed ALT and AST elevations and receipt of VFEND. LFTs appeared to decline several days after VFEND was discontinued. This finding is further supported by the well-characterized association between azole antifungals and elevations in hepatic enzymes. Alternative etiologies, such as acute viral hepatitis were evaluated with hepatic serologies, and were ruled out (CMV, VZV not checked).*

**Study A1501085**

*Subjects Aged 2 to <12 years*

All 14 subjects ages 2 to <12 in Study A1501085 were noted to have TEAEs. Two subjects in this age group incurred treatment emergent SAEs (PT: febrile neutropenia and pneumonia), none of which were fatal SAEs. Study investigators concluded that both SAEs were unrelated to VFEND therapy and no dose adjustments were made. Upon review of these treatment emergent SAEs, this reviewer concurred with the study investigators' assessments.

Please refer to **Section 13 Appendix** of this review for a tabular listing of all SAEs occurring in the 2 to <12 years old age cohort.

*Subjects Aged 12 to <18 years*

Six of the total seven subjects ages 12 to <18 years old who comprised the safety analysis population were reported as having sustained at least one SAE. A single patient, Subject (b) (6) (b) (6) was assessed by the investigator as having experienced a potentially treatment emergent, VFEND related SAE. However, in this reviewer's opinion the reported SAE represented a treatment failure, as opposed to a true VFEND related safety event.

**Subject** (b) (6) (SAE/Treatment withdrawal: Splenic Candidiasis)**:**
A 12 year old Czech female weighing 25.0-kg with a primary diagnosis of esophageal candidiasis and a prior medical history notable for acute lymphocytic leukemia and esophagitis. She enrolled into Study A1501085 and was administered her first dose of IV VFEND on Study Day 1. Ultrasonography from Study Day 10 demonstrated multiple hypoechogenic splenic lesions that were not reported at study enrollment. This was further confirmed with abdominal CT obtained on Study Day 16. VFEND was discontinued after this patient was suspected to have splenic candidiasis on Study Day 17, with progression of disease in days to follow. At the end of the study, this patient was assessed by the study investigator as having a clinical response of cure. Afterwards, the patient received several therapies for splenic candidiasis in sequential order: amphotericin B, amphotericin B/micafungin; micafungin; micafungin/posaconazole. Prolonged therapy with posaconazole solution was administered through Study Day 390 with a CT demonstrating resolution of all splenic lesions. The investigator assessed there to be a causal relationship between splenic candidiasis and VFEND.

**Medical Reviewer's Comments:**
*In this reviewer's opinion, the described event was a complicated episode of treatment failure more so than a VFEND related adverse event. While the subject was successfully treated for her underlying esophageal candidiasis, VFEND failed to prevent spread of initial disease, and thereby resulted in splenic candidiasis.*

A table of all SAEs occurring in Study A1501085 is found in **Section 13 Appendix**.

**Legacy Data: Pediatric Subjects from Original Registrational Trials**

Thirty (57.7%) of the 52 pediatric subjects in the legacy data set were reported to have had SAEs. Most SAEs occurred under the Investigations and Respiratory, Thoracic and Mediastinal Disorders SOCs. Notably, there were a total of six patients reported to have had hepatic related SAEs. These SAEs were coded under the following PT terms: ALT increased (Subject (b) (6) (b) (6) blood alkaline phosphatase increased (Subjects (b) (6) and (b) (6) , blood bilirubin increased (Subjects (b) (6) and (b) (6) ), drug-induced liver injury (Subject (b) (6) ; jaundice (Subject (b) (6) , and liver function test abnormal (Subjects (b) (6) and (b) (6) . Two patients experienced more than one hepatic related SAE (Subjects (b) (6) and (b) (6) .

Other potential VFEND related SAEs included: thrombocytopenia (1 patient) under the Blood and Lymphatic System disorders SOC; tachycardia (one patient) under the Cardiac Disorders SOC; scleral disorder (one patient), the only SAE under the Eye Disorders SOC; vomiting (one patient), the only SAE under the Gastrointestinal SOC; hypercreatininaemia (one patient), under the Metabolism and Nutrition Disorders SOC; convulsion and hemiplegia (both in the same patient) under the Nervous System Disorders SOC; one subject each coded under PT terms renal impairment and renal failure, under the Renal and Urinary Disorders SOC; and lastly two patients each coded to PT terms hypertension and hypotension (1 under the Vascular Disorders SOC.

### 8.4.3 Dropouts, Discontinuations, and/or Dose Reductions/Interruptions Due to Adverse Events

Study A1501080

*Subjects Ages 2 to <12 years old*

*Treatment Discontinuations*
In Study A1501080, only a single subject, (Subject (b) (6) , in the 2 to <12 age group was discontinued from VFEND therapy. This patient is discussed in greater detail below.

**Subject** (b) (6) PT/Study Treatment Discontinuation: Secondary to Sepsis):
A 7 year old Dutch male weighing 25.6-kg upon enrollment into Study A1501980 had a primary diagnosis of aspergillosis. He received his first dose of IV VFEND on day of enrollment (Study Day 1). Subject had a medical history significant for acute myeloid leukemia (diagnosed 2012).

His final VFEND dose was administered on (Study Day 3) when this subject experienced the SAE sepsis. This event was assessed by investigator to be due to infection with coagulase negative (CoN) *Staphylococcus aureus* and possible *Candida albicans* infection. This event was deemed a moderate severity event and resulted in VFEND being permanently withdrawn on Study Day 3. The event resolved on (Study Day 9) and the study investigator determined that this event was unrelated to VFEND treatment.

**Medical Reviewer's Comments:**
*Based on the above described narrative, this reviewer concurs with the investigator that the patient's permanent withdrawal from VFEND was unrelated to VFEND treatment but rather was the result of CoN S. aureus bacteremia.*

*Subjects Ages 12 to <18 years old*

While no patients in the 12 to <18 years old cohort permanently discontinued VFEND therapy, a total of four patients either had reductions to their VFEND therapy (Subjects (b) (6); (b) (6); (b) (6) or sustained an interruption in VFEND dosing (Subject (b) (6). Subject (b) (6) sustained a total of 7 distinct SAEs resulting in reductions in VFEND dosage, several of which occurred on the same day, and was discussed above in **Section 8.4.1 Deaths.** Subjects (b) (6) experienced changes in their hepatic enzymes, with events coded under the PT terms "ALT increased," "liver function test abnormal," and "transaminases increased," respectively. These cases are further referenced in **Section 13 Appendix**

Study A1501085

*Subjects Ages 2 to <12 years old*

*Treatment Discontinuations*

Two patients, Subjects (b) (6) and (b) (6) out of the total 14 subjects in the 2 to <12 age cohort, were permanently withdrawn from VFEND treatment for hepatic related events. Subject (b) (6) a 9 year old Mexican female with a history of a baseline elevated bilirubin (4.2 mg/dL), neoplasm (not otherwise specified), and an SAE of pneumonia is discussed below.

**Subject** (b) (6) (SAE: Pneumonia, nosocomial; PT/ Drug withdrawn: Hyperbilirubinemia)**:**
A 9 year old Mexican female weighing 50.0-kg was diagnosed with systemic *candidiasis*. Her past medical history was noted for a history of "neoplasm" for which she was status post a Whipples surgery in 2011; cardiac failure; hyperbilirubinemia; and a history of *Candida* colonization. She enrolled in Study A1501085 and received her first dose of IV voriconazole on (Study Day 1). On Study Day 4, she was observed to be tachypneic to 40 breaths/minute; febrile to 38 C and hypoxic to 78% on ambient air, and was discovered to have a right basal opacity on chest x-ray for which she diagnosed with a nosocomial pneumonia and treated with piperacillin/tazobactam, dexamethasone, fluticasone, and racepinefrine (an inhaled bronchodilator solution). She developed mild jaundice on Study Day 8. The last dose of voriconazole was administered on Study Day 12 and was permanently withdrawn this same day for hyperbilirubinemia, with an increase in her baseline Tbili from 4.2 mg/dL (Study Day 1), to

6.4 mg/dL (Study Day 8), and 8.2 mg/dL (Study Day 11). There were minimal increases in her baseline ALT (post-baseline maximal was 85 U/L from baseline of 47 U/L) and AST values (post-baseline maximal was 91U/L from baseline of 71 U/L). Baseline alkaline phosphatase was 685 U/L. No post-baseline alkaline phosphatase levels exceeded this value. Pneumonia resolved on Study Day 15.

**Medical Reviewer's Comments:**
*This reviewer concurs with the investigator's assessment that this subject's SAE of pneumonia was unrelated to VFEND therapy. This reviewer also agrees that one cannot exclude the possibility that the patient's elevation in Tbili was unrelated to VFEND therapy. However, this worsening of baseline elevated Tbili could have also been related to nosocomial pneumonia sepsis and/or additional medications superimposed upon underlying medical conditions.*

Subject (b) (6) a 5 year old male with a primary diagnosis of EC and an SAE of febrile neutropenia, sustained a non-serious, investigator- assessed, treatment related AE coded under the PT term "liver disorder" and is discussed below.

**Subject** (b) (6) (SAE: Febrile Neutropenia; PT/Drug withdrawal: Liver Disorder)**:** A 5 year old male from the Czech Republic with a primary diagnosis of EC. The subject was enrolled in the study on Study Day 1 and received the first dose IV VFEND this same day. He received his last dose of VFEND on Study Day 23. He had a medical history significant for acute lymphocytic leukemia (diagnosed 2012) for which he was receiving chemotherapy (cyclophosphamide, cytarabine, methotrexate); a history of antithrombin III deficiency complicated by deep vein thrombosis. On Study Day 18, the patient developed febrile neutropenia for which he was hospitalized. On Study Days 22 and 23, the patient developed elevations in his baseline AST (Day 1: 29.4 IU/L/Day 22: 229.8 IU/L/Day 23: 661.2 IU/L); and ALT (Day 1:43 IU/L/Day 22: 66.6 IU/L/ Day 23: 282 IU/L) which prompted the study investigator to permanently discontinue VFEND therapy. Alkaline phosphatase remained within normal limits and subject experienced only slight elevation in his bilirubin from 0.16 mg/dL on Day 1 to 2.06 mg/dL on Day 23. Febrile neutropenia (an SAE) resolved on Study Day 26 and he was discharged the same day.

**Medical Reviewer's Comments:**
*The reviewer agrees that the observed hepatic elevations could be potentially related to VFEND therapy. A further discussion of this patient can be found in* ***Section 8.4.6 Laboratory Findings***

*Treatment Reductions*
A total of three subjects were reported as having reductions in their VFEND dosing (Subjects (b) (6) discussed above], (b) (6), and (b) (6), due to non-serious, investigator-assessed treatment related TEAEs under the Hepatobiliary Disorders and Investigations SOC. A listing of treatment withdrawals, discontinuations, and reductions is found in **Section 13 Appendix.**

***Medical Reviewer's Comments:***
*Investigator assessed treatment discontinuations and/or treatment reductions occurring in the 2-<12 age group were non-serious, hepatic related events. All events were assessed by investigators as being related to the study drug. Given the temporal relationship to hepatic elevations with VFEND therapy in conjunction with well-known azole-associated hepatotoxicity, this reviewer agrees with the investigators assessments. However, it is understood that as these patients were critically ill, and on multiple medications, one can expect that there may have been several confounders impacting any observed liver enzyme elevations.*

*Subjects Ages 12 to <18 years*

Two of the seven subjects ages 12 to <18 years old were withdrawn from VFEND due to a TEAE (Subjects (b) (6) and (b) (6). Subject (b) (6) was discussed above under **Section 8.4.2 Ser erse Events.** Subject (b) (6) was withdrawn from VFEND treatment and is briefly discussed below.

**Subject** (b) (6) (PT/Drug withdrawal: Pulmonary Aspergillosis)**:**
A 14 year old Mexican female weighing 44.0-kg was enrolled into the Study A1501085 for a primary diagnosis of esophageal candidiasis. She had a medical history noted for acute myeloid leukemia (AML) (on chemotherapy); epilepsy, and febrile neutropenia. She enrolled in and began VFEND treatment on the same day (Study Day 1) and her final dose of voriconazole treatment was administered on Study Day 14 after which she was assessed by the investigator as having a clinical response of improvement. Patient was reported as having a non-serious but severe AE of bronchopulmonary aspergillosis (Study Day 5) for which voriconazole therapy was discontinued on Study Day 14.

**Medical Reviewer's Comments:**
*Based on the above described narrative, this reviewer concurs with the study investigator that this subject's VFEND was withdrawn due to a failure in efficacy and not due to reasons of safety.*

No subjects in the 12 to <18 age cohort had any reductions in voriconazole dosing due to TEAEs.

**Original Registrational Trials**

In response to an informational request, the Applicant confirmed that a total of 7 (13.5%) of 52 patients in the registrational trials permanently discontinued VFEND due to an AE. Most treatment discontinuations were due to hepatically related events coded to such PT terms as "blood alkaline phosphatase increased," "blood bilirubin increased," "jaundice" (all occurring in a single subject, Subject (b) (6); "alanine aminotransferase increased" (Subject (b) (6) (b) (6) " and "liver function test abnormal (Subjects (b) (6) and (b) (6) ." The other treatment discontinuations (PT terms: pneumonia, hypotension, and fungal infection) appeared to be unrelated to VFEND therapy. Two subjects in the legacy data temporarily discontinued VFEND: Subjects (b) (6) (PT terms: abdominal pain, blood alkaline

phosphatase increased, blood bilirubin increased, cholestasis) and (b) (6) PT term: blood creatinine increased) and a single subject, Subject (b) (6) had their VFEND dose reduced for an AE coded to the PT term: renal impairment.

No additional information was supplied by the Applicant on these events. For further discussion of these cases, the reader is referred to the clinical review for the original VFEND NDA.

## 8.4.5 Treatment Emergent Adverse Events and Adverse Reactions

### Overview

The majority of patients in the ISS population had non-serious TEAEs. Non-serious TEAEs were similar in patients ages 2 to <12 years old and those ages 12-<18 years old. Moreover, rates of non-serious TEAEs were similar when comparing the 53 subjects enrolled in the Phase 3 pediatric trials against the 52 subjects from the initial registrational trials. The most commonly cited TEAEs were observed in the Gastrointestinal SOC, under such PT terms as vomiting (20%), nausea (13%), abdominal pain (12%), and diarrhea (11%). This was followed by the General Disorders and Administration Site SOC, under the AE pyrexia (25%). There was no distinguishable pattern of TEAEs among the two age cohorts. Approximately 25% of patients experienced at least 1 visual disturbance, which was a catchall phrase comprised of such adverse reactions as vision blurred, visual brightness, visual impairments etc. Electrolyte abnormalities such as hypokalemia (11%), hypomagnesemia (7%), hypophosphatemia (7%), and hypocalcemia (6%), were also commonly observed at rates of ≥5%. For a more detailed overview of non-serious treatment emergent adverse reactions, the reader is referred to **Table 12** below.

**Table 12: Treatment Emergent Adverse Reactions, ISS Population**

| Body System | Adverse Reaction | Pooled Pediatric Data N=105 n (%) |
|---|---|---|
| **Blood and Lymphatic Systems Disorders** | Thrombocytopenia | 10 (10) |
| **Cardiac Disorders** | Tachycardia | 7 (7) |
| **Eye Disorders** | Visual Disturbances[a] | 27 (26) |
| | Photophobia | 6 (6) |
| **Gastrointestinal Disorders** | Vomiting | 21 (20) |
| | Nausea | 14 (13) |
| | Abdominal pain[b] | 13 (12) |
| | Diarrhea | 12 (11) |
| | Abdominal distention | 5 (5) |
| | Constipation | 5 (5) |
| **General Disorders and Administration Site Conditions** | Pyrexia | 25 (25) |
| | Peripheral edema | 9 (9) |
| | Mucosal inflammation | 6 (6) |
| **Infections and Infestations** | Upper respiratory tract infection | 5 (5) |
| **Investigations** | ALT abnormal[c] | 9 (9) |
| | LFT abnormal | 6 (6) |

| Body System | Adverse Reaction | Pooled Pediatric Data N=105 n (%) |
|---|---|---|
| **Metabolism and Nutrition Disorders** | Hypokalemia | 11 (11) |
| | Hyperglycemia | 7 (7) |
| | Hypocalcemia | 6 (6) |
| | Hypophosphotemia | 6 (6) |
| | Hypoalbuminemia | 5 (5) |
| | Hypomagnesemia | 5 (5) |
| **Nervous System Disorders** | Headache | 10 (10) |
| | Dizziness | 5 (5) |
| **Psychiatric Disorders** | Hallucinations[d] | 5 (5) |
| **Renal and Urinary Disorders** | Renal impairment[e] | 5 (5) |
| **Respiratory Disorders** | Epistaxis | 17 (16) |
| | Cough | 10 (10) |
| | Dyspnea | 6 (6) |
| | Hemoptysis | 5 (5) |
| **Skin and Subcutaneous Tissue Disorders** | Rash[f] | 14 (13) |
| **Vascular Disorders** | Hypertension | 12 (11) |
| | Hypotension | 9 (9) |

[a]Pooled reports include such terms as: amaurosis (partial or total blindness without visible change in the eye); asthenopia (eye strain); chromatopsia (abnormally colored vision); color blindness; diplopia; photopsia; retinal disorder; vision blurred, visual acuity decreased, visual brightness; visual impairment. Several patients had more than one visual disturbance.
[b]Pooled reports include such terms as: abdominal pain and abdominal pain, upper
[c]Pooled reports include such terms as: ALT abnormal and ALT increased
[d] Pooled reports include such terms as: hallucination; hallucination, auditory; hallucination, visual. Several patients had both visual and auditory hallucinations.
[e]Pooled reports include such terms as: renal failure and a single patient with renal impairment
[f]Pooled reports include such terms as: rash; rash generalized; rash macular; rash maculopapular; rash pruritic
Abbreviations: ALT= alanine aminotransferase; LFT= liver function test

***Medical Reviewers Comments:***
*The Applicant provided comparative incidence rates of TEAEs occurring within pediatric and adult studies. With the exception of hepatic enzyme elevations and visual disturbances, where a higher incidence of adverse reactions were observed within the pediatric population, most treatment emergent adverse reactions in the pediatric population were comparable to those observed in adults. There were, however, no pediatric patients with photosensitivity reactions in the Phase 3 studies. This finding is inconsistent with what has been observed and reported in the postmarket setting.*

### 8.4.6 Laboratory Findings

*Study A1501080*
*Liver Function Tests*

**Table 13** provides descriptive statistics for liver related enzymes (i.e. ALT, AST, Tbili, alkaline phosphatase) and creatinine (Cr) for all patients with evaluable liver enzymes in Study A1501080.

**Table 13: StudyA1501080 Descriptive Statistics for Select Chemistries at Baseline, Treatment, and Post-Treatment Visits Safety Population Subjects, Ages 2 to <18 Years Old**

| Chemistry Lab Parameter | Study A1501080 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | AGES 2 to <12 Years Old | | | AGES 12 to <18 Years Old | | | ALL AGES | | |
| **Alanine Aminotransferase (ALT) (U/L)** | | | | | | | | | |
| | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** |
| Pre-Treatment | 10 | 14.7 (5.7) | 13 (4, 24) | 19 | 47.8 (53.6) | 37.8 (2, **246**) | 29 | 36.4 (46.0) | 22 (2, 246) |
| Treatment | 48 | 23.9 (20.1) | 19 (3, 102) | 87 | 65.0 (97.5) | 33 (3, **684**) | 135 | 50.4 (81.4) | 24 (3, 684) |
| Post Treatment | 10 | 43.8 (29.3) | 39.5 (10, 78) | 17 | 57.5 (52.5) | 42 (6, **228**) | 27 | 52.3 (45.1) | 42 (6, 228) |
| **Aspartate Aminotransferase (AST) (U/L)** | | | | | | | | | |
| | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** |
| Pre-Treatment | 10 | 17.7 (7.4) | 17.5 (6, 29) | 18 | 39.9 (46.5) | 24.5 (9, 181) | 28 | 32.0 (38.7) | 21 (6, 181) |
| Treatment | 48 | 31.9 (19.8) | 26 (7, 123) | 85 | 62.4 (99.2) | 33 (7, **694**) | 133 | 51.4 (81.4) | 30 (7, 694) |
| Post Treatment | 10 | 29.7 (11.9) | 28 (13, 47) | 17 | 56.9 (55.4) | 40 (12,233) | 27 | 46.8 (46.0) | 31 (12, 233) |
| **Total Bilirubin (mg/dL)** | | | | | | | | | |
| | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** |
| Pre-Treatment | 10 | 0.42 (0.20) | 0.37 (0.2, 0.8) | 19 | 0.79 (0.62) | 0.51 (0.13, 2.39) | 29 | 0.67 (0.54) | 0.47 (0.13, 2.39) |
| Treatment | 49 | 0.41 (0.42) | 0.33 (0.1, 2.3) | 85 | 0.75 (1.09) | 0.49 (0.1, **6.4**) | 134 | 0.62 (0.91) | 0.41 (0.1, 6.4) |
| Post Treatment | 9 | 0.46 (0.16) | 0.47 (0.2, 0.7) | 16 | 0.55 (0.24) | 0.55 (0.1, 1.0) | 25 | 0.5 (0.21) | 0.5 (0.1, 1.0) |
| **Alkaline Phosphatase (U/L)** | | | | | | | | | |
| | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** |
| Pre-Treatment | 9 | 113.0 (69.2) | 114 (5.3, 249) | 18 | 124.5 (103.0) | 99.0 (3.2, 464) | 27 | 120.7 (91.9) | 114 (3.2, 464) |
| Treatment | 46 | 155.9 (66.3) | 137 (41, 361) | 83 | 206.0 (219.2) | 136 (44, **1272**) | 129 | 188.1 (181.4) | 136 (41, 1272) |
| Post Treatment | 11 | 114.8 (61.9) | 83 (52, 265) | 16 | 146.8 (80.1) | 111.5 (62.0, 361.0) | 27 | 133.7 (73.7) | 108 (52, 361) |
| **Creatinine (mg/dL)** | | | | | | | | | |

| Chemistry Lab Parameter | Study A1501080 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | AGES 2 to <12 Years Old | | | AGES 12 to <18 Years Old | | | ALL AGES | | |
| | n | Mean (SD) | Median (min, max) | n | Mean (SD) | Median (min, max) | n | Mean (SD) | Median (min, max) |
| Pre-Treatment | 11 | 0.34 (0.12) | 0.3 (0.2, 05) | 22 | 0.49 (0.13) | 0.46 (0.3, 0.8) | 33 | 0.44 (0.14) | 0.4 (0.2, 0.8) |
| Treatment | 52 | 0.36 (0.12) | 0.4 (0.2, 0.8) | 74 | 0.52 (0.24) | 0.5 (0.26, 1.8) | 126 | 0.46 (0.21) | 0.41 (0.2, 1.8) |
| Post Treatment | 11 | 0.34 (0.09) | 0.36 (0.2, 0.5) | 18 | 0.48 (0.11) | 0.46 (0.3, 0.7) | 29 | 0.43 (0.13) | 0.4 (0.2, 0.7) |

**Source:** Trial A1501080. ADLB (AdAM) data set.
**Note:** Several subjects had multiple vital sign readings at the treatment time point. Created by clinical reviewer using JMP software. The highest elevated maximal post-baseline values are highlighted in table in with **red** text.

Hepatic Enzymes

Twenty-nine (93.6%) of the 31 patients comprising the safety population had baseline and post baseline ALT values. No patients ages 2 to <12 years old had ALT >3x the upper limit of normal (ULN) or higher; however, a total of 10 of the 19 patients with both baseline and post-baseline ALT values had maximal post-baseline values at least >3x the ULN or higher. Subject (b) (6) a 14 year old male with IA, who was described above in **Section 8.4.2 Serious Adverse Events** was observed to have the highest ALT, AST and Tbili levels. Summaries of select patients with hepatic elevations are summarized below.

**Baseline normal → >15x-20x ULN (1 subject; 12 to <18 years old cohort)**

- **Subject** (b) (6) 14 year old Asian male (Thailand). He received 40 days of therapy: 14 days of IV and 26 days of oral therapy. Initial dose was 330-mg of IV VFEND. VFEND treatment was completed on Study Day 40. Key AEs: muscular weakness (severe); **drug induced liver injury (severe)(Study Day 40);** mucosal inflammation (moderate). Concomitant medications (notable): acyclovir, amikacin, amphotericin B, trimethoprim-sulfamethoxazole, ceftazidime, cefotaxime, dexamethasone, methotrexate, oseltamivir, vincristine. This subject is also discussed in greater detail in **Section 8.4.2 Serious Adverse Events.**

| Laboratory Parameter | Baseline | Day 40 | Day 72 |
|---|---|---|---|
| **ALT U/L [range: 0-56]** | 22 | **684 H** | **85 H** |
| **AST U/L [range: 5-30]** | 9 | **694 H** | **80 H** |
| **Total bili mg/dL [range: 0-1]** | **2.2 H** | **6.4 H** | 0.6 |
| **Alkaline Phosphatase U/L [range: 74-390]** | 174 | 346 | 115 |

**Baseline →2x-3x→ >5x-10x ULN (1 subject; 12 to <18 years old cohort)**

- **Subject** (b) (6) 5 year old Asian male with a primary diagnosis of IA an ute myeloid leukemia. Received 85 days of therapy: 7 days of IV and 78 days of oral. Initial VFEND dose was 300-mg followed by 200-mg . Key AEs were: **LFT abnormal (mild) (Study Day 7);**

pyrexia (mild); epistaxis (mild); gingival bleeding (severe); thrombocytopenia (moderate); nausea (mild); hemoptysis (mild); febrile neutropenia (mild); hepatic candidiasis; liver abscess; hepatic hematoma (non-treatment emergent). Notable concomitant medications included: amphotericin B, caspofungin, ceftazidime, cytarabine, hydrocortisone, methotrexate, tranexamic acid. Hepatic enzyme elevations are displayed below.

| Laboratory Parameter | Baseline | Day 7 | Day 118 |
|---|---|---|---|
| **ALT U/L [range: 0-56]** | **91 H** | **455 H** | **228 H** |
| **AST U/L [range: 5-30]** | **44 H** | **258 H** | **131 H** |
| **Total bili mg/dL[range: 0-1]** | 0.5 | 0.5 | 0.6 |
| **Alkaline Phosphatase U/L [range: 119-351]** | 123 | **359 H** | 191 |

**Baseline >2x-3x→ >10x-15x ULN (1 subject; 12 to <18 years old cohort)**

- **Subject** (b) (6) Dose Reduction PT: Transaminase Increased)**:** A 14 year old White female (USA) with a primary diagnosis of IA and a history of recurrent medulloblastoma and veno-occlusive liver disease. She received 20 days of VFEND treatment: 20 days of IV and no days of oral. She was initiated on IV VFEND at 146.4-mg, which she received from Study Day 1 through Study Day 8. However, on Study Day 13, she experienced a moderate elevation in her LFTs and her VFEND dose was reduced to 108-mg IV. LFT elevations gradually declined by Study Day 14. Her VFEND treatment was prematurely discontinued for reasons unrelated to LFT elevations on Study Day 20 (Reason: non-study physician decided to add another antifungal medication for additional aspergillus coverage following CT findings and increasing galactomannan titers). Key TEAEs: **blood bilirubin increased (mild) (Study Day 4);** back pain (moderate); **LFT abnormal (moderate) (Study Day 13);** fatigue (severe); **transaminase increased (moderate) (Study Day 24);** hepatomegaly (mild); gallbladder disorder (mild). Concomitant medications (notable): trimethoprim-sulfamethoxazole, ceftazidime, diazepam, micafungin, meropenem, hydromorphone, vancomycin. Hepatic enzyme elevations are displayed below.

| Laboratory Parameter | Day -1 | Day 7/Day 13 | Day 20 |
|---|---|---|---|
| **ALT U/L [range: 0-56]** | **83 H** | **115 H/ 435 H** | **120 H** |
| **AST U/L [range: 5-30]** | **62 H** | **120 H/ 449 H** | **63 H** |
| **Total bili mg/dL[range: 0-1]** | 1.4 | **2.6 H/** 1.0 | 0.8 |
| **Alkaline Phosphatase U/L [range: 39-274]** | **464 H** | **1002 H/ 1264 H** | **808 H** |

**Baseline normal → >3x-5x ULN (1 subject; 12 to <18 years old cohort)**

- **Subject** (b) (6) Dose Reduction/Transaminase Increased): 17 year old Asian male (Singapore) received 62 days of VFEND treatment: 8 days of IV treatment and 55 days of oral treatment. He had a primary diagnosis of IA and a past medical history of acute lymphocytic leukemia. Patient was begun on VFEND 270-mg IV and switched to 300-mg oral dose on Study Day 8. On Study

Day 12, VFEND dose was reduced after he was noted to have a mild increase in transaminases which resolved on Study Day 15. VFEND was not discontinued due to adverse event. Key AEs included: cough (mild); diplopia (mild); insomnia (mild); hypomagnesemia (mild); dyspnea (mild); **vision blurred (mild);** epistaxis (moderate); **transaminases increased (mild) (Study Days 7, 12, and 28);** nausea (mild); conjunctivitis (mild); ALL (severe); tachycardia (mild); pyrexia (moderate); **visual impairment (severe).** Relevant concomitant medications: paracetamol; meropenem; brimonidine tartrate; travoprost; rabeprazole; timolol. Hepatic enzyme elevations are displayed below.

| Laboratory Parameter | Baseline | Day 13/15 | Day90 |
|---|---|---|---|
| **ALT U/L [range: 0-56]** | 35 | **86H/** 69 | **55 H** |
| **AST U/L [range: 5-30]** | 27 | **88H/115H** | **233 H** |
| **Total bili mg/dL[range: 0-1]** | 0.9 | 0.6/0.5 | 0.5 |
| **Alkaline Phosphatase U/L [range: 40-130]** | 102 | **227H/ 315 H** | 108 |

**Baseline normal → >5x-10x ULN (1 subject; 12 to <18 years old cohort)**

- **Subject** (b) (6) 12 year old white male (Poland) with a primary diagnosis of IA and a medical history noted for acute lymphocytic leukemia for which he was s/p an allogeneic stem cell transplant and acute graft versus host disease. He received 84 days of VFEND treatment, including: 10 days of IV VFEND and 75 days of oral VFEND. Initial IV VFEND dosing was 140-mg voriconazole. No discontinuation of therapy. Key TEAEs: loss of consciousness (moderate); pyrexia (mild); hypertension (mild); headache (mild); flushing (mild). LFTs are summarized below.

| Laboratory Parameter | Day -1 | Day 7/ Day 42 | Day 84 |
|---|---|---|---|
| **ALT U/L [range: 0-56]** | **54 H** | **215 H/ 153 H** | **56 H** |
| **AST U/L [range: 5-30]** | **181 H** | **43 H/ 70 H** | **49 H** |
| **Total bili mg/dL[range: 0-1]** | 0.7 | 0.83/ 0.76 | 0.86 |
| **Alkaline Phosphatase U/L [range: 108-360]** | 76 L | 76/ 121 | 135 |

Creatinine

As demonstrated in **Table 13**, in Study A1501080, mean and median creatinine (Cr) values remained largely consistent across all phases of treatment.

*Trial A1501085*

*Liver Function Tests*

**Table 14** provides descriptive statistics for hepatic enzymes (i.e ALT, AST, Tbili, alkaline phosphatase) and Cr for all patients in Study A1501085 with evaluable laboratory data.

**Table 14: Study A1501085 Descriptive Statistics for Select Chemistries at Baseline, Treatment, and Post-Treatment Visits in Subjects with EC AND ICC Safety Population Subjects, Ages 2 to <18 Years Old**

| Chemistry Lab Parameter | StudyA1501085 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | AGES 2 TO <12 YEARS OLD | | | AGES 12 TO <18 YEARS OLD | | | ALL Subjects | | |
| **Alanine Aminotransferase (ALT) (U/L)** | | | | | | | | | |
| | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** |
| Pre-Treatment | 14 | 59.3 (54.3) | 45.4 (8, **175.2**) | 11 | 57.5 (87.5) | 21.6 (9, **283.2**) | 25 | 58.5 (69.2) | 36.6 (8, 283.2) |
| Treatment | 43 | 49.8 (57.3) | 29 (6.6, **282**) | 18 | 45.5 (42.9) | 25.9 (8, 133.2) | 61 | 48.5 (53.2) | 28.8 (6.6, 282) |
| Post Treatment | 13 | 31.7 (21.5) | 25 (9, 85) | 8 | 50.9 (50.5) | 28.9 (15.6, 162) | 21 | 39.0 (35.5) | 28.8 (9, 162) |
| **Aspartate Aminotransferase (AST) (U/L)** | | | | | | | | | |
| | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** |
| Pre-Treatment | 13 | 36.0 (19.0) | 32 (8, 71) | 11 | 19.4 (8.8) | 18 (9, 31.8) | 24 | 28.4 (17.1) | 28.2 (8, 71) |
| Treatment | 38 | 71.7 (109.8) | 42.4 (16, **661**) | 17 | 28.5 (15.0) | 22.8 (11, 55.8) | 55 | 58.3 (93.5) | 38.4 (11, 661.2) |
| Post Treatment | 13 | 37.6 (22.0) | 30.6 (13.2, 91) | 8 | 38.2 (21.1) | 30 (19.8, 79.8) | 21 | 37.8 (21.1) | 30.6 (13.2, 91) |
| **Total Bilirubin (mg/dL)** | | | | | | | | | |
| | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** |
| Pre-Treatment | 13 | 0.99 (1.24) | 0.51 (0.16, **4.2**) | 11 | 0.82 (0.78) | 0.77 (0.14, **3.0**) | 24 | 0.91 (1.03) | 0.58 (0.14, 4.2) |
| Treatment | 42 | 0.86 (1.6) | 0.3 (0.07, **8.2**) | 18 | 0.50 (0.31) | 0.45 (0.1, 1.06) | 60 | 0.75 (1.31) | 0.32 (0.07, 8.2) |
| Post Treatment | 13 | 0.53 (0.38) | 0.43 (0.12, 1.5) | 8 | 0.48 (0.22) | 0.45 (0.24, 0.83) | 21 | 0.51 (0.33) | 0.44 (0.12, 1.5) |
| **Alkaline Phosphatase (U/L)** | | | | | | | | | |
| | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** |
| Pre-Treatment | 12 | 203.5 (201.8) | 134.5 (60, **626**) | 9 | 101.9 (50.1) | 97 (51, 210) | 21 | 159.9 (161.4) | 118 (51, 626) |
| Treatment | 39 | 191.6 (81.2) | 167 (88.2, 377) | 16 | 141.0 (92.4) | 109 (69, 421) | 55 | 176.8 (87.0) | 161 (69, 421) |
| Post Treatment | 13 | 179.7 (52.3) | 162.3 (97.2, 292) | 8 | 150.8 (78.1) | 119.7 (84, 274) | 21 | 168.7 (63.1) | 162 (84, 292) |
| **Creatinine (mg/dL)** | | | | | | | | | |
| | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** |
| Pre-Treatment | 13 | 0.35 (0.13) | 0.29 (0.23, 0.69) | 11 | 0.55 (0.23) | 0.52 (0.23, 0.92) | 24 | 0.44 (0.21) | 0.39 (0.23, 0.92) |
| Treatment | 44 | 0.36 (0.14) | 0.34 (0.13, 0.75) | 18 | 0.50 (0.17) | 0.22 (0.85) | 62 | 0.40 (0.16) | 0.38 (0.13, 0.85) |

| Chemistry Lab Parameter | StudyA1501085 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | AGES 2 TO <12 YEARS | | | AGES 12 TO <18 | | | ALL Subjects | | |
| Post Treatment | 13 | 0.38 (015) | 0.36 (0.21, 0.82) | 8 | 0.46 (0.16) | 0.45 (0.24, 0.72) | 21 | 0.41 (0.15) | 0.37 (0.21, 0.82) |

**Source:** Trial A1501085. ADLB (AdAM) data set.
**Note:** Several subjects had multiple vital sign readings at the treatment time point. Created by clinical reviewer using JMP software. Highest baseline and maximal post-baseline values are highlighted above in **red** text.

**Medical Reviewer's Comments:**
*LFTs and Cr were comparable between age cohorts in Study A1501085. There was a single patient noted to have post-baseline LFT elevations of ≥5-10 x ULN. This patient is reviewed below:*

**Baseline normal → >5x-10x ULN (1 subject)**

- **Subject** (b) (6) A 5 y/o white male (CZE) with a primary diagnosis of EC and a medical history noted for acute lymphocytic leukemia and deep vein thrombosis received VFEND as primary therapy for his EC. He was treated for a total of 23 days: 6 days of IV VFEND and 17 days of oral VFEND. Starting dose was 31-mg voriconazole, then 200-mg of voriconazole at treatment period 2; and 200-mg voriconazole treatment period 3 Discontinued therapy due to adverse event. Final Dose 160-mg. Key AEs included: **liver disorder** (Study Days 22 and 23); febrile neutropenia, cough). Notable concomitant medications included: cytarabine, methotrexate. Hepatic enzyme elevations are displayed below.

| Laboratory Parameter | Day 1 | Day 22 | Day 23 |
|---|---|---|---|
| **ALT U/L [range: 0-56]** | **42.9 H** | **65 H** | **276 H** |
| **AST U/L [range: 5-30]** | 28.8 | **225 H** | **648 H** |
| **Total bili mg/dL[range: 0-1]** | 0.16 | 0.72 | **2.06 H** |
| **Alkaline Phosphatase U/L [range: 81-450]** | 68 | 211 | **354 H** |

### 8.4.7 Vital Signs

**Table 15** summarizes descriptive statistics, by infection type, for select vital sign parameters (i.e. systolic blood pressure [SBP]; diastolic blood pressure [DBP], and heart rate [HR]) for Studies A1501080 and A1501085. The Applicant did not provide vital sign data for subjects in the original legacy trials. Please refer to the original VFEND NDA for further discussion of vital signs parameters during the registrational trials.

**Table 15: Trials A1501080 and A1501085 Descriptive Statistics for Select Vital Signs at Baseline, Treatment, and Post-Treatment Visits Safety Population Subjects, Ages 2 to <18 Years Old**

| Parameter | Study A1501080 | | | Study A1501085 | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | IA N=30 | | | EC N=11 | | | ICC N=11 | | |
| **Systolic Blood Pressure (mmHg)** | | | | | | | | | |
| | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** |
| Pre-Treatment | 30 | 109.8 (12.3) | 111 (88, 132) | 16 | 107.4 (13.1) | 110 (89, 125) | 16 | 110 (17.9) | 106.5 (80, 146) |
| Treatment | 117 | 110.2 (12.9) | 111 (78, 140) | 66 | 104.6 (10.8) | 103 (85, 129) | 84 | 104.5 (14.5) | 104 (80, 174) |
| Post Treatment | 24 | 110.5 (10.9) | 110.5 (91, 141) | n/a | n/a | n/a | n/a | n/a | n/a |
| **Diastolic Blood Pressure (mmHg)** | | | | | | | | | |
| | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** |
| Pre-Treatment | 30 | 66.7 (12.6) | 67.5 (40, 88) | 16 | 66 (8.3) | 67 (48, 78) | 16 | 65 (14.0) | 63.5 (42, 89) |
| Treatment | 117 | 66.6 (10.1) | 66 (40, 95) | 66 | 63.9 (10.1) | 63 (38,87) | 84 | 65.7 (12.2) | 60.5 (43, 105) |
| Post Treatment | 24 | 67.2 (10.7) | 65.5 (51, 97) | n/a | n/a | n/a | n/a | n/a | n/a |
| **Heart Rate (beats/min)** | | | | | | | | | |
| | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** | **n** | **Mean (SD)** | **Median (min, max)** |
| Pre-Treatment | 30 | 105 (23.4) | 102.5 (65, 185) | 16 | 110.3 (18.2) | 109.5 (72, 137) | 16 | 112.1 (20.0) | 115.5 (79,149) |
| Treatment | 117 | 104.3 (19.8) | 102 (54, 180) | 66 | 96.3 (15.4) | 97 (64, 132) | 84 | 105.0 (17.4) | 102 (66, 141) |
| Post Treatment | 24 | 96 (19.4) | 92.5 (62, 150) | n/a | n/a | n/a | n/a | n/a | n/a |

**Source:** Trials A1501080 and A1501085. ADVS (AdAM) data sets.
**Note:** Several subjects had multiple vital sign readings at the various visits. Table created by clinical reviewer using JMP software.

**Medical Reviewer's Comments:**
*Despite study size limitations and patients being critically ill, pre-treatment, treatment, and post-treatment (when available) median vital sign measurements were largely comparable across Phase 3 studies/infection types. It is noted that the PT terms hypertension, hypotension and tachycardia occurred in ≥5% of TEAE in the ISS population. It is this reviewer's opinion that such findings were most likely unrelated to VFEND therapy and may have been the result of a host of reasons, not limited to the following: underlying medical condition, pain, dehydration, alternative medications, receipt of blood products etc.*

### 8.4.8 Electrocardiogram (ECG)

#### Study 1501080

All 31 patients in Study A1501080 had at least one documented ECG. Most patients were reported as having either normal sinus rhythm (NSR) or minor ECG abnormalities (i.e. sinus tachycardia, or a T-wave abnormality) on their baseline ECGs. Only two patients (Subjects (b) (6) were reported as having prolonged baseline QTc intervals despite otherwise having unremarkable baseline ECGs. Posttreatment ECG results were provided for 23 patients, most of whom were documented as either having NSR or minor ECG findings (i.e. sinus arrhythmia, sinus bradycardia, sinus tachycardia, T-wave abnormalities).

***Medical Reviewer's Comments:***
*There were no clinically significant ECG abnormalities for any patients with ECGs at any treatment or posttreatment time points.*

#### Study 1501085

All 22 patients in Study A1501085 had at least one recorded ECG. Whereas 8 patients had normal baseline ECG readings, twelve patients were documented as having baseline abnormal ECGs characterized by such minor findings as sinus bradycardia, tachycardia, and T-wave abnormalities. However, one patient, Subject (b) (6) was documented as having a prolonged baseline QTc (QTcB of 492 msec/QTcF of 458 msec), albeit <500 msec. A total of twenty patients had both end of treatment (EOT) and 1-month follow-up post baseline ECGs. Most subjects with EOT and post-baseline ECGs demonstrated insignificant ECG abnormalities (i.e. sinus bradycardia, sinus tachycardia, and T-wave abnormalities). Only 3 subjects had slight elevations in their QTcB or QTcF interval, with all QTc values being <500 msec (range: 395msec-484msecs).

***Medical Reviewer's Comments:***
*Overall, there were no significant ECG abnormalities among patients with documented ECGs at any treatment or posttreatment time point in Study A1501085.*

### 8.4.9 QT Prolongation

#### Study A1501080

No patient was recorded as having either a Bazett's QTc (median 429.5 msec; range: 366 msec to 479 msec) or Fridericia's QTc (median 395.5 msec; range: 345-467) value greater than 500 millisecs at any time point.

#### Study 1501085

No patient had either a QTcB (median 413 msec; min-max: 297 msec to 492 msec) or QTcF (median 397 msec; range: 297 msec-458 msec) value greater than 500 msec at any time point.

***Medical Reviewer's Comments:***
*For both Studies A1501080 and A1501085, there were no patients with ECGs demonstrating any significant QTc prolongations (≥ 500 msec) for either the Bazett's or Fridericia's QTc intervals.*

### 8.4.10 Immunogenicity

VFEND is not a peptide. Therefore, its potential for immunogenicity was not anticipated and thus immunogenicity was not evaluated during any of the Phase 3 clinical studies.

## 8.5 Analysis of Submission-Specific Safety Issues

The Applicant identified seven VFEND-associated AEs of special interest that have been observed in adult populations, each of these is discussed in greater detail below.

### 8.5.1 Hepatic Toxicity

Azole antifungals, including VFEND, contain a warning cautioning of instances of hepatic reactions, including hepatitis and jaundice, which have occurred during administration of VFEND and other azoles. Using MAED, this reviewer generated a customized MedDRA query (CMQ) consisting of both standardized MedDRA queries (SMQs) as well as select hepatic related preferred terms (PT). In addition, the reviewer searched an Applicant generated listing of TEAEs occurring in both their adult and pediatric trials. In so doing, this reviewer identified several hepatic related AEs coded under the Hepatobiliary Disorders systems organ classification (SOC) and the Investigations SOC. This approach resulted in the identification of the following hepatic related PT terms among pediatric patients: cholestasis (1 subject, 0.95% vs 1.5% in adults ); drug-induced liver injury (2 subjects, 1.9% vs 0.06% in adults); gallbladder disorder (0.95% vs 0% in adults); hyperbilirubinemia (0.95% vs 1.8% in adults) (non-treatment emergent); hypertransaminasaemia (non-treatment emergent); jaundice (1.9% vs 1.7% in adults); jaundice cholestatic (0.95% vs 0.25% in adults); ALT abnormal/increased (9 subjects combined, 8.6%); AST abnormal/increased (3 subjects combined, 2.9% vs 2.7 in adults); liver function test abnormal (5.7 vs 3.9% in adults); liver disorder (0.95% vs 0.12% in adults); transaminases increased (1.9% vs 2.1% in adults); blood alkaline phosphatase increased (2.9% vs. 6.4% in adults); blood bilirubin increased (2.9% vs 1.8% in adults); hepatic enzyme increased (1.9% vs 1.4% in adults); GGT abnormal/increased (3.8% vs 0.81% in adults) in pediatric patients.

Additional PT terms, for example, such as biliary tract disorder (0.12%); gallbladder disorder (0.95%); hepatic enzyme abnormal (0.25%); hepatitis (0.25%); hepatitis cholestatic (0.19%); hepatic failure (10 subjects, 0.62%), hepatic function abnormal (12 subjects, 0.75%); heptatocellular injury (4 subjects, 0.25%); hepatotoxicity (0.12%) were identified as *only* having occurred in adults but were not observed in the Phase 3 pediatric studies.

The overall incidence of transaminase increases >3x upper limit of normal (ULN) was 27.2% (28/103) in pediatric and 17.7% (268/1514) in adult patients treated with VFEND in pooled clinical trials. The majority of abnormal liver function tests either resolved on treatment with or without dose adjustment or after VFEND discontinuation.

A higher frequency of clinically significant liver laboratory abnormalities, irrespective of baseline laboratory values (>3x ULN ALT or AST), was consistently observed in the combined therapeutic pediatric population (16% AST and 23% ALT) when compared to adults (12.9% AST and 11.6% ALT). The incidence of bilirubin elevation was comparable between adult and pediatric patients.

**Table 16: Incidence of Hepatic Abnormalities among Pediatric Subjects**

| Liver Function Parameter | Criteria | n/N (%) |
|---|---|---|
| Total bilirubin | >1.5 x ULN | 19/102 (19%) |
| Aspartate aminotransferase (AST) | >3.0x ULN | 16/103 (16%) |
| Alanine aminotransferase (ALT) | >3.0x ULN | 23/102 (23%) |
| Alkaline Phosphatase | >3.0x ULN | 8/97 (8%) |

### 8.5.2 Visual Events

Visual disturbances were prominent findings in the adult therapeutic trials. The VFEND label currently warns that "There have been post-marketing reports of prolonged visual adverse events, including optic neuritis, and papilledema. If treatment continues beyond 28 days, visual function, including visual acuity, visual field and color perception should be monitored." Using the same approach described in Section 8.5.1 Hepatic Toxicity, this reviewer identified the following PT terms suggestive of VFEND related visual events: amaurosis (1 subject, 0.95%); asthenopia (eye strain) (0.95%); chromatopsia (0.95%); diplopia (2 subjects, 1.9%); photophobia (6 subjects, 5.71%); photopsia (0.95%); retinal disorder (0.95%); vision blurred (10 subjects, 9.5%); visual acuity reduced (0.95%); visual brightness (4 subjects; 3.8%) and visual impairment (5 subjects, 4.8%) and in so doing identified approximately 27 patients with presumed voriconazole related visual events. As noted above, photophobia, vision blurred, visual impairment, and visual brightness accounted for the majority of all visual events. The incidence of photophobia was higher in the pediatric population than in the adult population with rates of 5.7% and 2.6%, respectively. The incidence of visual disturbances, as described in the current VFEND label (i.e. changes in visual acuity, visual fields, and color perception), were near equivalent in the pediatric and adult cohorts[1] with incidence rates of 25.7% and 27.3%,

[1] The following PT terms were included in determining the incidence rate of visual disturbance in the adult cohort: blindness; blindness, unilateral; chloropsia; chromatopsia; color blindness acquired; cyanopsia; diplopia; halo

respectively. Please refer to the footnote *a* in Table 12 of this review for a listing of all PT terms used to calculate the rate of visual disturbances in all pediatric patients included in the Applicant's VFEND studies.

Most visual events were recorded as being either mild or moderate intensity events. Two patients described as having either a severe intensity or serious visual event are found below.

**Subject** (b) (6) PT: Visual acuity reduced): An 8 year old female, was categorized as having a severe intensity event coded to PT term "visual acuity reduced" on Study Day 14 secondary to a leukemic infiltrate. Patient eventually recovered from this event on Study Day 49. The reviewer agrees with the investigator that this event was unrelated to the study drug.

**Subject** (b) (6) (SAE: Visual impairment): A 17 year old male patient with a history of relapsed acute lymphocytic leukemia (Study Day 48) (with a presenting wbc count of 142K) received 62 days of VFEND and was evaluated as having a serious adverse event coded to the PT term: visual impairment. On Study Day 54, the patient complained of "cloudy vision and mist over the eyes." A fundoscopic examination revealed leukemic infiltrates in both his left and right eyes. This event was assessed by the study investigator as being unrelated to study treatment. This reviewer agrees with the investigator's assessment based on the provided details. The event had not resolved while patient was in the study.

This reviewer did not believe there to be a causal association between VFEND and such eye related PT terms as abnormal sensation in eye (1 subject; 0.95%); cataract (0.95%); conjunctival hemorrhage (0.95%); corneal opacity (0.95%); dry eye (2 subjects, 1.9%); eye discharge (0.95%); eye irritation (0.95%); eye pain (0.95%); eye pruritus (0.95%); eyelid disorder (0.95%); keratitis (1.9%); mydriasis (0.95%); pupils unequal (1.9%); scleral disorder (0.95%) found in pediatric patients.

Notable, visual events occurring in the original registrational trials but not in the pediatric studies included such PT terms as: blindness (1 subject, 0.06%); blindness, unilateral (0.06%); chloropsia (two subjects, 0.12%) (visual defect in which objects appear green); cyanopsia (0.12%) (visual defect in which everything appears blue); halo vision (0.12%); night blindness (0.06%); papilledema (6 subjects, 0.37%); optic atrophy (0.06%)optic disc disorder (3 subjects, 0.19%); oscillopsia (0.06%) (visual disturbance in which objects in the visual field appear to oscillate); retinal detachment (0.06%); scintillating scotoma (0.06%); uveitis (0.06%); vitreous floaters (0.19%); visual field defect (10 subjects, 0.62%); vitreous hemorrhage (0.06%); and xanthopsia (9 subjects, 0.56%) (a color vision deficiency in which there is a predominance of yellow in vision due to a yellowing of the optical media of the eye). Visual disturbances, as alluded to in Section 5 Warnings and Precautions

vision; night blindness; oscillopsia; photopsia; retinal detachment; retinal disorder; uveitis; vision blurred; visual acuity; visual brightness; visual field defect; and visual impairment.

### 8.5.3 Phototoxicity/Photosensitivity

The currently available VFEND USPI warns that VFEND has been associated with photosensitivity skin reactions and recommends that "Patients, including pediatric patients, should avoid exposure to direct sunlight during VFEND treatment and should use measures such as protective clothing and sunscreen." After conducting a CMQ that included select PT terms and SMQs, as well as, upon review of the Applicant's listing of all causality TEAEs in both pediatric and adult subjects, the reviewer identified a single PT term (PT: skin burning sensation) under the Skin and Subcutaneous Tissue Disorders SOC that was potentially suggestive of a photosensitivity reaction. The event was reported by Subject (b) (6) a 9 year old male, however, the details were limited and the terminology equivocal (as it could have also been reflective of a neuropathy). Eleven adults (0.69%) experienced TEAEs coded to the PT term photosensitivity reaction and 1 was coded to solar urticaria (0.06%). No such events were reported in the Phase 3 pediatric studies.

### 8.5.4 QTc Prolongation

Using the same above-mentioned approach, the reviewer noted that two pediatric patients were coded to PT terms loss of consciousness, syncope and presyncope (non-treatment emergent event). A total of two patients in the legacy and Phase 3 studies were coded as having a cardiac arrest or cardio-respiratory arrest; however, the single case of cardiac arrest in a patient in the Phase 3 trials (Subject (b) (6) was unrelated to VFEND therapy and was discussed in Section 8.4.1 Deaths above. A single patient each had a non-treatment emergent event coded to PT terms: ventricular extrasystoles and cardio-respiratory arrest. This is compared with adult subjects who experienced TEAEs coded to such PT terms as ECG QT prolonged (2 subjects, 0.12%); torsades de pointes (1 subject, 0.06%); ventricular arrhythmia (0.06%); ventricular extrasystoles (12 subjects, 0.75%); ventricular fibrillation (4 subjects, 0.25%); ventricular tachycardia (10 subjects, 0.62%) to name a few. As articulated in **Section 8.5.4 QTc Prolongation,** there were no subjects in the pediatric phase 3 trials who were observed on ECG to have a QTc interval of ≥ 500 msec (consistent with prolonged QTc).

### 8.5.5 Skin Cancers (Squamous Cell Carcinoma [SCC]/Non-SCC)

Upon conducting a CMQ containing select PTs and SMQs, this reviewer identified no TEAEs related to either squamous cell carcinoma (SCC) or non-SCCs among patients in the pediatric ISS population.

### 8.5.6 Peripheral neuropathy

The reviewer identified a total of three pediatric subjects with treatment emergent adverse events coded under PT terms related to the AESI peripheral neuropathy, including such terms as: paresthesias (3 subjects, 2.9%) (versus 1.3% [20 patients in adult subjects]). The PT terms hypoesthesia (1 subject); and neuritis (1 subject) occurred as non-treatment emergent events in the pediatric population. Additional PT terms, such as dysesthesia (2 subjects, 0.12%); hyperesthesia (0.12%); hypoesthesia (10 subjects, 0.62%); neuropathy, peripheral (8 subjects, 0.50%), peroneal nerve palsy (6 subjects, 0.37%); polyneuropathy (3 subjects, 0.19%); VIIth

nerve paralysis (0.06%); and VIth nerve paralysis (0.06%) were observed in adult subjects but not in any pediatric subjects enrolled in any of the Applicant's studies.

### 8.5.7 Suicide-related disorders

Upon review of TEAEs in the pediatric studies, the reviewer failed to identify any suicide-related disorders. However, TEAEs such as hallucinations (auditory and visual) (a total of 5 patients), anxiety (3 patients; 2.9%), and depression/depressed mood (5 patients; 4.8%) were coded under the Psychiatric Disorders SOC in the Phase 3 pediatric studies. Suicidal ideation and suicide attempt were coded in one patient each (0.06% for each event) among adult patients who received VFEND during the original registrational trials.

## 8.6 Safety Analyses by Demographic Subgroups

### Age

In spite of small numbers, which limited the ability to draw any meaningful age specific conclusions among the ISS population, adverse reactions between patients ages 2 to <12 years old and 12 to <18 year old were comparable.

### Sex

In all, the ISS population was comprised of 51 (49%) females and 54 (51%) males. There were no distinguishable sex-specific patterns of TEAEs observed among pediatric patients.

### Race/Ethnicity

The ISS was primarily comprised of White and Asian patients. Due to overall limited numbers of patients by racial and ethnic groups, it was difficult to draw any meaningful race or ethnic specific safety conclusions based on the ISS safety population.

# 8.8 Additional Safety Explorations

### 8.8.2 Human Reproduction and Pregnancy

Given the patient population, there were limited numbers of females of childbearing potential in the pediatric ISS population. This reviewer conducted a Pubmed search using search terms voriconazole in pregnancy and retrieved a single case report describing a 28-year-old woman who at 16 weeks of gestation developed aplastic anemia. This patient was subsequently hospitalized and on hospital day 12 she developed IA for which she received a course of voriconazole. Despite treatment with voriconazole, she delivered a healthy male infant at 35-weeks of gestation (Tehrani, MS; Antimicrob Agents Chemother Feb 2013).

There is limited data in the medical literature documenting the impact of VFEND in pregnant women. The VFEND label presently states that there are no adequate and well-controlled studies of VFEND in pregnant women.

### 8.8.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no accidental overdoses reported in the Phase 3 pediatric studies. VFEND is an antifungal agent with no drug abuse, drug withdrawal, or drug rebound potential.

## 8.9 Safety in the Postmarket Setting

### 8.9.1 Safety Concerns Identified Through Postmarket Experience

The Applicant reported conducting an evaluation of postmarketing reports, from 2002 through February 2017, in their safety database of reported AEs. They noted that the following adverse events were the most frequently cited:

- **Photosensitivity reactions** reported under the Skin and Soft Tissue SOC were the most commonly reported AEs among pediatric patients between the ages of 2 and 11 years, accounting for 16.5% of all cumulative pediatric AEs reported to the safety database. Both serious and non-serious events were reported. The Applicant notes that the current USPI warns that an increased incidence of photosensitivity reactions is observed among pediatric patients. The label recommends sun avoidance and dermatologic follow-up of pediatric patients with evidence of phototoxic skin damage or side effects.

- **Drug-Drug Interactions (DDI)** were also frequently identified in the Applicant's pediatric postmarket database and comprised 5.8% of all reported cumulative AEs. DDIs typically occurred upon co-administration of VFEND with medications which utilize similar metabolic pathways as VFEND, such as CYP2C19, -2C9 and -3A4. Cited medication culprits included vitamin A (in patients with cystic fibrosis) and methotrexate. The Applicant failed to identify any significant additional DDIs than what is already contained in the VFEND label. The most frequently reported AEs associated with DDIs included such PT terms as photosensitivity reaction and visual impairment.

- **Erythema** accounted for 4.6% of all cumulatively reported pediatric AEs. Both serious and non-serious events were coded to this PT. Most events reportedly resolved and had favorable outcomes. The Applicant reported that erythema was most commonly reported in patients 2 to 11 years old.

- **Additional Frequently Reported Pediatric Adverse Events** included PT terms such as visual impairment, drug ineffective, hallucination, liver function test abnormal, photophobia, ALT increased, convulsion, renal failure, vomiting, pyrexia, and vision blurred.

**Medical Reviewer's Comments**

*Post-marketing events reported to the Applicant's safety database from 2002 through February 2017 did not alter the existing knowledge of VFEND's safety profile and as such does not support any changes to the existing VFEND label. Most reported postmarket events are presently included in the USPI. Moreover, all such events have also been previously reported among adults.*

### 8.10 Integrated Assessment of Safety

The overall VFEND safety profile in pediatric patients aged 2 to <12 years old is comparable to the safety observed in adults and older children. This has been established through pediatric safety data collected from two non-comparative, open-label, multi-center pediatric studies (Studies A1501080 and A1501085) comprised of 53 patients infected with either IA, EC, or ICC as well as 52 pediatric patients ages 12 to <18 years old who were included in the original registrational trials. Despite limitations of study design and patient numbers, this reviewer concurs with the Applicant that the safety data included in this sNDA is similar to safety in adults and further supports an expansion of VFEND's indication for the treatment of IA (including serious fungal infections caused by *Scedosporium* and *Fusarium*), EC, and ICC from pediatric patients 12 years and older to pediatric patients ages 2 to and older.

It is noted that a marginally higher incidence of liver enzyme elevations and visual events were observed in pediatric patients relative to adults. This is consistent with what has been reported in the postmarketing setting among pediatric patients. Although not observed in the dedicated Phase 3 pediatric studies, an increased incidence of photosensitivity reactions have been observed in pediatric patients relative to adult patients and is incorporated in the existing VFEND label.

## 9 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not convened for this submission.

## 10 Labeling Recommendations

Key clinical changes to the Applicant's proposed label are addressed in this section. Each number below corresponds to a section in the label.

**Section 2 Dosage and Administration**

The Applicant proposed dosing for pediatric patients 2 to <12 years of age for the treatment of the following fungal infections: invasive aspergillosis, candidemia and other deep tissue *Candida* infections, esophageal candidiasis, serious fungal infections caused by *Scedosporium* and *Fusarium*. Pediatric subjects with hepatic and renal insufficiency were not evaluated in any of the pediatric PK studies and hence dosing recommendations for these pediatric subpopulations were not recommended.

***Medical Reviewer's Comments***
*This reviewer agrees with the Applicant's proposed labeling in this section. Although there were no subjects in either of the Phase 3 pediatric studies with Fusarium or Scedoporium, since the clinical course of these fungal infections in children is comparable to adults and the dosage regimens are similar to the treatment of IA, the recommended dosing recommendation for these infections will be similar to IA regimen.*

**Sections 5 Warnings and Precautions and Section 6 Adverse Reactions**

These sections address the higher incidence of hepatic and photosensitivity reactions observed among pediatric patients when compared to adults.

***Medical Reviewer's Comments***

*This reviewer finds the Applicant's overall proposed language and content for both Sections 5 and 6 for pediatric patients acceptable. The review team has proposed a table of Common adverse reactions observed at 5% and higher in the 105 pediatric patients comprising the ISS population. In addition, a listing of adverse reactions less than 5% was incorporated into Section 6.*

**Section 8 Use in Specific Populations**

This section indicates that VFEND safety and efficacy has not been established for pediatric patients younger than 2 years of age. This section further informs that established safety in children aged 2 to <12 was obtained from 105 patients stratified into two pediatric age groups: patients 2 to <12 years old and patients 12 to <18 years old. This section additionally reiterates that a higher incidence of liver enzyme elevations and phototoxicity reactions were observed among pediatric patients relative to adults.

***Medical Reviewer's Comments***

*This reviewer finds the Applicant's overall proposed language and content of Section 8.4 Pediatric Use for the pediatric population acceptable. The review team did propose additional revisions to this section of the label.*

**Section 14 Clinical Studies**

A description of the efficacy outcomes (global response) in the Applicant's Phase 3 non-comparative IA, ICC, and EC studies, as observed in the MITT populations, was provided in this section.

***Medical Reviewer's Comments***

*The review team amended the originally proposed language contained in this section and incorporated tables of global response rates in support of the Phase 3 pediatric efficacy findings.*

## 11 Risk Evaluation and Mitigation Strategies (REMS)

No new Risk Evaluation and Mitigation Strategies (REMS) were applicable to this submission.

## 12 Postmarketing Requirements and Commitments

With the submission of this sNDA, the Applicant has fulfilled their PREA postmarketing requirement (PMR).

# 13 Appendix

Clinical Investigator Financial Disclosure
Review Template

**Application Number:**

21-266 (oral tablets); 21-267 (IV for injection); 21-630 (oral suspension)

**Submission Date(s):** June 1, 2017

**Applicant:** Pfizer, Inc.

**Product:** Voriconazole (VFEND)

**Reviewer:** Caroline J. Jjingo, MD, MPH

**Date of Review:** 8 November 2017

**Covered Clinical Study** (Name and/or Number): **A1501080**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from applicant) |
| Total number of investigators identified: 50 | | |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: 1<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☒ | No ☐ (Request details from applicant) |

| | | |
|---|---|---|
| Is a description of the steps taken to minimize potential bias provided: | Yes ☒ | No ☐ (Request information from applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 111 with no financial interest in this product. There were two subjects for whom due diligence was performed to obtain disclosures from investigators (Dr. Jade Schiffman and Stella K. Kim). Page 8 of 12 of financial certification Section 1.3.4 | | |
| Is an attachment provided with the reason: | Yes ☒ | No ☐ (Request explanation from applicant) |

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[2] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

[2] See [web address].

**Clinical Investigator Financial Disclosure Review Template**

**Application Number:**

21-266 (oral tablets); 21-267 (IV for injection); 21-630 (oral suspension)

**Submission Date(s):** 1 June 2017

**Applicant:** Pfizer, Inc.

**Product:** Voriconazole (VFEND®)

**Reviewer:** Caroline J. Jjingo, MD, MPH

**Date of Review:** 8 November 2018

**Covered Clinical Study** (Name and/or Number): **A1501085**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from applicant) |
| Total number of investigators identified: 36 . This number includes previous site principal investigators. | | |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☒ | No ☐ (Request details from applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☒ | No ☐ (Request information from applicant) |

| | | |
|---|---|---|
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 55 investigators disclosed that they have no financial interests in this product. | | |
| Is an attachment provided with the reason: | Yes ☒ | No ☐ (Request explanation from applicant) |

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[3] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

[3] See [web address].

**Table 17:Study A1501080 Treatment Emergent Serious Adverse Events (SAEs), Subjects Ages 2 to <12 Years Old**

| Unique Subject Identifier | Age/Sex | System Organ Class | Dictionary Derived Term | Relatedness to Study Treatment | Severity | Action Taken | Duration of Study Treatment (days) | Study Day of Start of SAE | Study Day of End of SAE |
|---|---|---|---|---|---|---|---|---|---|
| **Ages 2 to <12 years old** | | | | | | | | | |
| (b) (6) | 3/M | Infections and Infestations | Pneumonia parainfluenzae, viral[a] | Not Related | Moderate | Drug Not Changed | 85 | 107 | 134 |
| | 6/F | Metabolism and nutrition Disorders | Hypokalemia | Not Related | Severe | Drug Not Changed | 18 | 1 | 3 |
| | 7/M | Infections and Infestations | Sepsis | Not Related | Moderate | Drug Withdrawn | 3 | 3 | 9 |
| | 8/M | Blood and Lymphatic System Disorders | Febrile neutropenia | Not Related | Severe | Drug Not Changed | 84 | 57 | 68 |
| | | | Febrile neutropenia | Not Related | Severe | Drug Not Changed | | 108 | 115 |
| | 8/F | Vascular Disorders | Aneurysm rupture | Not Related | Severe | Drug Not Changed | 18 | 18 | |
| | | Cardiac Disorders | Cardiac Arrest | Not Related | Severe | Drug Not Changed | | | |
| | 11/F | Infections and Infestations | Aspergillosis | Not Related | Severe | Drug Not Changed | 30 | 21 | 21 |
| | | | Septic Shock | Not Related | Severe | Drug Not Changed | | 28 | |
| | | | Disease Progression[a] | Not Related | | Drug Not Changed | | | |
| | | Gastrointestinal Disorders | Lower Gastrointestinal hemorrhage | Not Related | | Drug Not Changed | | 7 | 10 |
| | | Gastrointestinal Disorders | Lower Gastrointestinal hemorrhage | Not Related | Severe | Drug Not Changed | | 15 | 17 |
| | 11/F | Metabolism and nutrition Disorders | Hypoglycemia | Not Related | Severe | Drug Not Changed | 37 | 37 | not available |
| | | Blood and Lymphatic System Disorders | Neutropenia | Not Related | Severe | Drug Not Changed | | 35 | not available |
| | | Renal and Urinary Disorders | **Renal failure, acute[c]** | Related | Severe | Drug Not Changed | | 34 | not available |
| | | Infections and Infestations | Septic shock | Not Related | Severe | Drug Not Changed | | 37 | not available |

**Source:** ADSL and ADAE (AdAM data sets).
Footnotes: [a] Denotes a non-treatment emergent SAE. [b] Denotes subject had a fatal treatment emergent SAE. [c] Denotes an investigator assessed treatment related SAE, however, the clinical reviewer determined that there was a potential relationship between the SAE and VFEND therapy. [d] Denotes a patient who sustained non-treatment

| Unique Subject Identifier | Age/Sex | System Organ Class | Dictionary Derived Term | Relatedness to Study Treatment | Severity | Action Taken | Duration of Study Treatment (days) | Study Day of Start of SAE | Study Day of End of SAE |
|---|---|---|---|---|---|---|---|---|---|
| emergent SAEs (namely Subjects: (b) (6) | | | | | | | | | |

**Table 18: Study A1501080 Treatment Emergent Serious Adverse Events (SAEs), Subjects Ages 12 to <18 Years Old**

| Unique Subject Identifier | Age/Sex Country | System Organ Class | Dictionary Derived Term | Severity | Duration of Treatment | Study Start Day of AE | Study End Day of AE | Related | Action Taken with the Study Drug |
|---|---|---|---|---|---|---|---|---|---|
| (b) (6) | 12/F USA | Respiratory, thoracic and mediastinal Disorders | Pleural effusion | Moderate | 87 | 41 | 153 | Not Related | Dose not changed |
| | 12/F Singapore | Blood and Lymphatic System Disorders | Febrile neutropenia[a] | Moderate | 9 | 22 | 25 | Not Related | Dose not changed |
| | | General Disorders and Administration | Pyrexia[a] | Moderate | | 35 | 39 | Not Related | Dose not changed |
| | 12/M Poland | Nervous System Disorders | Loss of consciousness | Moderate | 84 | 40 | 40 | Not Related | Dose not changed |
| | 13/M Netherlands | Blood and Lymphatic System Disorders | Febrile neutropenia | Severe | 59 | 66 | 72 | Not Related | Dose not changed |
| | 13/F Thailand | Blood and Lymphatic System Disorders | Febrile neutropenia[a] | Severe | 75 | 54 | Not available | Not Related | Dose reduced |
| | | Blood and Lymphatic System Disorders | Thrombocytopenia | Severe | | 55 | Not available | Not Related | Dose reduced |
| | | Cardiac Disorders | Cardiac failure congestive | Moderate | | 73 | Not available | Not Related | Dose not changed |
| | | Gastrointestinal Disorder | Upper gastrointestinal hemorrhage | Mild | | 55 | 56 | Not Related | Dose reduced |
| | | Infections and Infestations | Pneumonia | Severe | | 72 | Not available | Not Related | Dose reduced |
| | | Infections and Infestations | Septic Shock | Severe | | 54 | 57 | Not Related | Dose reduced |
| | | Neoplasm benign | Acute lymphocytic leukemia | Severe | | 72 | Not available | Not Related | Dose reduced |
| | | Renal and Urinary Disorders | Renal failure, acute | Mild | | 55 | 60 | Not Related | Dose reduced |

| Unique Subject Identifier | Age/Sex Country | System Organ Class | Dictionary Derived Term | Severity | Duration of Treatment | Study Start Day of AE | Study End Day of AE | Related | Action Taken with the Study Drug |
|---|---|---|---|---|---|---|---|---|---|
| (b) (6) | 13/F USA | Injury, poisoning and procedural complications | Contusion[a] | Moderate | 82 | 107 | Not available | Not Related | Dose not changed |
| | | Injury, poisoning and procedural complications | Joint Injury[a] | Moderate | | 107 | 122 | Not Related | Dose not changed |
| | | General Disorders and Adminstration | Pneumatosis[a] | Severe | | 107 | 122 | Not Related | Dose not changed |
| | 14/F USA | Surgical and medical procedures | Endotracheal intubation | Severe | 20 | 1 | 4 | Not Related | Dose not changed |
| | 14/M Thailand | Hepatobiliary Disorders | **Drug induced liver injury[c]** | **Severe** | 40 | **40** | **64** | **Related** | Dose not changed |
| | | Musculoskeletal and Connective Tissues Disorders | Muscular weakness | Severe | | 34 | 61 | Not Related | Dose not changed |
| | 15/M Singapore | Gastrointestinal Disorders | Gingival bleeding | Severe | 85 | 30 | 31 | Not Related | Dose not changed |
| | | Infections and Infestations | Hepatic candidiasis[a] | Moderate | | 94 | Not available | Not Related | Dose not changed |
| | | Infections and Infestations | Liver abscess[a] | Severe | | 94 | Not available | Not Related | Dose not changed |
| | 15/F Czech Republic | Respiratory, thoracic and mediastinal Disorders | Epistaxis[a] | Severe | 5 | 24 | 25 | Not Related | Dose not changed |
| | | Blood and Lymphatic System Disorders | Febrile neutropenia[a] | Severe | | 27 | 35 | Not Related | Dose not changed |
| | 15/F Netherlands | Blood and Lymphatic System Disorders | Coagulopathy | Moderate | 10 | 12 | Not available | Not Related | Dose not changed |

| Unique Subject Identifier | Age/Sex Country | System Organ Class | Dictionary Derived Term | Severity | Duration of Treatment | Study Start Day of AE | Study End Day of AE | Related | Action Taken with the Study Drug |
|---|---|---|---|---|---|---|---|---|---|
| | | Respiratory, thoracic and mediastinal Disorders | Respiratory failure | Severe | | 11 | 19 | Not Related | Dose not changed |
| | | Infections and Infestations | Sepsis | Severe | | 11 | 21 | Not Related | Dose not changed |
| | | Gastrointestinal Disorders | Small intestinal hemorrhage | Severe | | 11 | 23 | Not Related | Dose not changed |
| (b) (6) | 16/F Spain | Blood and Lymphatic System Disorders | Pancytopenia[a] | Severe | 5 | 32 | 43 | Not Related | Dose not changed |
| | 16/M Thailand | Respiratory, thoracic and mediastinal Disorders | Pulmonary edema | Severe | 19 | 18 | Not available | Not Related | Dose not changed |
| | | Infections and Infestations | Septic Shock | Severe | | 19 | Not available | Not Related | Dose not changed |
| | 17/M Singapore | Neoplasm, benign, malignant | Acute lymphocytic leukemia | Severe | 62 | 46 | Not available | Not Related | Dose not changed |
| | | Blood and Lymphatic System Disorders | Febrile neutropenia | Severe | | 64 | 72 | Not Related | Dose not changed |
| | | Vascular Disorders | Hypotension[a] | Severe | | 77 | 82 | Not Related | Dose not changed |
| | | Infections and Infestations | Neutropenic sepsis | Severe | | 77 | 82 | Not Related | Dose not changed |
| | | Infections and Infestations | Sepsis | Severe | | 89 | 91 | Not Related | Dose not changed |
| | | Eye disorders | Visual impairment | Severe | | 54 | Not available | Not Related | Dose not changed |

**Source:** ADSL and ADAE (AdAM data sets).

| Unique Subject Identifier | Age/Sex Country | System Organ Class | Dictionary Derived Term | Severity | Duration of Treatment | Study Start Day of AE | Study End Day of AE | Related | Action Taken with the Study Drug |
|---|---|---|---|---|---|---|---|---|---|
| Footnotes: [a] Denotes a non-treatment emergent SAE. [b] Denotes subject had a fatal treatment emergent SAE. [c] Denotes an investigator assessed treatment related SAE, that the clinical reviewer also determined was potentially related to VFEND therapy. [d] Denotes a patient who sustained non-treatment emergent SAEs (namely Subjects: (b) (6) ). | | | | | | | | | |

**Table 19: Study A1501085 Treatment Emergent Serious Adverse Events (SAEs), Subjects Ages 2 to <12 Years Old**

| Unique Subject Identifier | Age (years)/Sex | System Organ Class | Dictionary Derived Term | Duration of Study Treatment | SAE Start Date/ (Study Day) | SAE End Date/ (Study Day) | Severity | Related | Action Taken with the Study Drug |
|---|---|---|---|---|---|---|---|---|---|
| **Patients Aged 2 to <12 years old** | | | | | | | | | |
| (b) (6) | 2/M Hong Kong | Blood and lymphatic system disorders | Febrile neutropenia[a] | 8 | (48) | (55) | Mild | Not Related | Dose not changed |
| | 5/M Czech Republic | Blood and lymphatic system disorders | Febrile neutropenia | 23 | (18) | (26) | Moderate | Not Related | Dose not changed |
| | 9/F Mexico | Infections and Infestations | Pneumonia | 12 | (4) | (15) | Severe | Not Related | Dose not changed |
| | 9/M Czech Republic | Nervous Systems Disorders | Posterior reversible encephalopathy syndrome[a] | 6 | (33) | (33) | Severe | Not Related | Dose not changed |
| | 10/M Hong Kong | Blood and lymphatic system disorders | Febrile neutropenia[a] | 42 | (63) | (75) | Severe | Not Related | Dose not changed |
| | | Infections and Infestations | Klebsiella bacteraemia[a] | | (63) | (75) | Severe | Not Related | Dose not changed |

**Source:** ADSL and ADAE (AdAM) data sets

**Table 20: Study A1501085 Treatment Emergent Serious Adverse Events (SAEs)**

| Unique Subject Identifier | Age (years)/Sex | Country | System Organ Class | Dictionary Derived Term | Duration of Study Treatment | Study Day of Start of SAE (Day) | Study Day of End of SAE (Day) | Severity | Related | Action Taken with the Study Drug |
|---|---|---|---|---|---|---|---|---|---|---|
| **Patients Ages 12 to <18 years** | | | | | | | | | | |
| (b) (6) | 12/F | Czech Republic | Infections and Infestations | Splenic candidiasis (hospitalization) | 17 | (17) | (390) | Severe | Not related (efficacy related not safety) | **Drug withdrawn** |
| (b) (6) | 12/F | Czech Republic | Gastrointestinal Disorders | Stomatitis(hospitalization)[a] | 8 | (18) | (24) | Moderate | Not related | Dose not changed |
| | 14/M | Hong Kong | Blood and lymphatic System Disorders | Febrile neutropenia[a] | 14 | (25) | (52) | Severe | Not related | Dose not changed |
| | 14/F | Mexico | Vascular Disorders | Shock[a] | 6 | (67) | (72) | Severe | Not related | Dose not changed |
| | 15/F | Mexico | Infections and Infestations | Esophageal candidiasis[a] | 14 | (30) | (40) | Severe | Not related | Dose not changed |
| | 16/F | Hungary | Infections and Infestations | Febrile infection[a] | 14 | (34) | (40) | Moderate | Not related | Dose not changed |

**Source:** ADSL and ADAE (AdAM) data sets
**Footnotes:** [a] Denotes a non-treatment emergent SAE. [b]Denotes a patient who sustained a non-treatment emergent SAE (Subject: (b) (6)

**Table 21: Study A1501080 Treatment Emergent Adverse Events Resulting in Drug Discontinuation or Dose Reductions**

| Unique Subject Identifier | Age (years)/Sex | System Organ Class | Dictionary Derived Term | SAE Start Date (Study Day) | SAE End Date/ (Study Day) | Serious | Related | Severity | Action Taken with the Study Drug |
|---|---|---|---|---|---|---|---|---|---|
| **Ages 2 to <12 years old** | | | | | | | | | |
| (b) (6) | 7/M Netherlands | Infections and Infestations | Sepsis | (3) | (9) | Yes | Not Related | Moderate | Dose withdrawn |
| **Ages 12 to <18 years old** | | | | | | | | | |
| (b) (6) | 12/M Thailand | Investigations | ALT increased | (20) | (28) | No | Related | Moderate | Dose interrupted |
| (b) (6) | 13/F Thailand | Neoplasms, Benign, Malignant, and Unspecified | Acute lymphocytic leukemia | (72) | (missing) | Yes | Not Related | Severe | Dose reduced |
| | | Blood and lymphatic System Disorders | Febrile neutropenia | (54) | (missing) | Yes | Not Related | Severe | Dose reduced |
| | | Infections and Infestations | Pneumonia | (72) | (missing) | Yes | Not Related | Severe | Dose reduced |
| | | Renal and Urinary Disorders | Renal failure, acute | (55) | (60) | Yes | Not Related | Mild | Dose reduced |
| | | Infections and Infestations | Septic shock | (54) | (57) | Yes | Not Related | Severe | Dose reduced |
| | | Blood and lymphatic System Disorders | Thrombocytopenia | (55) | (missing) | Yes | Not Related | Severe | Dose reduced |
| | | Gastrointestinal Disorders | Gastrointestinal hemorrhage, upper | (55) | (56) | Yes | Not Related | Mild | Dose reduced |
| (b) (6) | 14/F USA | Investigations | Liver function test abnormal | (13) | (14) | No | Related | Moderate | Dose reduced |
| | 17/M Singapore | Investigations | Transaminases increased | (12) | (15) | No | Related | Mild | Dose reduced |

**Source:** ADSL and ADAE (AdAM) data set

**Table 21: Study A1501085 Treatment Emergent Adverse Events Resulting in Drug Discontinuation or Dose Reductions**

| Unique Subject Identifier | Age (years)/Sex | System Organ Class | Dictionary Derived Term | Duration of Study Treatment | SAE Start Date/ (Study Day) | SAE End Date/ (Study Day) | Action Taken with the Study Drug | Serious | Related | Severity |
|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Withdrawals (Ages 2 to <12 years old)** | | | | | | | | | | |
| (b) (6) | 5/M Czech Republic | Hepatobiliary Disorders | Liver disorder | 23 | (23) | (27) | **Drug withdrawn** | No | Related | Severe |
| | 9/F Mexico | Hepatobiliary Disorders | Hyperbilirubinemia | 12 | (11) | (17) | **Drug withdrawn** | No | Related | Moderate |
| **Treatment Reductions (Ages 2 to <12 years old)** | | | | | | | | | | |
| (b) (6) | 5/M Czech Republic | Hepatobiliary Disorders | Liver disorder | 23 | (22) | (23) | Dose Reduced | No | Related | Mild |
| | 6/M China | Investigations | Hepatic enzyme increased | 8 | (8) | (43) | Dose Reduced | No | Related | Mild |
| | 11/M | Investigations | ALT abnormal | 40 | (5) | (18) | Dose Reduced | No | Related | Moderate |
| | | | AST abnormal | | (5) | (18) | Dose Reduced | No | Related | Moderate |
| | | | GGT abnormal | | (5) | (18) | Dose Reduced | No | Related | Moderate |
| **Treatment Withdrawals (Ages 12 to <18 years old)** | | | | | | | | | | |
| (b) (6) | 12/F Czech Republic | Infections and Infestations | Splenic candidiasis | 17 | (17) | (390) | **Drug withdrawn** | Yes | Related | Severe |
| | 14/F Mexico | Infections and Infestations | Bronchopulmonary aspergillosis | 6 | (5) | Missing | **Drug withdrawn** | No | Not Related | Severe |

**Source:** ADSL and ADAE (data set)

**Table 22: Tabular Summary of Registrational Trials**

| Trial Number | Phase | Trial Design | Regimen/Schedule/ Route | Treatment Duration/ Follow-Up | Study Endpoints | Number of Patients Enrolled | Study Population | Number of Centers and Countries |
|---|---|---|---|---|---|---|---|---|
| **Aspergillosis** | | | | | | | | |
| **150-303** | Phase 2/3 | **Non-comparative**, Open-Label, Multicenter of voriconazole in patients with chronic fungal infections study of primary and salvage therapy for Aspergillosis | | | | 31 patients enrolled; Safety population: 30 subjects | Pediatric Patients: age 12 to <18 years with Invasive Aspergillosis N=2 | Europe |
| **150-304** (January 1994 to July 1996) | Phase 2/3 | **Non-comparative**, Open-Label, Multicenter of IV and oral voriconazole in immunocompromised patients with acute invasive aspergillosis with or without previous anti-fungal treatment | | **Total duration:** 4-24 week | | 31 patients enrolled; Safety population: 30 subjects | Pediatric Patients: age 12 to <18 years with Invasive Aspergillosis<br><br>N=4 | Europe |
| **307-602 (combined)**<br>**307:** (July 1997 to February 2001)<br>**602:** (September 1997 to June 2001) | | **Comparative**, Randomized, Open-Label, Multicenter of voriconazole versus amphotericin B in immunocompromised patients with acute invasive aspergillosis followed by other | Voriconazole: 200-mg by mouth every 12 hours Fluconazole: 400-mg x 24 hours, followed by 200-mg once daily | **Total duration:** maximum of 12 weeks | **Primary End Point:** Global response at Week 12 as assessed by the data review committee | **Voriconazole:** 196 subjects randomized/ 116 completed study **Amphotericin B:** 185 subjects randomized/88 completed study | **Eligible Patient** Population: 12 years and older with a diagnosis of definite or probable acute invasive aspergillosis **Pediatric Patients:** N= 3 | **307:** Australia, Europe, Israel **602:** Canada, India, South America, |

| Trial Number | Phase | Trial Design | Regimen/Schedule/ Route | Treatment Duration/ Follow-Up | Study Endpoints | Number of Patients Enrolled | Study Population | Number of Centers and Countries |
|---|---|---|---|---|---|---|---|---|
| | | licensed antifungal therapy (OLAT) | | | | | | United States |
| **Candidiasis** | | | | | | | | |
| **150-305** (September 1995 to January 1999) | | **Comparative,** double-blind, double- dummy randomized, multicenter study of voriconazole and fluconazole in the treatment of esophageal candidiasis | **Voriconazole:** 200-mg by mouth every 12 hours **Fluconazole:** 400-mg x 24 hours, followed by 200-mg once daily | **Total duration:** 2-6 weeks | **Primary End Point:** Non-inferiority of voriconazole to fluconazole in the treatment of *Candida* esophagitis in immunocompromised patients at EOT (success) | **Voriconazole:** 200 randomized subjects/131 completed study **Fluconazole:** 191 randomized/ 136 completed the study | **Eligible Patients:** 18 years and older, immunocompromised with *Candida* esophagitis N=0 (no pediatric patients) | Australia, Europe, Russia, Singapore, South Africa, Thailand, |
| **150-309** (July 1998 to October 2000) | **Phase 3** | **Non-comparative**, Open-Label, Multicenter of voriconazole in patients with systemic and invasive fungal failing or intolerant of treatment with approved antifungal agents | **Intravenous (IV) loading dose:** 6-mg/kg every 12 hours x 24 hours (x 2 doses) **Maintenance dose:** (4) OR 3-mg/kg every 12-hours IV **Oral dosing:** Loading dose: 400-mg every 12 hours x 24 hours (x 2 doses) Maintenance dose: 200-mg by mouth twice daily | **Total duration:** 12 weeks (maximum) [potentially longer if deemed necessary by investigator] | **Primary End Point: Investigator evaluated** Global response (complete, partial, stable, or failure) at End of therapy (EOT)/Week 16 based on overall clinical, mycological, radiological, and serological responses | 166 randomized/(73) 74 completed study; Safety population: 166 | **Eligible** Patients: 12 years and older N= 12 | Australia; Europe |
| **150-604** (December 1997 to June 2000) | **Phase 3** | **Non-comparative**, Open-Label, Multicenter of voriconazole in patients with systemic | **Intravenous (IV) loading dose:** 6-mg/kg every 12 hours x 24 hours (x 2 doses) | **Total duration:** 12 weeks (maximum) | **Primary End Point: Investigator evaluated** Global response (complete, partial, stable, or | 206 patients randomized/ 94 completed study Safety | **Eligible Patients:** 12 years and older Pediatric Patients: N= 13 | United States, Canada, Thailand |

| Trial Number | Phase | Trial Design | Regimen/Schedule/ Route | Treatment Duration/ Follow-Up | Study Endpoints | Number of Patients Enrolled | Study Population | Number of Centers and Countries |
|---|---|---|---|---|---|---|---|---|
| | | and invasive fungal failing or intolerant of treatment with approved antifungal agents | **Maintenance dose:** (4) OR 3-mg/kg every 12-hours IV **Oral dosing:** *Patients (weighing ≥ 40 kg):* Loading dose: 400-mg every 12-hours x 24 hours (x 2 doses) **Maintenance dose:** 200-mg by mouth twice daily *Patients (weighing < 40 kg):* **Loading dose:** 200-mg x 12 hours x 24 hours (x 2 doses) **Maintenance dose:** 100-mg by mouth twice daily **Amphotericin B:** 0.7mg/kg/day x 3-7 days, followed by fluconazole IV or oral minimum dose of 400-mg/day | | failure) at End of therapy (EOT)/Week 16 based on overall clinical, mycological, radiological, and serological responses | population: 206 subjects | | |
| **150-608** | | **Comparative**, Randomized, Open-Label Multicenter study of voriconazole versus conventional | **Intravenous (IV):** Loading dose: 6-mg/kg every 12 hours x 24 hours (x 2 doses) | **Total duration:** Dosing continued until 2 weeks | **Primary End Point:** Clinical Response (cure, improvement, or failure) at Week 12 follow-up visit in the | **Voriconazole:** 110 subjects randomized/40 subjects completed | Pediatric Patients: age 2 to <18 years with Invasive Aspergillosis N= 5 | Europe |

| Trial Number | Phase | Trial Design | Regimen/Schedule/ Route | Treatment Duration/ Follow-Up | Study Endpoints | Number of Patients Enrolled | Study Population | Number of Centers and Countries |
|---|---|---|---|---|---|---|---|---|
| | | amphotericin followed by fluconazole (2:1 ratio) in the treatment of candidemia in non-neutropenic patients | Maintenance dose: 3-mg/kg every 12-hours IV<br>**Oral dosing:**<br>*Patients (weighing ≥ 40 kg):*<br>Loading dose: 400-mg every 12-hours x 24 hours (x 2 doses)<br>Maintenance dose: 200-mg by mouth twice daily<br>*Patients (weighing < 40 kg):*<br>Loading dose: 200-mg x 12 hours x 24 hours (x 2 doses)<br>Maintenance dose: 100-mg twice daily<br>**Amphotericin B:** 0.7mg/kg/day x 3-7 days, followed by fluconazole IV or oral minimum dose of 400-mg/day | after resolution of infection | MITT population as assessed by the data review committee assessment of response to an | treatment<br>**Amphotericin B/ Fluconazole:** 52 randomized/ 20completed treatment | | |
| **150-603** | | **Comparative**, Open-Label, Multicenter of voriconazole with liposomal amphotericin B in the empirical treatment of | **Intravenous (IV):**<br>Loading dose: 6-mg/kg every 12 hours x 24 hours (x 2 doses)<br>Maintenance dose: | **Total duration:** 12 weeks | **Primary End Point:** Composite endpoint of overall response (success vs failure) deaths and discontinuations due to | **Voriconazole:** 421 subjects randomized/310 subjects completed treatment | Patients with neutropenia induced by cancer chemotherapy or bone marrow/ | United States and Canada |

| Trial Number | Phase | Trial Design | Regimen/Schedule/ Route | Treatment Duration/ Follow-Up | Study Endpoints | Number of Patients Enrolled | Study Population | Number of Centers and Countries |
|---|---|---|---|---|---|---|---|---|
| | | immunocompromised patients with persistent fever and neutropenia (1:1 ratio) (IA and ICC) | 3-mg/kg every 12-hours IV x (minimum of 3 days)<br>**Oral dosing:**<br>200-mg by mouth twice daily ≥ 40 kg<br>100-mg by mouth twice daily <40-kg<br>**Amphotericin B (liposomal):** 3-mg/kg/day | | toxicity or lack of efficacy | **Amphotericin B:** 428 randomized/ 335 completed treatment | peripheral stem cell transplantation ages 12 and older<br>Pediatric Patients: N= 13 | |

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/s/

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