U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	21266 /S-039
	21267 / S-050
	21630 / S-029
Drug Name:	Vfend (voriconazole) Tablets
	Vfend (voriconazole) Injection
	Vfend (voriconazole) Oral Suspension
Indication(s):	Pediatric labeling for the treatment of invasive aspergillosis, candidemia, esophageal candidiasis, and infections caused by *Scedosporium* spp. and *Fusarium* spp.
Applicant:	Pfizer
Date(s):	Stamp date: Original submission November 30, 2015
	Resubmission after withdrawal June 1, 2017
	PDUFA date: December 1, 2017
	Review date: November 3, 2017
Review Priority:	Priority
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Keywords: clinical studies, pediatrics, invasive fungal infections

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1 EXECUTIVE SUMMARY

In this submission, the Applicant is seeking the approval of Vfend (voriconazole) dosing recommendations for the pediatric population (2 to< 18 years) for the indications previously approved for the adult population. The evidence of efficacy of voriconazole in the pediatric population is primarily based on extrapolation from the known efficacy in adults. Limited efficacy data for the pediatric population is provided by 2 non-comparative trials. Study A1501080 was a trial to evaluate the safety, tolerability and efficacy of voriconazole in pediatric subjects 2 to < 18 years of age with invasive fungal infection due to *Aspergillus* and Study A1501085 was a trial to evaluate the safety, tolerability and efficacy of voriconazole in pediatric subjects 2 to < 18 years of age with invasive candidiasis/candidemia (ICC) or esophageal candidiasis (EC).

Study A1501080 enrolled 31 patients with proven, probable, or possible invasive aspergillosis (IA). Fourteen of the 31 patients had proven or probable IA and were included in the modified intent to treat (mITT) population. Of these 14 patients, 5 were 2 to < 12 years old and 9 were 12 to < 18 years old. A successful global response was defined as resolution or improvement in clinical signs and symptoms and at least 50% resolution of radiological lesions attributed to IA. The overall rate of successful global response at 6 weeks was 64% (9/14). By age group, the rate of successful global response at 6 weeks was 40% (2/5) for patients aged 2 to < 12 years and 78% (7/9) for patients aged 12 to < 18 years.

Study A1501085 enrolled 22 patients with ICC or EC requiring either primary or salvage therapy. Seventeen of the 22 patients had confirmed *Candida* infection and were included in the mITT population. Of these 17 patients, 9 were 2 to < 12 years old (7 with ICC and 2 with EC) and 8 were 12 to < 18 years old (all with EC). For ICC and EC, a successful global response was defined as clinical cure or improvement with microbiological eradication or presumed eradication. The overall rate of successful global response at end of treatment (EOT) was 86% (6/7) for patients with ICC and 70% (7/10) for patients with EC. All patients with ICC were aged 2 to < 12 years. By age group for patients with EC, the rate of successful global response at EOT was 100% (2/2) for patients aged 2 to < 12 years and 63% (5/8) for patients aged 12 to < 18 years.

Given the similarity in the infections in the adult and pediatric population, efficacy in the pediatric population for IA and ICC/EC is primarily extrapolated from the efficacy results for the adult population. The limited data provided for the pediatric population in the non-comparative studies A1501080 and A1501085, indicate rates of global response consistent with the known global response profile of voriconazole in adult subjects with IA and ICC/EC, respectively and do not provide evidence to suggest that extrapolation of efficacy from adults is not appropriate.

2 INTRODUCTION

2.1 Overview

This is a supplemental NDA submission for the Vfend NDAs. The purpose of these supplemental NDAs is to update the Vfend pediatric dosing recommendations and pharmacokinetic information based on the results of two Phase 3 trials. Study A1501080 was a non-comparative, descriptive study to evaluate the safety, tolerability and efficacy of voriconazole in pediatric subjects 2 to < 18 years of age with invasive fungal infection due to *Aspergillus*, *Scedosporium*, or *Fusarium* spp. Study A1501085 was a non-comparative, descriptive study to evaluate the safety, tolerability and efficacy of voriconazole in pediatric subjects 2 to < 18 years of age with invasive candidiasis, candidemia, or esophageal candidiasis. In Study A1501085, voriconazole could be given as primary or salvage therapy. The primary objective of both trials was to assess the safety and tolerability of voriconazole. The assessment of efficacy was a secondary objective in both trials. Both trials were conducted to satisfy a Post Marketing Commitment following the approval of the original Vfend NDAs.

Table 1
Listing of Studies Included in Review

Protocol	Phase and Design	Dosing Regimen/ Duration of Treatment	# of Subjects per Arm	Study Population
A1501080	Phase 3 multi-center, uncontrolled	Dose dependent on age and weight; IV for first week then switch to oral allowed; minimum of 6 weeks to a maximum of 12 weeks	31 Voriconazole	Pediatric subjects aged 2 to < 18 years with IFI due to *Aspergillus*, *Scedosporium*, or *Fusarium* spp
A1501085	Phase 3 multi-center, uncontrolled	Dose dependent on age and weight; IV for at least 5 days then switch to oral allowed; duration for at least 14 days following last positive culture for ICC or at least 7 days after resolution of signs and symptoms for EC to a maximum of 42 days	22 voriconazole	Pediatric subjects aged 2 to < 18 years with ICC or EC

ICC: Invasive candidiasis/candidemia; EC: Esophageal candidiasis

2.2 Data Sources

The data analyzed in this review comes from the two Phase 3 trials submitted as the evidence to support the pediatric dosing recommendations for the approved adult indications. The final A1501080 and A1501085 Study Reports, and datasets for the two studies were reviewed. The study reports can be found in the electronic submission located at: \\CDSESUB1\evsprod\NDA021266\0084\m5\53-clin-stud-rep\535-rep-effic-safety-stud . The datasets for the study reports can be found in the electronic submission located at: \\CDSESUB1\evsprod\NDA021266\0094\m5\datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The datasets submitted were of acceptable quality. Minimal programming was necessary to reproduce the results presented by the Applicant.

Reviewer's Comment: *Unless otherwise indicated, tables presented in this review are based on analyses conducted by this reviewer using the analysis datasets submitted by the Applicant and confirm the results of those presented by the Applicant in the A1501080 and A1501085 Study Reports.*

3.2 Evaluation of Efficacy

3.2.1 Study A1501080

3.2.1.1 Study Design and Endpoints

A1501080 was a Phase 3, multicenter, non-comparative study designed to describe the safety, tolerability, and efficacy of voriconazole in pediatric subjects from 2 to < 18 years of age who had invasive aspergillosis (IA) or rare molds such as *Scedosporium* or *Fusarium.* The study was conducted at 42 investigational sites of which 15 sites enrolled subjects. The sites that enrolled subjects included 5 in the United States, 3 in Thailand, 2 in Singapore, 2 in Spain, 1 in Poland, 1 in the Netherlands, and 1 in the Czech Republic.

Subject eligibility was determined at the screening visit. Males or females aged 2 to < 18 years of age with a diagnosis of proven or probable IA (based on a modified version of the revised European Organization for Research and Treatment of Cancer/Mycoses Study Group [EORTC)/MSG] consensus definitions) or a diagnosis of infection due to *Scedosporium* or *Fusarium* spp. were eligible for enrollment. Subjects with possible IA could be enrolled in the study but needed to be upgraded to proven or probable within 1 week to remain in the trial. Subjects with sarcoidosis, aspergilloma, or allergic bronchopulmonary aspergillosis; chronic IA; who received more than 96 hours of systemic antifungal treatment for the current episode of infection; or were not expected to survive for at least 5 days were not eligible.

All subjects received voriconazole therapy for at least 6 weeks up to a maximum of 12 weeks. Voriconazole was administered IV for the first week of therapy. When clinical improvement was noted, subjects could be switched to oral voriconazole therapy (tablet or suspension) at the discretion of the investigator. Dosing was dependent on age and weight as described in Table 2.

Table 2
A1501080
Voriconazole Dosing

	Loading Dose	Maintenance Dose	
	IV	IV	Oral
Children (2 to < 12 years) and young adolescents (12 to 14 years weighing < 50 kg)	9 mg/kg IV every 12 hours for first 24 hours	8 mg/kg IV every 12 hours	9 mg/kg PO every 12 hours (maximum dose 350 mg)
Adolescents (12 to < 18 years) excluding 12 to 14 years weighing < 50 kg	6 mg/kg IV every 12 hours for first 24 hours	4 mg/kg IV every 12 hours	200- 300 mg PO every 12 hours

Source: Table 2 of A1501080 Study Report

Study visits occurred at baseline, Weeks 1, 2, 4, 6, and 12, end of treatment (EOT) which could occur any day between Week 6 and 12, and follow-up 1 month after EOT. Adverse events were monitored throughout the study. Hematology and blood chemistry were assessed at screening and all post baseline study visits. Complete physical exams were conducted at screening, Week 12 or EOT, and the 1 month follow-up visit and a targeted physical exam was conducted at the remaining visits. Clinical signs and symptoms were evaluated at baseline, Weeks 1, 2, 4, 6, and 12 or EOT. Radiological assessments were done at baseline, Week 6, and Week 12 or EOT.

The primary objective of the study was to evaluate the safety and tolerability of 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. The secondary objective of the study was to describe the response to therapy with 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.

Primary endpoints were based on the safety and tolerability. Secondary endpoints were the rate of global response at 6 weeks and EOT, all cause and attributable mortality at 6 weeks and EOT, and time to death. A successful global response was defined as 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 was defined as stable disease (i.e., 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). Exploratory endpoints were a description of the serum *Aspergillus* galactomannan antigenemia at EOT in relation to global response, the effect of duration of IV dosing on estimated creatinine clearance, the effect of IV and oral dosing duration on changes in LFT values, the relationship between the voriconazole concentration and the efficacy and safety endpoints, and the correlation between CYP2C19 genotype status and voriconazole exposure.

3.2.1.2 Statistical Methodologies

All efficacy analyses were descriptive and no statistical tests of hypotheses were performed. Results were presented by age group (age 2 to < 12 years or 12 to < 18 years) as well as overall. The rate of global response was presented with exact 95% confidence interval for the binomial proportion using the Clopper-Pearson method. Subjects with missing data were treated as failures.

The primary efficacy analysis population was the modified intent to treat (mITT) population. The mITT population was defined as all subjects who received at least 1 dose of study drug and who were diagnosed with proven or probable IA as defined by the modified EORTC/MSG criteria. Any subject who had *Scedosporium* or *Fusarium* infection microbiologically confirmed from the local or central laboratory and who received at least 1 dose of study drug was evaluable for the efficacy endpoints for these molds.

The safety population was defined as all subjects who received at least 1 dose of study medication. This population was used for all safety analyses which were descriptive and based on rates of discontinuation, adverse events, laboratory abnormalities, ECG changes, vital sign changes, and changes in visual assessments.

No statistical computations were used to determine the sample size. A total of 36 subjects was targeted to have a minimum of 15 evaluable subjects diagnosed with proven or probable IA. A minimum of 10 subjects were to be enrolled in the 2 to < 12 years of age group.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

Overall 31 subjects were enrolled into the study and received treatment with voriconazole, 25 subjects completed the study, and 16 subjects completed treatment. Of the 6 subjects who discontinued the study, 5 subjects died and 1 declined further participation in the study. Of the 15 subjects who discontinued treatment, 5 discontinued due to death, 1 due to insufficient clinical response, 1 due to an adverse event of sepsis, 1 declined further participation in the study, 5 because IA was not confirmed, 1 due to the need for combination antifungal therapy, and 1 was discontinued because required visual safety tests could not be completed. Reasons for discontinuation from the study and treatment are summarized in Table 3.

Table 3
A1501080
Patient Disposition

	Age 2 to < 12 years	Age 12 to < 18 years	Overall
Enrolled/treated	11	20	31
Completed Study	8	17	25
Discontinued Study	3	3	6
Died	3	2	5
Subject's request	0	1	1
Discontinued Treatment	6	9	15
Died	3	2	5
Insufficient clinical response	1	0	1
Adverse Event	1	0	1
Subject's request	0	1	1
IA not confirmed	0	5	5
Need for combination antifungal therapy	0	1	1
Incomplete visual safety tests	1	0	1

All subjects enrolled received treatment and are included in the Safety Population. Fourteen subjects were diagnosed with proven or probable IA and were included in the mITT population. No subjects were enrolled with *Scedosporium* or *Fusarium* infections.

Table 4
A1501080
Analysis Populations

	Age 2 to < 12 years	Age 12 to < 18 years	Overall
Safety	11	20	31
mITT Population	5	9	14

Table 5 summarizes the demographic and baseline characteristics of the Safety and mITT populations. Overall, the mean age of both populations was 12 years and approximately a third of the study subjects were in the 6 to < 12-year age range. Similar numbers of male and female subjects were enrolled in the study but more males than females were included in the mITT population. Most subjects were either Asian or white. In the mITT population, the site of the infection was pulmonary for all subjects and 2 subjects in the 12 to < 18-year age group also had sinus involvement.

Table 5
A1501080
Demographic and Baseline Characteristics

	Safety Population	mITT population
# Patients	31	14
Age mean (SD)	11.9 (3.5)	12.1 (2.9)
min, max	3, 17	6, 17
2 to < 6 years	1 (3.2)	0
6 to < 12 years	10 (32.3)	5 (35.7)
12 to < 18 years	20 (64.5)	9 (64.2)
Race		
White	11 (35.5)	4 (28.6)
Black	1 (3.2)	0
Asian	18 (58.1)	9 (64.3)
Other	1 (3.2)	1 (7.1)
Sex		
Male	16 (51.6)	9 (64.3)
Female	15 (48.4)	5 (35.7)
Country		
United States	7 (22.6)	5 (35.7)
Thailand	11 (35.5)	5 (35.7)
Singapore	5 (16.1)	2 (14.3)
Netherlands	4 (12.9)	1 (7.1)
Spain	2 (6.5)	1 (7.1)
Poland	1 (3.2)	0
Czech Republic	1 (3.2)	0

Table 6 summarizes the duration of treatment for the Safety and mITT populations. For the Safety population, the median duration of all treatment (IV and oral) was 41 days. The median duration of IV treatment was 8 days and no subject received more than 33 days of IV treatment. A total of 22 subjects switched to oral treatment and received a median duration of 59.5 days of oral treatment.

Table 6
A1501080
Duration of Treatment

	Safety Population	mITT population
# Patients	31	14
Total Duration		
mean (SD)	46.2 (31.7)	52.9 (27.5)
median	41	41.5
min, max	3, 90	20, 90
Duration of IV		
mean (SD)	11.4 (7.2)	15.1 (8.8)
median	8	14.5
min, max	3, 33	3, 33
Switch to Oral	22 (71.0)	12 (85.7)
Duration of Oral		
mean (SD)	49.9 (28.0)	44.9 (28.7)
median	59.5	47.5
min, max	2, 81	2, 81

3.2.1.4 Results and Conclusions

The results for global response at Week 6 are presented in Table 7 for the mITT population. The overall rate of successful global response was 64.3% (exact 95% CI: 35.1, 87.2). The successful global response rate was numerically higher in the 12 to < 18 year age group than in the 2 to < 12 year age group but the number of subjects in each age group is too small to draw meaningful conclusions.

Five subjects have missing assessments of response at Week 6 due to discontinuing from the study prior to Week 6. This includes 2 subjects who died prior to Week 6, 1 subject who discontinued treatment on Day 21 due to insufficient clinical response, 1 subject who withdrew due to the need for combination antifungal therapy, and 1 subject who withdrew consent to continue participation in the study. It should be noted that 1 subject in the 12 to < 18 year age group did not have an Investigator assessment of response at Week 6. However, this subject had an Investigator assessment at EOT (complete response) which occurred on Day 40. Since the window for Week 6 was Day 40 to 44, the assessment of response at EOT was used for the Week 6 assessment. It should also be noted that the Investigator's assessment of global response for one subject in the 12 to < 18 age group was partial; however, the assessment radiological response was indeterminate. Therefore, the global response should have also been considered indeterminate. The Applicant, however, allowed this assessment to stand based on the Investigator's clinical judgment. If this subject is considered as having an indeterminate global response at Week 6, the overall successful global response at Week 6 becomes 57.1% (95% confidence interval: 28.9, 82.3).

Table 7
A1501080
Global Response at Week 6 (mITT Population)

	Age 2 to < 12 years (n=5)	**Age 12 to < 18 years** (n=9)	**Overall** (n=14)
Successful Global Response	2 (40.0)	7 (77.8)	9 (64.3)
Exact 95% Confidence Interval	(5.3, 85.3)	(40.0, 97.2)	(35.1, 87.2)
Response:			
Complete	1	3	4
Partial	1	4	5
Missing	3*	2	5*

*Includes 2 deaths prior to Week 6

The results for global response at EOT are presented in Table 8 for the mITT population. The rates of successful global response at EOT were the same as those seen at Week 6. The EOT assessment was performed on the last day of treatment which could occur before or after Week 6. Five subjects discontinued treatment prior to Week 6 and the remaining 9 subjects had an completed treatment after Week 6. Although the Investigator assessment of global response for 2 subjects in the 12 to < 18 age group was partial, the assessment of radiological response was stable for one subject and indeterminate for the other. Therefore, global response should have been assessed as stable and indeterminate, respectively. The Applicant allowed the assessment to stand based on the Investigator's clinical judgement, however, if these subjects are considered as such, the overall successful global response at EOT becomes 50% (95% confidence interval: 23.0, 77.0).

Table 8
A1501080
Global Response at EOT (mITT Population)

	Age 2 to < 12 years (n=5)	**Age 12 to < 18 years** (n=9)	**Overall** (n=14)
Successful Global Response	2 (40.0)	7 (77.8)	9 (64.3)
Exact 95% Confidence Interval	(5.3, 85.3)	(40.0, 97.2)	(35.1, 87.2)
Response:			
Complete	2	5	7
Partial	0	2	2
Indeterminate	0	1	1
Failure	1	0	1
Missing	2*	1	3*

*Includes 2 deaths

Overall in the Safety population, 5 (16.1%) subjects died (3 in the 2 to < 12 year age group and 2 in the 12 to < 18 year age group). Four of the 5 deaths were before Day 64 (days of death were Days 8, 20, 30, 38, and 75). There were 2 (14.3%) deaths (both in the 2 to < 12 year age group) in the mITT population. The deaths occurred at Day 30 and Day 38.

3.2.2 Study A1501085

3.2.2.1 Study Design and Endpoints

A1501085 was a Phase 3, multicenter, non-comparative study of voriconazole in pediatric subjects from 2 to < 18 years of age who had ICC or EC. Voriconazole could be initiated either as primary therapy or as therapy for refractory ICC or EC that was unresponsive to treatment with at least 1 other antifungal agent. The study was conducted at 33 investigational sites of which 11 sites enrolled subjects. The sites that enrolled subjects included 2 each from China, Hong Kong, and Hungary and 1 each from the Czech Republic, Mexico, the Philippines, Poland, and Slovakia.

Subject eligibility was determined at the screening visit. Males or females aged 2 to < 18 years of age with a diagnosis of ICC or EC were eligible for enrollment. A diagnosis of *Candida* infection was to be based on the growth of *Candida* sp. or mycologic evidence indicative of *Candida* sp. (eg, the presence yeast, hyphae, pseudohyphae) and later confirmed as *Candida* sp. from a specimen obtained from a sterile site within 7 days prior to the first dose of study medication for primary therapy and within 14 days prior to the first dose of study medication for salvage therapy. Subjects for whom culture confirmation was not obtained within 7 days post study drug initiation were to be discontinued from the study. For a diagnosis of ICC, subjects were also to have at least one of the following: fever, hypothermia, systolic blood pressure < 100 mmHg or a decrease in systolic blood pressure of at least 30 mm Hg, site-specific signs and symptoms of *Candida* infection, or radiologic findings consistent with *Candida* infection. For a diagnosis of EC, subjects must have had the following within 7 days prior to enrollment: clinical symptoms consistent with EC (dysphagia, odynophagia, and retrosternal pain) with or without concomitant oropharyngeal candidiasis; lesion characteristic of EC visualized by esophagoscopy; and a positive microscopy and/or mycological culture for yeast (later confirmed as *Candida* sp.) or *Candida* sp. from a brush biopsy or tissue biopsy of esophageal lesions. To be eligible to receive salvage therapy, subjects must have had a clinical and/or microbiological response deemed as unsatisfactory to at least 1 other antifungal after at least 7 days of therapy at clinically recognized effective doses.

All subjects received voriconazole therapy. Treatment for ICC started with a loading dose of IV voriconazole for the first 24 hours followed by a maintenance dose for at least 14 days after the last positive culture up to a maximum of 42 days. Treatment for EC started with no loading dose of IV voriconazole and was to continue for at least 7 days after the resolution of clinical and symptoms up to a maximum of 42 days. A switch to oral therapy was allowed after at least 5 days of IV therapy and clinical improvement was noted. Dosing was dependent on age and weight as described in Table 9.

Table 9
A1501085
Voriconazole Dosing

		Loading Dose	Maintenance Dose	
		IV	IV	Oral
ICC	Children (2 to < 12 years) and young adolescents (12 to 14 years weighing < 50 kg)	9 mg/kg IV every 12 hours for first 24 hours	8 mg/kg IV every 12 hours	9 mg/kg PO every 12 hours (maximum dose 350 mg)
	Adolescents (12 to < 18 years) excluding 12 to 14 years weighing < 50 kg	6 mg/kg IV every 12 hours for first 24 hours	4 mg/kg IV every 12 hours	200- 300 mg PO every 12 hours
EC	Children (2 to < 12 years) and young adolescents (12 to 14 years weighing < 50 kg)	n/a	4 mg/kg IV every 12 hours	9 mg/kg PO every 12 hours (maximum dose 350 mg)
	Adolescents (12 to < 18 years) excluding 12 to 14 years weighing < 50 kg	n/a	3 mg/kg IV every 12 hours	200 mg PO every 12 hours

The study period started with the screening visit and ended with a 1-month following EOT visit. Adverse events were monitored daily through EOT, every 7 days after EOT, and at the 1-month follow-up visit. Hematology and blood chemistry were assessed at screening/Day 1, every 7 days, at Day 42/EOT, and at the 1-month follow-up visit. A complete physical exam was conducted at screening and a targeted physical exam was conducted every 7 days and at Day 42 or EOT. Clinical signs and symptoms of *Candida* infection including radiological findings were evaluated at screening/Day 1, every 3 days for hospitalized subjects and every 7 days for outpatients, and at Day 42 or EOT. Subjects with candidemia were to have blood cultures performed daily until 2 consecutive negative cultures for yeast or *Candida* sp., separated by at least 24 hours, were obtained and at Day 42/EOT. Fungal cultures at sterile sites other than blood were to be recorded if procedures were performed as part of the subject's routine care.

The primary objective of the study was to evaluate the safety and tolerability of voriconazole for the treatment of ICC and EC in pediatric subjects from 2 to <18 years of age. The secondary objectives of the study were to assess the efficacy of voriconazole for the treatment of ICC and EC in pediatric subjects from 2 to <18 years of age and to assess time to death and all-cause mortality during study therapy, at Day 28 and at the 1-month follow-up visit.

Primary endpoints were based on the safety and tolerability as determined by the rate of AEs (serious and non-serious) including visual-, cardiac-, and liver-related AEs, and treatment discontinuations due to AEs. Secondary endpoints were the rate of global response at EOT, all-cause mortality at Day 28 and the 1 month follow-up visit, and time to death. A successful global response was defined for a subject who achieved clinical cure or improvement and microbiological eradication or presumed eradication. An unsuccessful global response was defined for a subject with a clinical response of failure and/or a microbiological response of persistence. A subject was categorized as indeterminate if there was a clinical response of indeterminate and/or microbiological response of indeterminate and neither clinical response is a failure nor microbiological response is persistence.

3.2.2.2 Statistical Methodologies

All efficacy analyses were descriptive and no statistical tests of hypotheses were performed. Results were presented by age group (age 2 to < 12 years or 12 to < 18 years) as well as overall. Results were also presented by ICC vs EC and primary vs salvage.

Global response rates were presented with exact 95% confidence interval for the binomial proportion using the Clopper-Pearson method. Subjects with indeterminate and missing data were treated as failures. Mortality rates at Day 28 and the 1-month follow-up visit were presented separately with exact 95% CIs for the binomial proportion, using the Clopper-Pearson method.

The main efficacy analysis population was the mITT population. The mITT population was defined as all subjects who received at least 1 dose of study drug and who were have confirmed ICC, EC, or subjects with EC who do not have confirmation of EC by esophagoscopy but who have confirmation of oropharyngeal candidiasis.

The safety population was defined as all subjects who received at least 1 dose of study medication. This population was used for all safety analyses which were descriptive and based on rates of discontinuation, adverse events, laboratory abnormalities, ECG changes, and changes in visual assessments.

No statistical computations were used to determine the sample size. A sample size of 30 subjects who met the mITT criteria was chosen to be necessary to provide adequate information for assessing safety and tolerability in children with ICC and EC. An attempt was made to enroll approximately equal numbers of children in each age group (2 to < 12 years and 12 to < 18 years). The study was stopped early due to slow enrollment and not due to safety issues or concerns. At the time study termination, 22 subjects had enrolled in the study.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

Overall 22 subjects were enrolled into the study and received treatment with voriconazole, 21 subjects completed the study and 13 subjects completed treatment. The one subject who did not complete the study withdrew due to lack of confirmation of *Candida* infection. Of the 9 subjects who discontinued treatment, 3 discontinued due to an adverse event related to the study drug, 1 discontinued due to an adverse event not related to study drug, 3 discontinued due to lack of confirmation of *Candida* infection, 1 due to a protocol violation, and 1 discontinued due to a medication error. Reasons for discontinuation from the study and treatment are summarized in Table 10.

Table 10
A1501085
Patient Disposition

	Age 2 to < 12 years	Age 12 to < 18 years	Overall
Enrolled/treated	14	8	22
Completed Study	13	8	21
Discontinued Study	1	0	1
Discontinued Treatment	7	2	9
Lack of confirmation of *Candida* infection	3	0	3
Adverse event related to study drug	2	1	3
Adverse event not related to study drug	0	1	1
Protocol violation	1	0	1
Medication error	1	0	1

All subjects enrolled received treatment and are included in the Safety Population. Five subjects were excluded from the mITT population due to lack of microbiological confirmation of *Candida* infection. Thus, 17 subjects were included in the mITT population.

Table 11
A1501085
Analysis Populations

	Age 2 to < 12 years	Age 12 to < 18 years	Overall
Safety	14	8	22
mITT Population	9	8	17

Table 12 summarizes the demographic and baseline characteristics of the Safety and mITT populations. Overall, the mean age was 9.5 to 10.5 years and less than a quarter of the study subjects were in the 2 to < 6 years age range. Slightly more females than males were enrolled in the study. Almost half of the subjects were white. Seven subjects had a diagnosis of ICC: 5 primary and 2 salvage. Ten subjects had a diagnosis of EC: 8 primary and 2 salvage.

Table 12
A1501080
Demographic and Baseline Characteristics

	Safety Population	mITT population
# Patients	22	17
Age mean (SD)	9.5 (4.5)	10.5 (4.4)
min, max	2, 16	2, 16
2 to < 6 years	5 (22.7)	3 (17.6)
6 to < 12 years	9 (40.9)	6 (35.3)
12 to < 18 years	8 (36.4)	8 (47.1)
Race		
White	10 (45.5)	7 (41.2)
Asian	6 (27.3)	4 (23.5)
Other	6 (27.3)	6 (35.3)
Sex		
Male	8 (36.4)	5 (29.4)
Female	14 (63.6)	12 (70.6)
Country		
China	2 (9.1)	1 (5.9)
Czech Republic	7 (31.8)	6 (35.3)
Hong Kong	3 (13.6)	2 (11.8)
Hungary	2 (9.1)	1 (5.9)
Mexico	5 (22.7)	5 (29.4)
Philippines	1 (4.5)	1 (5.9)
Poland	1 (4.5)	0
Slovakia	1 (4.5)	1 (5.9)
Diagnosis		
ICC	11 (50.0)	7 (41.2)
Primary	9	5
Salvage	2	2
EC	11 (50.0)	10 (58.8)
Primary	9	8
Salvage	2	2

Table 13 summarizes the duration of treatment for the Safety and mITT populations. For ICC subjects in the Safety population, the median duration of all treatment (IV and oral) was 19 days. The median duration of IV treatment was 8 days and no ICC subject received more than 24 days of IV treatment. A total of 6 ICC subjects switched to oral treatment and received a median duration of 15.5 days of oral treatment. For EC subjects in the Safety population, the median duration of all treatment (IV and oral) was 15 days and no subject received treatment more than 23 days. The median duration of IV treatment was 6 days and no EC subject received more than 17 days of IV treatment. A total of 7 EC subjects switched to oral treatment and received a median duration of 6 days of oral treatment.

Table 13
A1501085
Duration of Treatment

	Safety Population		mITT population	
	ICC (n=11)	EC (n=11)	ICC (n=7	EC (n=10)
Total Duration				
mean (SD)	16.1 (4.8)	12.9 (4.9)	24.3 (15.3)	13.6 (4.6)
median	19	15	19	14
min, max	2, 42	6, 23	2, 42	6, 23
Duration of IV				
mean (SD)	10.9 (7.7)	8.5 (4.0)	13.9 (8.4)	8.8 (4.1)
median	8	6	12	6.5
min, max	2, 24	5, 17	2, 24	5, 17
Switch to Oral	6 (54.5)	7 (63.6)	4 (57.1)	7 (70.0)
Duration of Oral				
mean (SD)	19.3 (13.8)	7.1 (5.0)	19.0 (11.2)	7.1 (5.0)
median	15.5	6	15.5	6
min, max	3, 37	2, 17	10, 35	2, 17

3.2.2.4 Results and Conclusions

The results for global response at EOT are presented in Table 14 for the mITT population. The overall rate of successful global response for ICC was 85.7% (exact 95% CI: 42.1, 99.6). All subjects with ICC were in the 2 to < 12 years age group. The one unsuccessful response for ICC was in a subject with primary infection who had indeterminate clinical and microbiological responses at EOT. The overall rate of successful global response for EC was 70.0% (exact 95% CI:34.8, 93.3). Two EC subjects were in the 2 to < 12 years age group and both were successfully treated. Two subjects with primary EC in the 12 to < 18 year age group had an unsuccessful response because of indeterminate or persistent microbiological response although they had a clinical response of cured. One subject with salvage EC in the 12 to < 18 year age group that had an unsuccessful response because of indeterminate microbiological response although the subject had a clinical response of improved.

Table 14
A1501085
Successful Global Response at EOT (mITT Population)

	Age 2 to < 12 years (n=9)	Age 12 to < 18 years (n=8)	Overall (n=17)
ICC			
Primary	4/5 (80.0)	-	4/5 (80.0)
Salvage	2/2 (100.0)	-	2/2 (100.0)
Total	6/7 (85.7)	-	6/7 (85.7)
EC			
Primary	2/2 (100.0)	4/6 (66.7)	6/8 (75.0)
Salvage	-	1/2 (50.0)	1/2 (50.0)
Total	2/2 (100.0)	5/8 (62.5)	7/10 (70.0)

3.3 Evaluation of Safety

For Study A1501080, the Safety population consisted of 31 subjects: 11 in the 2 to < 12 year age group and 20 in the 12 to < 18 year age group. All but one subject in the 12 to < 18 year age group experienced at least 1 treatment emergent adverse event (TEAE). Fifteen subjects (6 in the 2 to < 12 year age group and 9 in the 12 to < 18 year age group) had at least 1 serious TEAE. One subject in the 2 to < 12 year age group permanently discontinued treatment due to an adverse event and four subjects (all in the 12 to < 18 year age group) had dose reductions or temporary discontinuations of treatment due to an adverse event. As mentioned in Section 3.2.1.4, 3 subjects in the 2 to <12 year age group and 2 subjects in the 12 to <18 year age group died during the study.

For Study A1501085, the Safety population consisted of 22 subjects: 14 in the 2 to < 12 year age group and 8 in the 12 to < 18 year age group. Nineteen subjects (13 in the 2 to < 12 year age group and 6 in the 12 to < 18 year age group) experienced at least 1 TEAE. Two subjects in the 2 to < 12 year age group and 1 subject in the 12 to < 18 year age group had at least 1 serious TEAE. Two subjects in each age group permanently discontinued treatment due to an adverse event and three subjects (all in the 2 to < 12 year age group) had dose reductions due to an adverse event. No subjects died during the study follow-up period (i.e. 1 month after EOT). One subject died 455 days after EOT after the safety reporting period due to progression of underlying disease.

For a detailed review of the safety data, please see the Medical Officer's review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 15 summarizes the results by gender, race, and geographic region for global response at Week 6 in the mITT population of Study A1501080. The results should be interpreted with caution given the small sample sizes. Analyses by age group are presented in Section 3.2.1.4.

Table 15
A1501080
Global Response at Week 6 by Gender, Race, and Geographic Region (mITT)

	Voriconazole (n=14)
Gender	
Male	7/9 (77.8)
Female	2/5 (40.0)
Race	
White	3/4 (75.0)
Asian	5/9 (55.6)
Other	1/1
Geographic Region	
United States	3/5 (60.0)
Rest of World	6/9 (66.7)

Table 16 summarizes the results by gender, and race for global response at EOT in the mITT population of Study A1501085. The results should be interpreted with caution given the small sample sizes. Analyses by age group are presented in Section 3.2.2.4. Since all sites were outside the United States, no results by geographic region are presented.

Table 16
A1501085
Global Response at EOT by Gender and Race (mITT)

	ICC (n=7)	**EC** (n=10)
Gender		
Male	2/2 (100.0)	2/3 (66.7)
Female	4/5 (80.0)	5/7 (71.4)
Race		
White	-	5/7 (71.4)
Asian	3/3 (100.0)	1/1 (100.0)
Other	3/4 (75.5)	1/2 (50.0)

4.2 Other Special/Subgroup Populations
Not applicable.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues
Both studies were designed primarily to assess the safety and tolerability of voriconazole in the pediatric population. The assessment of efficacy was a secondary objective in both trials. Given the studies were uncontrolled and the sample sizes are extremely small, data is summarized only with descriptive statistics.

5.2 Collective Evidence
Two noncomparative trials that evaluated the safety, tolerability and efficacy of voriconazole in the pediatric population (ages 2 to < 18 years) were conducted. Study A1501080 was conducted in patients with IA and Study A1501085 was conducted in patients with ICC or EC. The overall efficacy results from the trials are presented in Table 17. Overall, voriconazole was effective for the treatment of pediatric patients with IA, ICC, or EC as the point estimates of successful global response were greater than 64%. However, the sample size was limited to draw definitive conclusions.

Table 17
A1501080 and A1501085
Summary of Global Response (mITT)

	Age 2 to < 12 years	Age 12 to < 18 years	Overall
A1501080- IA			
Global Response at Week 6	2/5 (40.0)	7/9 (77.8)	9/14 (64.3)
Exact 95% Confidence Interval	(5.3, 85.3)	(40.0, 97.2)	(35.1, 87.2)
A1501085- ICC			
Global Response at EOT	6/7 (85.7)	n/a	6/7 (85.7)
Exact 95% Confidence Interval	(42.1, 99.6)		(42.1, 99.6)
A1501085- EC			
Global Response at EOT	2/2 (100.0)	5/8 (62.5)	7/10 (70.0)
Exact 95% Confidence Interval	(15.8, 100.0)	(24.5, 91.5)	(34.8, 93.3)

As reported in the currently approved Vfend label for the clinical trials conducted in the adult population, a satisfactory global response rate for voriconazole at 12 weeks was 53% for IA and 41% for ICC. For the adult trial in EC, the assessment of response was primarily based on endoscopic response at EOT (i.e. normal endoscopy) unless a subject only had a baseline EOT endoscopy and then successful response was defined as symptomatic cure or improvement. The successful response at EOT was 87.5% for EC.

5.3 Conclusions and Recommendations

Efficacy in the pediatric population for IA and ICC/EC is primarily extrapolated from the efficacy results for the adult population. The limited data provided for the pediatric population in the non-comparative studies A1501080 and A1501085, indicate rates of global response consistent with the known global response profile of voriconazole in adult subjects with IA and ICC/EC, respectively.

5.4 Labeling Recommendations

The following labeling changes are recommended in Section 14.5 Pediatric Population under Clinical Studies.

- Discussion of the IA and ICC/EC trials should be separated.
- Results should be reported for ICC and EC separately and not combined.
- Definitions of the mITT population and successful global response should be included.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHERYL A DIXON
11/03/2017

KAREN M HIGGINS
11/06/2017
I concur.