Safety, Efficacy, and Exposure–Response of Voriconazole in Pediatric Patients With Invasive Aspergillosis, Invasive Candidiasis or Esophageal Candidiasis

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Background: Data on safety and efficacy of voriconazole for invasive aspergillosis (IA) and invasive candidiasis/esophageal candidiasis (IC/EC) in pediatric patients are limited.

Methods: Patients aged 2–<18 years with IA and IC/EC were enrolled in 2 prospective open-label, non-comparative studies of voriconazole. Patients followed dosing regimens based on age, weight and indication, with adjustments permitted. Treatment duration was 6–12 weeks for IA patients, ≥14 days after last positive *Candida* culture for IC patients and ≥7 days after signs/symptoms resolution for EC patients. Primary analysis for both the studies was safety and tolerability of voriconazole. Secondary end points included global response success at week 6 and end of treatment (EOT), all-causality mortality and time to death. Voriconazole exposure–response relationship was explored.

Results: Of 53 voriconazole-treated pediatric patients (31 IA; 22 IC/EC), 14 had proven/probable IA, 7 had confirmed IC and 10 had confirmed EC. Treatment-related hepatic and visual adverse events, respectively, were reported in 22.6% and 16.1% of IA patients, and 22.7% and 27.3% of IC/EC patients. All-causality mortality in IA patients was 14.3% at week 6; no deaths were attributed to voriconazole. No deaths were reported for IC/EC patients. Global response success rate was 64.3% (week 6 and EOT) in IA patients and 76.5% (EOT) in IC/EC patients. There was no association between voriconazole exposure and efficacy; however, a slight positive association between voriconazole exposure and hepatic adverse events was established.

Conclusions: Safety and efficacy outcomes in pediatric patients with IA and IC/EC were consistent with previous findings in adult patients.

Key Words: voriconazole, aspergillosis, candidiasis, pediatric, exposure–response

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Aspergillus and *Candida* species are the predominant causes of invasive fungal infection in pediatric patients.[1] The incidence of invasive fungal infection has increased substantially in recent years, largely because of the increasing number of children at risk of acquiring these infections.[1]

Invasive aspergillosis (IA) is observed in children with compromised phagocytic function,[2–4] as well as in patients with hematologic malignancies and specific immunosuppression, and recipients of allogeneic stem cell and solid organ transplants.[4] Although the lungs are the most common infection site,[4] the central nervous system, cardiovascular system and other tissues may be infected because of hematogenous dissemination in severely immunocompromised patients.[5] Invasive candidiasis (IC) may present as catheter-associated candidemia, single-organ candidiasis or disseminated candidiasis, with or without candidemia.[6] Risk factors for IC include intensive care unit admission, neutropenia, malignant diseases[7] and congenital immunologic deficiencies.[8]

Voriconazole is a broad-spectrum triazole with activity against a wide range of yeasts and filamentous fungi. It is a substrate and inhibitor of the cytochrome P450 (CYP) isoenzymes CYP2C19, CYP2C9 and CYP3A4. Voriconazole exhibits non-linear pharmacokinetics because of saturation of its metabolism; inter-individual variability in exposure is high.[9–11] In healthy adults, it has been demonstrated that CYP2C19 genotyping status, gender and age are key factors, which contribute to this variability.[12] In healthy adults, poor metabolizers of CYP2C19 have, on average, approximately 2–4-fold higher voriconazole levels than their homozygous extensive metabolizers and heterozygous extensive metabolizers counterparts, respectively, independent of ethnicity.[12,13] However, exposure of voriconazole varies widely within each genotype and overlaps considerably across genotypes.[12] Therefore, no dose adjustment based on CYP2C19 genotyping status is warranted in the current product label for voriconazole.

Although efficacy has been demonstrated in adults with IA, IC and esophageal candidiasis (EC),[14–16] published data on voriconazole use in children are limited.[10,11,17–20] Given the potentially life-threatening nature of invasive fungal infection, data on efficacy, safety and dosing of voriconazole in children will be of value to the medical community. Here, we evaluated safety, efficacy and exposure–response of voriconazole for the treatment of IA, IC and EC in pediatric patients using the recently revised dosing regimens in 2 prospective, open-label, noncomparative studies.

MATERIALS AND METHODS

Study A1501080 evaluated pediatric patients with IA (vori-IA study; NCT00836875), whereas Study A1501085 evaluated pediatric patients with IC/EC (vori-IC/EC study; NCT01092832). Both studies were conducted in compliance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice Guidelines and were approved by the appropriate individual Institutional Review Boards for each study site. Investigators obtained written, informed consent from legally acceptable representatives and patient assent, where applicable.

Study Design and Treatment

The vori-IA and vori-IC/EC studies were prospective, open-label, noncomparative phase 3 studies. The vori-IA study was conducted at 16 centers (Asia, Europe and North America) from 2009 to 2013; the vori-IC/EC study was conducted at 11 centers (Asia, Europe, North America) from 2010 to 2013.

In both studies, patients followed recently revised dosing regimens based on age, weight and indication (Table 1). These initial dosing regimens were based on an integrated population pharmacokinetic analysis of voriconazole data from children, adolescents and adults.[21] Patients initiated treatment with intravenous (IV) voriconazole and continued IV therapy until clinical improvement was observed. Treatment for IA and IC started with loading doses of 9 mg/kg every 12 hours (q12h) for the first 24 hours for children (aged 2–<12 years) and young adolescents (aged 12–14 years, weighing <50 kg), followed by maintenance doses of 8 mg/kg q12h. For all other adolescents (aged 12–<18 years, excluding 12–14-year olds weighing <50 kg), the loading doses were 6 mg/kg q12h for the first 24 hours followed by maintenance doses of 4 mg/kg q12h. Children with EC did not receive loading doses of IV voriconazole. Dosage for children (aged 2–<12 years) and young adolescents (aged 12–14 years, weighing <50 kg) began with 4 mg/kg q12h. Dosage for all other adolescents (aged 12–<18 years, excluding 12–14 year-olds weighing <50 kg) began with 3 mg/kg q12h.

Patients could switch to oral voriconazole after 1 week (vori-IA) or 5 days (vori-IC/EC) of IV therapy. In the vori-IA study, patients received voriconazole for ≥6 weeks, up to a maximum of 12 weeks. A minimum treatment duration of 6 weeks was chosen based on recent clinical observations that this duration is sufficient to evaluate clinical efficacy in patients receiving therapy for IA.[22] Duration of treatment was based on clinical improvement and improvement in radiologic findings. In the vori-IC/EC study, patients received voriconazole for ≥14 days after the last positive *Candida* culture from a normally sterile site (for IC) or ≥7 days after the resolution of clinical signs/symptoms (for EC), up to a maximum of 42 days. Patients had to return for the 1-month follow-up visit after end of treatment (EOT).

Dose Adjustments

Dose adjustments were made based on clinical response, tolerability or voriconazole plasma trough concentrations (C_{min}; collected before dosing on third day or later of IV therapy or after switching to oral therapy, as well as after each dose adjustment). Although no definitive relationship between voriconazole exposure and response has been established, provisional cut-off values of C_{min} were used to inform dose adjustment. It is of note that children have less accumulation in response to a given dose of voriconazole than adults because of their faster metabolism of voriconazole; as detailed in an earlier analysis, to achieve the same total exposure [ie, area under the curve from 0 to 12h (AUC_{0-12})], the corresponding C_{min} in children is expected to be lower than that in adults.[20] Therefore, the minimum of target voriconazole C_{min} in children in this study was lower than that used in adults.

For all treatments, the dose could be reduced by 1 mg/kg steps (or 50 mg steps if 350 mg oral dose was used) if it exceeded 6 µg/mL. If C_{min} was too high (eg, >10 µg/mL), the investigator could reduce the dose by >1 mg/kg or 50 mg, as needed and temporary discontinuation of dosing (eg, 24-hour washout) was allowed to avoid further accumulation of voriconazole in the body.

For IA and IC treatment, the dose could be increased in 1 mg/kg steps if C_{min} was <0.5 µg/mL during IV therapy or increased in 1 mg/kg or 50 mg steps if C_{min} was <0.2 µg/mL during step-down oral therapy. For EC treatment, the dose could be increased in 1 mg/kg or 50 mg steps if C_{min} was <0.2 µg/mL during IV or oral therapy. Close monitoring of adverse events (AEs) was implemented when the dose was increased.

To make voriconazole concentration data available to the investigators within 72 hours of receiving samples, trough plasma samples (approximately 1 mL) were analyzed at designated reference laboratories or locally.

CYP2C19 Genotyping

Buccal swab samples were collected for CYP2C19 genotyping and analyzed at Pfizer Pharmacogenomics Laboratory (Groton, CT) using a published method.[20]

Patients

Inclusion Criteria

In the vori-IA study, eligible patients were aged 2–<18 years, immunocompromised with a clinically compatible illness and had proven, probable or possible IA based on European Organization for Research and Treatment of Cancer/Mycoses Study Group consensus definitions.[23] Patients enrolled with possible IA were assessed again to determine whether they had proven or probable IA based on tests done within 7 days of the first dose of study drug. Patients with rare molds (eg, *Scedosporium* or *Fusarium* species) were also eligible. In the vori-IC/EC study, eligible patients were aged 2–<18 years with confirmed IC/EC. Invasive candidiasis diagnosis was based on growth of *Candida* species or mycologic evidence indicative

TABLE 1. Initial Voriconazole Dosing Scheme by Age, Weight and Indication

	Loading Dose	Maintenance Dose	
	IV	IV	Switched to Oral Voriconazole
Children (aged 2–<12 yr) and young adolescents (aged 12–14 yr weighing <50 kg)			
IA/IC	9 mg/kg q12h for first 24 h	8 mg/kg q12h	9 mg/kg q12h (maximum dose 350 mg)
EC	–	4 mg/kg q12h	9 mg/kg q12h (maximum dose 350 mg)
Adolescents (aged 12–<18 yr) excluding those aged 12–14 yr weighing <50 kg			
IA/IC	6 mg/kg q12h for first 24 h	4 mg/kg q12h	200 mg q12 h*
EC	–	3 mg/kg q12h	200 mg q12 h

*At the investigator's discretion, an oral dose of 300 mg q12 h may be used in adolescents with IA.
EC indicates esophageal candidiasis; IA, invasive aspergillosis; IC, invasive candidiasis; IV, intravenous; q12h, every 12 hours.

of *Candida* species and later confirmed as *Candida* species from a specimen obtained from a sterile site within 7 days (primary therapy) or 14 days (salvage therapy) of first voriconazole dose. Patients with clinical and/or radiologic findings consistent with disseminated disease and a positive *Candida* culture from a normally sterile site within previous 2 weeks of diagnosis were also eligible. Esophageal candidiasis diagnosis was based on the presence of clinical symptoms/lesions consistent with EC, or positive microscopy and/or mycologic culture for *Candida* species from brush/tissue biopsy of esophageal lesions within 7 days of enrollment.

Exclusion Criteria

The vori-IA study excluded patients with sarcoidosis, aspergilloma, allergic bronchopulmonary aspergillosis or chronic IA with the duration of symptoms or radiologic findings for >4 weeks before entry. Patients who received previous treatment or prophylaxis with systemic agents against *Aspergillus* species or systemic antifungal treatment for the current episode of IA or rare molds for >96 hours were also excluded. Patients were excluded from the vori-IC/EC study (for primary therapy) if they required treatment with another systemic antifungal agent or had >48 hours of antifungal therapy before first voriconazole dose.

Safety

In both studies, the primary end point was safety and tolerability of voriconazole, as determined by the rate of AEs and treatment discontinuations because of AEs. Adverse events were monitored by the study investigators from screening until the 1-month follow-up visit after EOT and were recorded and coded using the Medical Dictionary for Regulatory Activities (MedDRA, v16.0). Investigators assessed the causality of all AEs. An investigator's causality assessment was the determination of whether there was a reasonable possibility that the study drug caused or contributed to the AE. A serious adverse event (SAE) was defined as any untoward medical occurrence at any dose that resulted in death, was life-threatening (immediate risk of death), required inpatient hospitalization or prolonged hospitalization, resulted in significant or permanent disability/incapacity (substantial disruption of the ability to perform normal life functions) or resulted in congenital abnormality/birth defect.

Visual assessments were performed at baseline, and at weeks 1, 2, 4, 6 and 12 or EOT. In children aged ≥3 years, visual symptoms were assessed primarily by a visual questionnaire, by the Hardy–Rand–Rittler color vision test and by acuity and fixation indices of the Early Treatment Diabetic Retinopathy Study chart, used at the investigator's discretion. Patients with treatment-emergent visual AEs underwent ophthalmic fundoscopy, and all findings were recorded. Children aged <3 years had visual fixation assessed by the investigators. Liver function tests were monitored weekly up to week 6, at week 12 and at the 1-month follow-up visit. All clinically significant hepatic and other laboratory abnormalities were reported as AEs or SAEs, as appropriate. Potential Hy's Law cases were reported as SAEs and were defined as patients who had aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and total bilirubin baseline values within the normal range who, following treatment, presented with AST or ALT 3 × the upper limit of normal (ULN) concurrent with a total bilirubin 2 × ULN with no evidence of hemolysis and alkaline phosphatase 2 × ULN. Alternatively, if patients with pre-existing ALT, AST, or total bilirubin values above the ULN, then presented with AST or ALT 2 × baseline values and 3 × ULN or 8 × ULN (whichever was smaller) or total bilirubin increased by 1 × ULN or ≥3 × ULN (whichever was smaller), this was also considered a serious hepatic AE.

Efficacy

Efficacy assessments were secondary end points and included global response (success rate) at week 6 (vori-IA) and EOT (vori-IA and vori-IC/EC), all-causality mortality, and time to death. In the vori-IA study, successful global response was defined as clinical resolution or improvement of signs/symptoms plus complete/partial resolution of radiologic findings. In the vori-IC/EC study, successful global response was defined as clinical cure/improvement plus confirmed/presumed microbiologic eradication.

Exposure–Response Analyses

Voriconazole concentration data from 48 patients (96 observations) were analyzed using a nonlinear mixed-effects model using NONMEM system (version 7.2). Individual exposure parameters [area under the curve from 0 to 12 hours (AUC_{0-12}) and C_{min}] were estimated based on the final pharmacokinetic model. Relationships between voriconazole exposures and key safety (hepatic, visual, psychiatric, skin and subcutaneous tissue AEs) and efficacy (global response at EOT) end points were assessed by graphical examination or using a logistic regression model (NONMEM). The model selection was based on goodness-of-fit criteria, which included basic diagnostic plots, precision of parameter estimates and the objective function value. The graphic processing of the data and NONMEM output was performed with R (version 2.12.2).

As there could be multiple AE observations per patient, both single-panel (without counting the frequency of AE occurrence in each patient) and multiple-panel (includes all AE observations) analysis approaches were utilized for hepatic and visual AE analysis, including both all-causality and treatment-related events. As there were only a few psychiatric disorders and skin and soft tissue disorders reported, a simple descriptive check was performed for these 2 types of AEs.

The following hepatic AE terms were included in the analysis: ALT increased or abnormal, AST increased or abnormal, γ-glutamyl transferase increased or abnormal, bilirubin increased, hyperbilirubinemia, transaminases increased, liver function tests abnormal, gallbladder disorder, hepatosplenomegaly, jaundice cholestatic, liver disorder and drug-induced liver injury. The following visual AE terms were included in the analysis: abnormal sensation in the eye, asthenopia, chromatopsia, diplopia, photophobia, visual impairment, vision blurred and visual acuity reduced. There were 5 all-causality psychiatric disorders: insomnia (n = 2), depression, affect lability, and intentional self-injury. There were 6 treatment-related skin and subcutaneous tissue disorders: dermatitis exfoliative, rash maculopapular, skin burning sensation, skin lesion and rash (n = 2).

Statistical Analyses

The safety population comprised all patients who received ≥1 voriconazole dose. The modified intent-to-treat population for efficacy evaluation comprised all patients with proven/probable IA, microbiologically confirmed IC, presumed EC (patients with neutropenia, thrombocytopenia or advanced HIV/AIDS concurrent with oral candidiasis) or microbiologically confirmed EC who received ≥1 voriconazole dose. Safety and efficacy data for both the studies were descriptive in nature; thus, no statistical testing was performed.

RESULTS

Patient Disposition and Baseline Demographics
Vori-IA Study

Thirty-one patients received voriconazole, of whom 16 completed the treatment and 25 completed the study (ie, returned for 1-month follow-up visit; patients who did not return for the 1-month follow-up visit were considered to have discontinued the study; Fig. 1). Patient demographics are presented in Table 2. Most patients (82.8%) had a recent history of neutropenia, and 17.2% were recipients of hematopoietic stem cell transplants (allogeneic: 13.8%, autologous: 3.4%). Median (range) duration of IV treatment
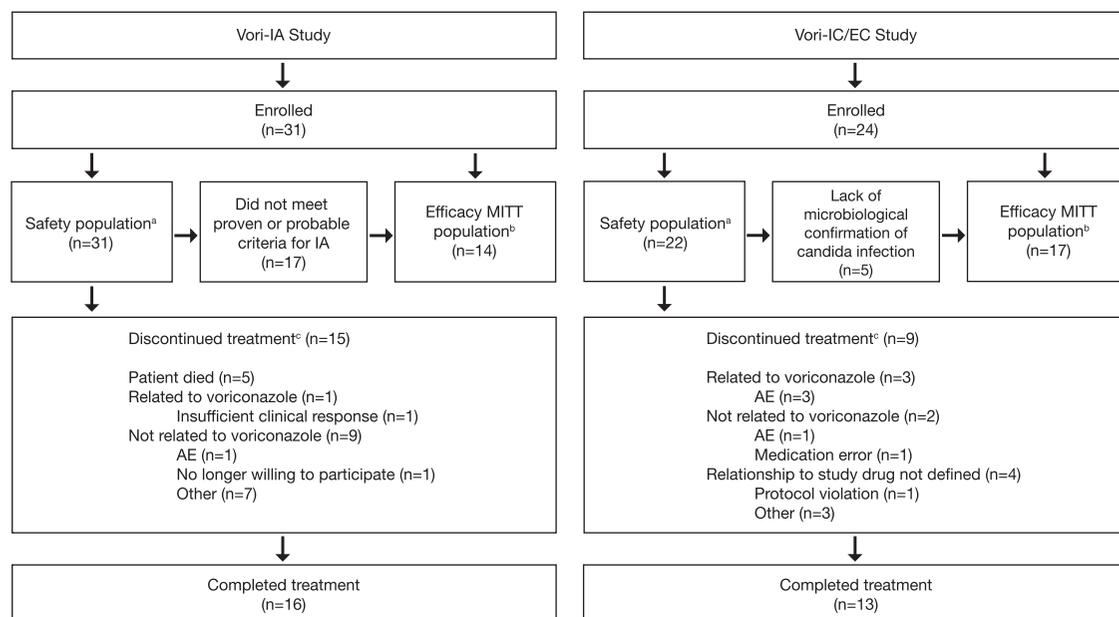
FIGURE 1. Patient disposition. [a]All patients who received ≥1 voriconazole dose. [b]All patients with proven/probable IA, microbiologically confirmed IC, presumed EC or microbiologically confirmed EC who received ≥1 voriconazole dose. [c]Patients who discontinued study treatment for any reason were not considered to have completed treatment. AE indicates adverse event; EC, esophageal candidiasis; IA, invasive aspergillosis; IC, invasive candidiasis; MITT, modified intent-to-treat.

TABLE 2. Patient Demographic Characteristics in the Vori-IA and Vori-IC/EC Studies (Safety Population)

	Vori-IA Study			Vori-IC/EC Study		
	2–<12 Yr (n = 11)	12–<18 Yr (n = 20)	Overall (n = 31)	2–<12 Yr (n = 14)	12–<18 Yr (n = 8)	Overall (n = 22)
Age in yr, mean (SD)	7.9 (2.3)	14.1 (1.7)	11.9 (3.5)	6.8 (2.9)	14.4 (1.7)	9.5 (4.5)
Sex, n (%)						
Female	4 (36.4)	11 (55.0)	15 (48.4)	8 (57.1)	6 (75.0)	14 (63.6)
Male	7 (63.6)	9 (45.0)	16 (51.6)	6 (42.9)	2 (25.0)	8 (36.4)
Race, n (%)						
White	3 (27.3)	8 (40.0)	11 (35.5)	5 (35.7)	5 (62.5)	10 (45.5)
Black	-	1 (5.0)	1 (3.2)	-	-	-
Asian	8 (72.7)	10 (50.0)	18 (58.1)	5 (35.7)	1 (12.5)	6 (27.3)
Other	-	1 (5.0)	1 (3.2)	4 (28.6)	2 (25.0)	6 (27.3)
Weight in kg, mean (SD)	26.7 (9.7)	50.1 (15.3)	41.7 (17.6)	23.9 (11.1)	54.6 (19.7)	35.1 (20.8)
Host factors for IA, n (%)						
Recent history of neutropenia	9 (81.8)	15 (83.3)*	24 (82.8)†	-	-	-
Hematopoietic stem cell transplant	2 (18.2)	3 (16.7)*	5 (17.2)†	-	-	-
Allogeneic	2 (18.2)	2 (11.1)*	4 (13.8)†	-	-	-
Autologous	-	1 (5.6)*	1 (3.4)†	-	-	-
Risk factors for IC/EC, n (%)						
Broad-spectrum antibiotics	-	-	-	12 (85.7)	7 (87.5)	19 (86.4)
Chemotherapy	-	-	-	12 (85.7)	7 (87.5)	19 (86.4)
Neutropenia	-	-	-	10 (71.4)	8 (100.0)	18 (81.8)
Central venous catheter	-	-	-	11 (78.6)	6 (75.0)	17 (77.3)
Duration of IV treatment in days, median (range)	8.0 (3–33)	8.5 (5–22)	8.0 (3–33)	6.5 (2–24)	8.0 (5–17)	7.0 (2–24)
Duration of oral treatment in days, median (range)	55.0 (2–78)	59.5 (8–81)	59.5 (2–81)	15.0 (3–37)	5.0 (2–8)	9.0 (2–37)
Duration of total treatment in days, median (range)	37.0 (3–85)	43.5 (5–90)	41.0 (3–90)	16.5 (2–42)	14.0 (6–17)	14.0 (2–42)

*n = 18; host factor case report form pages were not completed for 2 patients.
†n = 29; host factor case report form pages were not completed for 2 patients.
EC indicates esophageal candidiasis; IA, invasive aspergillosis; IC, invasive candidiasis; IV, intravenous; SD, standard deviation.

(n = 31), oral treatment (n = 22) and total treatment was 8.0 (3–33) days, 59.5 (2–81) days and 41.0 (3–90) days, respectively. Eleven patients (35.5%) required dose reduction, and 3 patients (9.7%) had a dose increase.

Of 31 enrolled patients, 14 were diagnosed with proven/probable IA and 17 were diagnosed with possible IA. Baseline characteristics for those patients with proven/probable IA are presented in Table 3. All patients had a blood and lymphatic system disorder. Metabolism and nutrition disorders, neoplasms, gastrointestinal disorders and infections were common. The lungs were a site of infection in all patients. All identified pathogens were *Aspergillus* species.

Vori-IC/EC Study

Twenty-two patients received voriconazole, of whom 13 completed the treatment and 21 completed the study. Patient demographics are presented in Table 2. Most patients had a recent history of broad-spectrum antibiotic therapy (86.4%), chemotherapy (86.4%), neutropenia (81.8%) and central venous catheter use (77.3%). Median (range) duration of IV treatment (n = 22), oral treatment (n = 13) and total treatment was 7.0 (2–24) days, 9.0 (2–37) days and 14.0 (2–42) days, respectively. Three patients (13.6%) required dose reduction, and 3 patients (13.6%) had a dose increase.

TABLE 3. Patient Baseline Characteristics in the Vori-IA Study (MITT Population)

	Vori-IA Study		
	2–<12 Yr (n = 5)	12–<18 Yr (n = 9)	Overall (n = 14)
Most common (occurring in ≥5 patients) medical conditions by SOC, n (%)			
Blood and lymphatic system disorders	5 (100.0)	9 (100.0)	14 (100.0)
Metabolism and nutrition disorders	3 (60.0)	7 (77.8)	10 (71.4)
Neoplasms (benign, malignant, and unspecified)	3 (60.0)	7 (77.8)	10 (71.4)
Gastrointestinal disorders	3 (60.0)	6 (66.7)	9 (64.3)
Infections	4 (80.0)	5 (55.6)	9 (64.3)
General disorders and administration site conditions	1 (20.0)	6 (66.7)	7 (50.0)
Renal and urinary disorders	1 (20.0)	4 (44.4)	5 (35.7)
EORTC criteria for IA, n (%)			
Proven	2 (40.0)	6 (66.7)	8 (57.1)
Probable	3 (60.0)	3 (33.3)	6 (42.9)
Host factors, n (%)			
Recent history of neutropenia	3 (60.0)	7 (87.5)*	10 (76.9)†
Hematopoietic stem cell transplant	1 (20.0)	2 (25.0)*	3 (23.1)†
Autologous	0 (0.0)	1 (12.5)*	1 (7.7)†
Allogeneic	1 (20.0)	1 (12.5)*	2 (15.4)†
Myeloablative	1 (20.0)	2 (25.0)*	3 (23.1)†
Corticosteroid therapy	1 (20.0)	1 (12.5)*	2 (15.4)†
Other T-cell immunosuppressants	0	2 (25.0)*	2 (15.4)†
Site of infection, n (%)‡			
Lung	5 (100.0)	9 (100.0)	14 (100.0)
Sinus	-	2 (22.2)	2 (14.3)
Other	2 (40.0)	-	2 (14.3)
Baseline pathogen, n (%)§			
Aspergillus species (unidentified)	3 (60.0)	7 (77.8)	10 (71.4)
Aspergillus flavus	-	1 (11.1)	1 (7.1)
Aspergillus fumigates	-	2 (22.2)	2 (14.3)

*n = 8. In 1 patient, the host factor case report form was not completed as the patient's medical condition (suspected congenital cystic adenomatoid malformation) was not prespecified; the patient was included in the efficacy (MITT) population based on recent lung lobectomy, lung tissue biopsy positive for *Aspergillus* species, positive serum galactomannan and pleural effusion.
†n = 13.
‡Patients could have multiple sites at baseline.
§Four patients did not have *Aspergillus* species isolated but were included in the efficacy (MITT) population based on the following: 3 patients had a positive serum galactomannan, 1 patient had sputum gram-stain sample positive for hyphae.
EORTC indicates European Organisation for Research and Treatment of Cancer; IA, invasive aspergillosis; MITT, modified intent-to-treat; SOC, system organ class.

TABLE 4. Patient Baseline Characteristics in the Vori-IC/EC Study (MITT Population)

	Vori-IC/EC Study		
	2–<12 Yr (n = 9)	12–<18 Yr (n = 8)	Overall (n = 17)
Most common (occurring in ≥5 patients) medical conditions by SOC, n (%)			
Neoplasms (benign, malignant and unspecified)	8 (88.9)	7 (87.5)	15 (88.2)
Blood and lymphatic system disorders	6 (66.7)	8 (100.0)	14 (82.4)
Infections	6 (66.7)	6 (75.0)	12 (70.6)
Metabolism and nutrition disorders	5 (55.6)	5 (62.5)	10 (58.8)
Gastrointestinal disorders	3 (33.3)	4 (20.0)	7 (41.2)
General disorders and administration site conditions	3 (33.3)	3 (37.5)	6 (35.3)
Nervous system disorders	1 (11.1)	5 (62.5)	6 (35.3)
Psychiatric disorders	-	5 (62.5)	5 (29.4)
Respiratory, thoracic, and mediastinal disorders	1 (11.1)	4 (20.0)	5 (29.4)
Fungal diagnosis, n (%)			
IC	7 (77.8)	-	7 (41.2)
Primary therapy	5 (55.6)	-	5 (29.4)
Salvage therapy	2 (22.2)	-	2 (11.8)
EC	2 (22.2)	8 (100.0)	10 (58.8)
Primary therapy	2 (22.2)	6 (75.0)	8 (47.1)
Salvage therapy	-	2 (25.0)	2 (11.8)
Candida risk factors, n (%)			
Chemotherapy	7 (77.8)	7 (87.5)	14 (82.4)
Use of broad-spectrum antibiotics	7 (77.8)	7 (87.5)	14 (82.4)
Neutropenia	5 (55.6)	8 (100.0)	13 (76.5)
Use of central venous catheter	7 (77.8)	6 (75.0)	13 (76.5)
Clinical sepsis	5 (55.6)	5 (62.5)	10 (58.8)
Immunosuppressive therapy	5 (55.6)	5 (62.5)	10 (58.8)
Mucosal colonization	5 (55.6)	5 (62.5)	10 (58.8)
Use of systemic corticosteroids/other immunosuppressive drugs	6 (66.7)	3 (37.5)	9 (52.9)
Multifocal colonization	2 (22.2)	3 (37.5)	5 (29.4)
Total parenteral nutrition	3 (33.3)	2 (25.0)	5 (2.4)
Length of ICU stay >4 d, n (%)	2 (22.2)	2 (25.0)	4 (23.5)
Surgery	3 (33.3)	-	3 (17.6)
Abdominal surgery	2 (22.2)	-	2 (11.8)
Other	1 (11.1)	-	1 (5.9)
Site of infection, n (%)*			
Esophagus	2 (22.2)	8 (100.0)	10 (58.8)
Oropharynx	3 (33.3)	5 (62.5)	8 (47.1)
Blood	7 (77.8)	-	7 (41.2)
Catheter	2 (22.2)	-	2 (11.8)
Left eye	1 (11.1)	-	1 (5.9)
Lung	1 (11.1)	-	1 (5.9)
Right eye	1 (11.1)	-	1 (5.9)
Skin (unspecified)	1 (11.1)	-	1 (5.9)
Baseline pathogen, n (%)†			
Candida albicans	4 (44.4)	8 (100.0)	12 (70.6)
Candida tropicalis	3 (33.3)	-	3 (17.6)
Candida glabrata	1 (11.1)	-	1 (5.9)
Candida parapsilosis	1 (11.1)	-	1 (5.9)

*Patients could have multiple sites at baseline.
†Patients could have multiple organisms at baseline.
EC indicates esophageal candidiasis; IC, invasive candidiasis; ICU, intensive care unit; MITT, modified intent-to-treat; SOC, system organ class.

Of 22 enrolled patients, 7 had confirmed IC and 10 had confirmed EC (the remaining 5 enrolled patients lacked microbiologic confirmation of *Candida*), with baseline characteristics presented in Table 4. The most common medical conditions were neoplasms, blood and lymphatic system disorders, infections and metabolism and nutrition disorders. The esophagus, oropharynx and blood were the most common sites of infection, and infection was related to central venous catheter use in 2 patients (data not shown). Most patients had infection caused by *Candida albicans*.

Safety
Vori-IA Study

A safety summary is presented in Table 5. Sixteen of 31 patients experienced 35 treatment-related AEs, most commonly blurred vision (n = 3) and photophobia, increased ALT, abnormal liver function test and transaminases increased (n = 2 each). Most treatment-related AEs were mild or moderate in severity. Treatment-related hepatic AEs were experienced by 7 patients (22.6%), and except for 1 patient with severe drug-induced liver injury (discussed below), all were mild or moderate in severity. Treatment-related

visual AEs were reported by 5 patients (16.1%) and were mild in severity. Four patients (12.9%) reported treatment-related skin AEs [exfoliative dermatitis (n = 1), maculopapular rash (n = 1), skin burning sensation (n = 1) and skin lesion (n = 1)], which were all mild in severity, and only 1 patient reported any psychiatric treatment-related AE (insomnia; data not shown). Serious adverse events were experienced by 15 of 31 patients. Two SAEs were considered treatment related. Specifically, an 11-year-old girl experienced acute renal failure on day 34. The patient also received concomitant treatment with other medications, including ganciclovir (days 7–36) and vancomycin (days 28–29), while receiving treatment with the study drug. On day 32, the patient switched from IV to oral voriconazole and continued treatment for an additional 5 days. The patient died on day 38 due to sepsis. A case of drug-induced liver injury leading to discontinuation was reported on day 40 in a 14-year-old boy; this patient's underlying medical conditions at baseline included acute lymphocytic leukemia relapse, febrile neutropenia, herpes zoster oticus, hyperbilirubinemia, hypocalcemia, hypokalemia, hypomagnesemia, mucosal inflammation, pancytopenia, pneumonia, renal tubular disorder, rhinitis, sinusitis and thrombophlebitis. On day 40, the patient was hospitalized

TABLE 5. Summary of Safety Data From the Vori-IA Study

| | Vori-IA Study | | | | | |
| | 2–<12 Yr (n = 11) | | 12–<18 Yr (n = 20) | | Overall* (n = 31) | |
	All-Causality	Treatment-Related	All-Causality	Treatment-Related	All-Causality	Treatment-Related
AEs, n	86	7	195	28	281	35
Patients with AEs, n (%)	11 (100.0)	5 (45.5)	19 (95.0)	11 (55.0)	30 (96.8)	16 (51.6)
Hepatic AEs, n (%)	-	-	8 (40.0)	7 (63.6)	8 (25.8)	7 (22.6)
ALT increased	-	-	2 (10.0)	2 (10.0)	2 (6.5)	2 (6.5)
Liver function test abnormal	-	-	2 (10.0)	2 (10.0)	2 (6.5)	2 (6.5)
Transaminases increased	-	-	2 (10.0)	2 (10.0)	2 (6.5)	2 (6.5)
AST increased	-	-	1 (5.0)	1 (5.0)	1 (3.2)	1 (3.2)
Blood bilirubin increased	-	-	1 (5.0)	1 (5.0)	1 (3.2)	1 (3.2)
Drug-induced liver injury	-	-	1 (5.0)	1 (5.0)	1 (3.2)	1 (3.2)
Jaundice cholestatic	-	-	1 (5.0)	-	1 (3.2)	-
Visual AEs, n (%)	3 (27.3)	1 (9.1)	6 (30.0)	4 (20.0)	9 (29.0)	5 (16.1)
Vision blurred	-	-	3 (15.0)	3 (15.0)	3 (9.7)	3 (9.7)
Visual impairment	-	-	2 (5.0)	1 (5.0)	2 (6.5)	1 (3.2)
Photophobia	1 (9.1)	1 (9.1)	1 (5.0)	1 (5.0)	2 (6.5)	2 (6.5)
Conjunctivitis	-	-	2 (10.0)	-	2 (6.5)	-
Abnormal sensation in the eye	-	-	1 (5.0)	1 (5.0)	1 (3.2)	1 (3.2)
Asthenopia	-	-	1 (5.0)	1 (5.0)	1 (3.2)	1 (3.2)
Chromatopsia	-	-	1 (5.0)	1 (5.0)	1 (3.2)	1 (3.2)
Diplopia	-	-	1 (5.0)	1 (5.0)	1 (3.2)	1 (3.2)
Cataract	-	-	1 (5.0)	-	1 (3.2)	-
Conjunctival hemorrhages	1 (9.1)	-	-	-	1 (3.2)	-
Dry eye	1 (9.1)	-	-	-	1 (3.2)	-
Eye discharge	1 (9.1)	-	-	-	1 (3.2)	-
Eye irritation	-	-	1 (5.0)	-	1 (3.2)	-
Eye pain	-	-	1 (5.0)	-	1 (3.2)	-
SAEs, n (%)	6 (54.5)	1 (9.1)	9 (45.0)	1 (5.0)	15 (48.4)	2 (6.5)
Treatment discontinuation, n (%)	6 (54.5)	1 (9.1)	9 (45.0)	-	15 (48.4)	1 (3.2)
AEs	1 (9.1)	-	-	-	1 (3.2)	-
Insufficient clinical response	1 (9.1)	1 (9.1)	-	-	1 (3.2)	1 (3.2)
No longer willing to participate	-	-	1 (5.0)	-	1 (3.2)	-
Patient died	3 (27.3)	-	2 (10.0)	-	5 (16.1)	-
Other	1 (9.1)†	-	6 (30.0)‡	-	7 (22.6)	-
Study discontinuation, n (%)	3 (27.3)	-	3 (15.0)	-	6 (19.4)	-
Patient died	3 (27.3)	-	2 (10.0)	-	5 (16.1)	-
No longer willing to participate	-	-	1 (5.0)	-	1 (3.2)	-

*All patients received at least 1 dose of voriconazole. In the vori-IA study the median (range) duration of IV treatment (n = 31), oral treatment (n = 22) and total treatment was 8.0 (3–33) days, 59.5 (2–81) days and 41.0 (3–90) days, respectively.

†Visual testing was not completed at screening and day 7.

‡Addition of another antifungal medication for additional coverage based on computed tomography findings and continued positive galactomannan with increasing titers (n = 1); IA not approved (n = 1); no proven or probable IA (n = 1); IA not identified, relapsing of lymphoma (n = 1); no longer possible IA (proven *Candida tropicalis* infection; n = 1); patient diagnosed with bacterial lung infection.

AE indicates adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IA, invasive aspergillosis; SAE, severe adverse event.

TABLE 6. Summary of Safety Data from the Vori-IC/EC Study (Safety Population)

	Vori-IC/EC Study					
	2–<12 Yr (n = 14)		12–<18 Yr (n = 8)		Overall* (n = 22)	
	All-Causality	Treatment-Related	All-Causality	Treatment-Related	All-Causality	Treatment-Related
AEs, n	78	13	35	5	113	18
Patients with AEs, n (%)	13 (92.9)	8 (57.1)	6 (75.0)	3 (37.5)	19 (86.4)	11 (50.0)
Hepatic AEs, n (%)	6 (42.9)	5 (35.7)	1 (12.5)	-	7 (31.8)	5 (22.7)
ALT abnormal	3 (21.4)	1 (7.1)	-	-	2 (9.1)	1 (4.5)
ALT increased	1 (7.1)	1 (7.1)	-	-	1 (4.5)	1 (4.5)
AST abnormal	1 (7.1)	1 (7.1)	-	-	1 (4.5)	1 (4.5)
AST increased	1 (7.1)	1 (7.1)	-	-	1 (4.5)	1 (4.5)
GGT abnormal	2 (14.3)	1 (7.1)	-	-	2 (9.1)	1 (4.5)
Hepatic enzyme increased	1 (7.1)	1 (7.1)	-	-	1 (4.5)	1 (4.5)
Hyperbilirubinemia	1 (7.1)	1 (7.1)	-	-	1 (4.5)	1 (4.5)
Liver disorder	1 (7.1)	1 (7.1)	-	-	1 (4.5)	1 (4.5)
Blood ALP abnormal	1 (7.1)	-	-	-	1 (4.5)	-
Gallbladder disorder	1 (7.1)	-	-	-	1 (4.5)	-
GGT increased	-	-	1 (12.5)	-	1 (4.5)	-
Hepatosplenomegaly	1 (7.1)	-	-	-	1 (4.5)	-
Jaundice	1 (7.1)	-	-	-	1 (4.5)	-
Visual AEs, n (%)	6 (42.9)	3 (21.4)	3 (37.5)	3 (37.5)	9 (40.9)	6 (27.3)
Photophobia	2 (14.3)	2 (14.3)	1 (12.5)	1 (12.5)	3 (13.6)	3 (13.6)
Conjunctivitis	1 (7.1)	1 (7.1)	-	-	1 (4.5)	1 (4.5)
Eye pruritus	-	-	1 (12.5)	1 (12.5)	1 (4.5)	1 (4.5)
Retinal disorder	-	-	1 (12.5)	1 (12.5)	1 (4.5)	1 (4.5)
Amaurosis	1 (7.1)	-	-	-	1 (4.5)	-
Corneal opacity	1 (7.1)	-	-	-	1 (4.5)	-
Eyelid disorder	1 (7.1)	-	-	-	1 (4.5)	-
Visual acuity reduced	1 (7.1)	-	-	-	1 (4.5)	-
SAEs, n (%)	2 (14.3)	-	1 (12.5)	1 (12.5)	3 (13.6)	1 (4.5)
Treatment discontinuation, n (%)	7 (50.0)	2 (14.3)	2 (25.0)	1 (12.5)	9 (40.9)	3 (13.6)
AEs	2 (14.3)	2 (14.3)	2 (25.0)	1 (12.5)	4 (18.2)	3 (13.6)
Medication error	1 (7.1)	-	-	-	1 (4.5)	-
Protocol violation	1 (7.1)	-	-	-	1 (4.5)	-
Other	3 (21.4)†	-	-	-	3 (13.6)	-
Study discontinuation, n (%)	1 (7.1)	-	-	-	1 (4.5)	-
Lack of confirmation of *Candida* infection	1 (7.1)	-	-	-	1 (4.5)	-

*All patients received at least one dose of voriconazole. In the vori-IC/EC study, the median (range) duration of IV treatment (n = 22), oral treatment (n = 13), and total treatment was 7.0 (2–24) days, 9.0 (2–37) days, and 14.0 (2–42) days, respectively.

†Lack of confirmation of *Candida* infection.

AE indicates adverse events; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EC, esophageal candidiasis; GGT, γ-glutamyl transferase; IC, invasive candidiasis; IV, intravenous; SAE, severe adverse event.
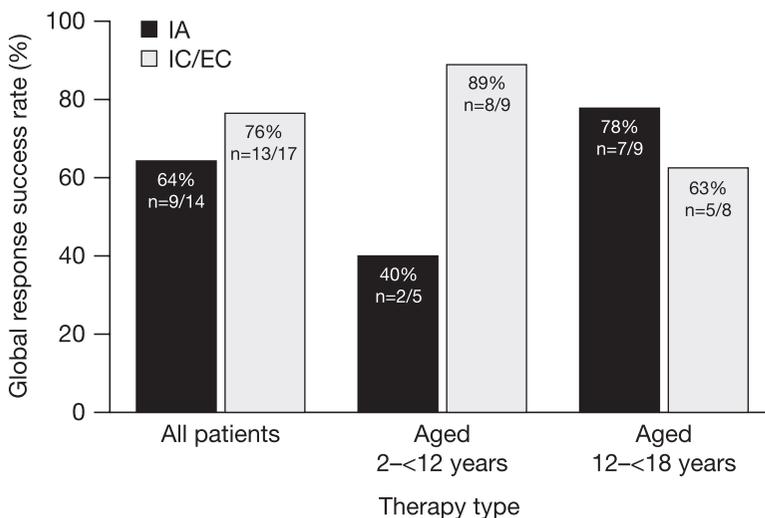

FIGURE 2. Global response success rates at EOT in patients with IA and IC/EC (MITT population). EC indicates esophageal candidiasis; EOT, end of treatment; IA, invasive aspergillosis; IC, invasive candidiasis; MITT, modified intent-to-treat.

for severe muscle weakness and fever. At that time, the patient's blood bilirubin was 6.4 mg/dL, AST 694 IU/L and ALT 684 IU/L. The patient was also diagnosed with steroid-related muscle weakness and parainfluenza type 1 bronchitis. The patient completed voriconazole therapy for the treatment of IA on day 40. Liver function tests returned to normal on day 64 (24 days after last voriconazole dose).

Fifteen patients discontinued treatment. Only 1 patient (7-year-old male) discontinued treatment because of an AE; this patient discontinued on day 3 because of an SAE of sepsis (unrelated to voriconazole) and recovered by day 9. One treatment discontinuation was considered to be treatment related (insufficient clinical response); 6 patients were subsequently discontinued from the study for other reasons.

Vori-IC/EC Study

A safety summary is presented in Table 6. Eleven of 22 patients experienced 18 treatment-related AEs, most commonly photophobia (n = 3). Most treatment-related AEs were mild or moderate. Treatment-related hepatic AEs were reported in 5 patients (22.7%) and were mild or moderate in severity except for 1 case of severe liver disorder. Treatment-related visual AEs were reported by 6 patients (27.3%) and were mild or moderate in severity. Only 2 patients (9.1%) reported any treatment-related skin AEs [rash (=2); data not shown], which were both mild in severity; no psychiatric treatment-related AEs were observed. Serious adverse events were experienced by 3 of 22 patients; 1 SAE (EC patient), recorded as progression of suspected splenic candidiasis later confirmed by biopsy, was considered treatment related. Splenic candidiasis progressed to the kidneys and eye, despite systemic voriconazole treatment. Subsequent use of lipid amphotericin B and micafungin treatment did not lead to improvement; however, neutrophil reconstitution in addition to micafungin and posaconazole treatment led to remission on day 390 (373 days after last voriconazole dose).

Nine patients discontinued the treatment. Four patients discontinued the treatment because of AEs and, of these, 3 discontinued because of treatment-related AEs. Specifically, a 9-year-old female with IC (salvage) and medical history of pancreatic tumor, hyperbilirubinemia and heart failure permanently discontinued treatment on

FIGURE 3. Basic goodness-of-fit plots for the final pharmacokinetic model, showing: observed concentrations versus population predicted concentrations (A); observed concentrations versus individually predicted concentrations (B); conditional weighted residuals versus individually predicted concentrations (C); conditional weighted residuals versus time (D). Open circles represent observed data; the dashed line represents the line of identity or unity; the solid line represents the local regression smooth line (loess smooth). The closer the smooth line is to the line of identity or unity, the more robust the model fit.
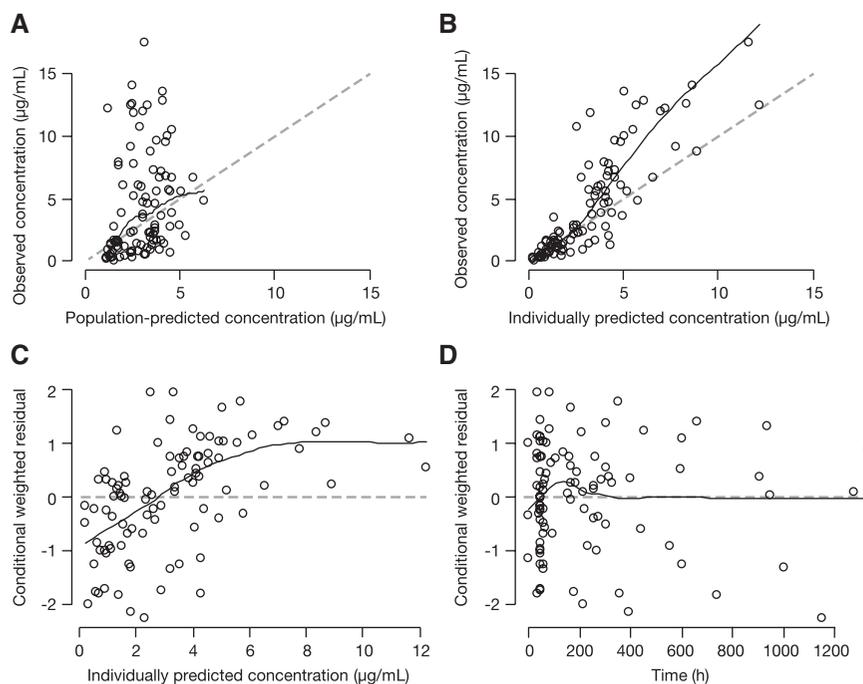
TABLE 7. Summary of Estimated Voriconazole Exposures in Pediatric Patients Based on Final Pharmacokinetic Model

	Voriconazole AUC_{0-12} (µg·h/mL)		Voriconazole C_{min} (µg/mL)	
	8 mg/kg IV q12 h	9 mg/kg oral q12 h*	8 mg/kg IV q12 h	9 mg/kg oral q12 h*
Children (n = 21)				
Regimen	8 mg/kg IV q12 h	9 mg/kg oral q12 h*	8 mg/kg IV q12 h	9 mg/kg oral q12 h*
Geometric mean (CV%)	49.63 (57)	46.86 (60)	2.65 (77)	3.56 (64)
Median (range)	51.54 (20.67–171.08)	45.66 (19.84–170.76)	2.95 (0.69–12.67)	3.48 (1.39–13.86)
Young adolescents aged 12–14 yr weighing <50 kg (n = 10)				
Regimen	8 mg/kg IV q12 h	9 mg/kg oral q12 h*	8 mg/kg IV q12 h	9 mg/kg oral q12 h*
Geometric mean (CV%)	54.91 (40)	50.57 (43)	3.0 (52)	3.86 (46)
Median (range)	68.24 (20.35–85.79)	62.02 (19.54–82.44)	4.19 (0.66–5.61)	4.84 (1.36–6.51)
All other adolescents (n = 17)				
Regimen	4 mg/kg IV q12 h	200 mg oral q12 h	4 mg/kg IV q12 h	200 mg oral q12 h
Geometric mean (CV%)	37.28 (59)	27.72 (65)	2.18 (75)	2.15 (67)
Median (range)	33.78 (17.7–110.05)	25.07 (8.89–79.36)	1.97 (0.76–8.27)	1.94 (0.65–6.46)

*Maximum oral dose was not to exceed 350 mg q12 h.

AUC_{0-12} indicates area under the curve from 0 to 12 hours; C_{min}, minimum plasma concentration (trough); CV%, coefficient of variation in percentage.
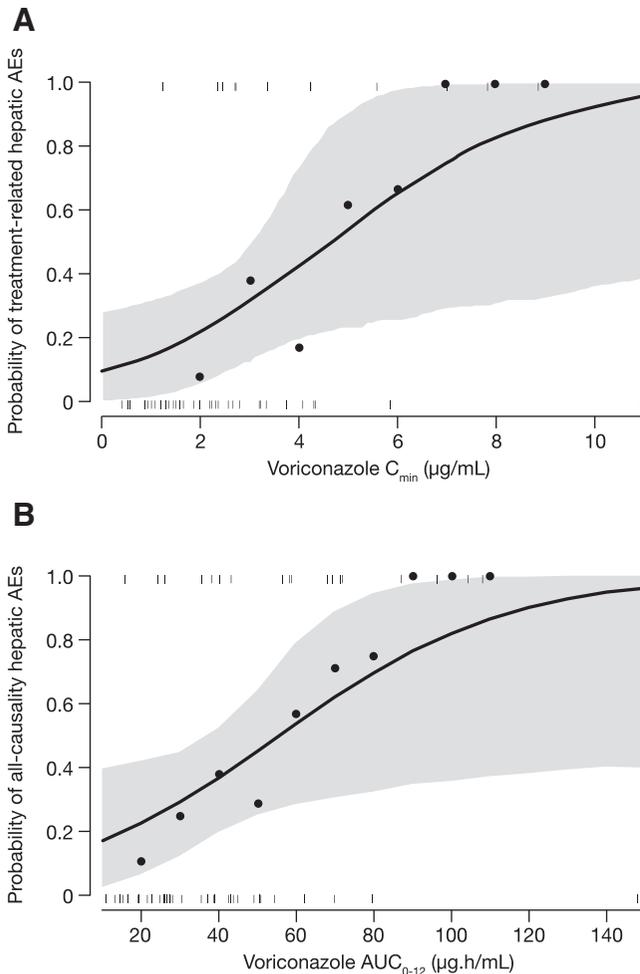
A

B

FIGURE 4. Observed and model-predicted probability of treatment-related hepatic AEs versus voriconazole C_{min} (A) and all-causality hepatic AEs versus voriconazole AUC_{0-12} (B) using multiple-panel data. "|" symbols represent observed individual data (AE present = 1, AE absent = 0); solid circles represent the observed probability of an AE at each concentration level (note: individual concentration values were rounded up to the next integral value for summary purposes). The line and the corresponding band represent the population-predicted probability and its 95% CI (computed with 1000 bootstrap). A wide 95% CI indicates low precision on the probability prediction. AE indicates adverse event; AUC_{0-12}, area under the curve from 0 to 12 hours; CI, confidence interval; C_{min}, minimum plasma concentration (trough).

day 12 after developing moderate hyperbilirubinemia, which resolved on day 17. A 5-year-old male with EC and medical history of acute lymphocytic leukemia, chemotherapy-related anemia, antithrombin III deficiency and hepatomegaly permanently discontinued the treatment on day 23 after developing severe liver disorder. On day 23, blood bilirubin was 2.1 mg/dL, AST 661.2 IU/L and ALT 282 IU/L. The event resolved by day 27 (4 days after last voriconazole dose). Concomitant medications taken within 2 weeks of the event of severe liver disorder included cytarabine, cyclophosphamide, pegaspargase, methotrexate and tioguanine. A 12-year-old girl with EC permanently discontinued the treatment on day 17 after developing severe

progression of suspected splenic candidiasis as described above. One patient lost to follow-up was discontinued from the study.

Efficacy

Vori-IA Study

The week 6 global success rate in patients with proven/probable IA (n = 14) was 64.3% [95% confidence interval (CI): 35.1–87.2] and was sustained at EOT. Success rates were numerically greater for adolescents aged 12–<18 years [77.8% (95% CI: 40.0–97.2)] versus children aged 2–<12 years [40.0% (95% CI: 5.3–85.3)]. EOT global response failures included an observed failure in 1 patient, indeterminate result in 1 patient and missing data in 3 patients. Four deaths due to septic shock (n = 3) and ruptured mycotic aneurysm (n = 1) were reported before week 6 (up to day 63), and 1 death due to acute lymphocytic leukemia was reported on day 75. There were 2 deaths in modified intent-to-treat patients aged <12 years; none were attributed to voriconazole. One patient died on day 30 and the other died on day 38.

Vori-IC/EC Study

EOT global success rate in patients with IC/EC (n = 17) was 76.5% (95% CI: 50.1–93.2). EOT global success rates were 88.9% (95% CI: 51.7–99.7) for patients aged 2–<12 years and 62.5% (24.5, 91.5) for those aged 12–<18 years. Global response for IC patients (n = 7) included success in 6 patients and indeterminate result in 1 patient. Global response for EC patients (n = 10) included success in 7 patients, failure in 1 patient and indeterminate results in 2 patients. Two EC patients with a successful EOT global response had recurrence of EC (14 and 16 days after last voriconazole dose). One EC patient with a successful EOT global response developed suspected splenic candidiasis during therapy. EOT global response success rates by therapy and baseline pathogen are presented in Figure 2. No patients died by the 1-month follow-up visit.

Exposure–Response Analyses

For all age groups, a 2-compartment pharmacokinetic model with first-order absorption and linear elimination reasonably described voriconazole data, with the caveat of some underestimation of high concentrations, as shown in the basic diagnostic plots (Fig. 3). These plots showed that the data points were generally distributed symmetrically across the line of identity or line of unity, although many data points appeared to be widely spread, and several higher concentration data points were skewed from the line of identity or unity. This is not unexpected given the sparse data from phase 3 studies.

The equations for the final pharmacokinetic model are presented below, and interindividual variability was estimated for clearance only, given the limited concentration data.

$$CL = \theta_{CL}\left(WT / 70\right)^{0.75}$$
$$V_2 = \theta_{V2}\, WT / 70$$
$$V_3 = \theta_{V3}\, WT / 70$$
$$Q = \theta_Q\left(WT / 70\right)^{0.75}$$
$$\text{logit}\left(F1\right) = \theta_{F1}$$
$$k_a = \theta_{ka}$$
$$\text{Rate} = \theta_{rate}$$

CL indicates linear clearance; V_2, central volume of distribution; V_3, peripheral volume of distribution; Q, intercompartmental clearance; $F1$, oral bioavailability; k_a, first-order absorption rate constant; rate, infusion rate used to estimate voriconazole concentration from prior treatment; and θ, estimate of fixed effects in NONMEM.

At matching doses, voriconazole exposures in children and young adolescents with low body weight were comparable with those in heavier or older adolescents, given the large interindividual variability (Table 7). Although average voriconazole exposures tended to be greater in CYP2C19 poor metabolizers (n = 3) and heterozygous extensive metabolizers (n = 12) than homozygous extensive metabolizers (n = 17), substantial overlap in exposure distributions was seen across groups because of large interindividual variability (data on file; 16 patients did not have genotyping information available).

An association between increased voriconazole exposures (AUC_{0-12} and C_{min}) and treatment-related hepatic AEs was established (Fig. 4A). For all-causality hepatic AEs, the association was only related to voriconazole AUC_{0-12} but not C_{min} (Fig. 4B). The wide 95% CIs for the population predictions of probability of hepatic AE occurrence as a function of voriconazole exposure reflect the large uncertainty of the prediction (Fig. 4A and B). Note that this positive association was identified only when multiple-panel data (all AE occurrences) were analyzed. When single-panel data (without counting AE frequency in each patient) were analyzed, this positive association diminished for both treatment-related and all-causality hepatic AEs. No associations between voriconazole exposures and visual AEs, psychiatric or skin and subcutaneous tissue disorders were identified.

Given the limited sample size and high success rate, no association between voriconazole exposures and efficacy was established for IA and EC patients (Fig. 5A and B). All patients with IC for whom exposure data were available (n = 6) had global success at EOT; the exposure–response analysis was not performed because of the lack of failure cases. The average voriconazole AUC_{0-12} in IC patients ranged from 27.2 to 62 µg·h/mL, and average C_{min} ranged from 1.09 to 4.32 µg/mL.

DISCUSSION

These data suggest that voriconazole is generally effective in pediatric patients with IA and IC/EC, with a favorable risk–benefit balance. Overall, the safety of voriconazole in this small number of pediatric patients was similar to the known safety profile in adults. Pediatric patients had a numerically greater frequency of hepatic-related AEs associated with liver enzyme elevations; however, the nature and severity of hepatic AEs in the pediatric population was similar to that seen in adults. Hepatic AEs (all-causality and treatment related) in the vori-IA study only occurred in patients aged 12–<18 years, whereas most hepatic AEs in the vori-IC/EC study occurred in patients aged 2–<12 years. Because visual disturbances are known side effects of voriconazole use in adults, visual symptoms were
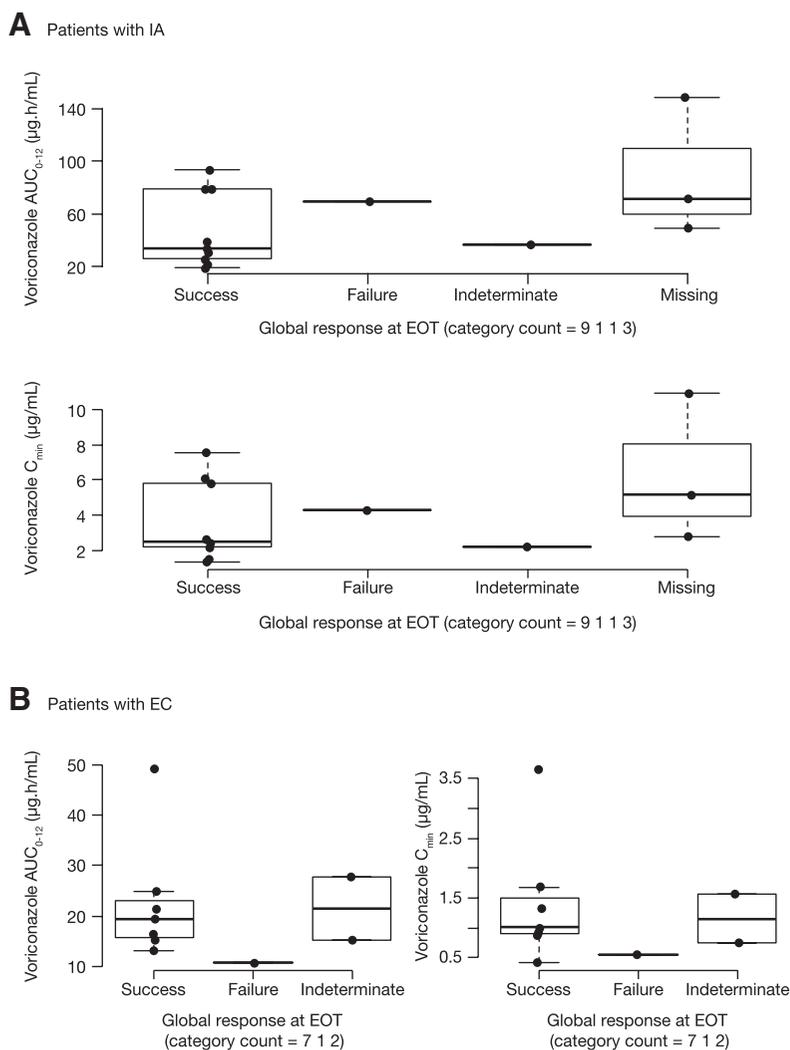

A Patients with IA

B Patients with EC

FIGURE 5. EOT global response versus voriconazole AUC_{0-12} and C_{min} in patients with IA (A) and patients with EC (B). Horizontal center line represents the median; box represents the interquartile distance; whiskers represent ≤1.5 × interquartile range; solid circles represent the estimated individual exposure parameters. AUC_{0-12} indicates area under the curve from 0 to 12 hours; C_{min}, minimum plasma concentration (trough); EC, esophageal candidiasis; EOT, end of treatment; IA, invasive aspergillosis.

closely monitored throughout these studies. However, whether the tests used accurately assess visual AEs in children is unclear. It may be the case that children are unable to accurately report visual symptoms using these tests, instead, any visual disturbances manifest themselves as atypical behaviors. Of note, we did attempt to assess behavioral change in patients by administering the visual questionnaire, but no clear pattern of change was observed.

End of treatment global success rate in pediatric patients with IA was 64.3% (n = 9/14), similar to that seen in the adult therapeutic IA study (52.8%; n = 76/144) at 12 weeks.[15] In addition, EOT global success rates in pediatric patients with IC and EC were 85.7% (n = 6/7) and 70.0% (n = 7/10; indeterminate: n = 2/10), respectively, and comparable with those reported in the adult therapeutic studies for IC (65.3%; n = 162/248) and EC (98.3%; n = 113/115).[14,16] In the IA study, the success rate was numerically greater in patients aged 12–<18 years (77.8%) than in patients aged 2–<12 years (40.0%). In the IC/EC study, the reverse was true with greater success rate in patients aged 2–<12 years (88.9%) than in patients aged 12–<18 years (62.5%). However, any interpretation of these data is limited by the small subgroup sample sizes and by the open-label, non-comparative design of the presented studies.

Compared with the previously developed pharmacokinetic model for immunocompromised pediatric patients,[21] this model was simplified by removing the nonlinear component of clearance, without substantial degradation of model performance. The model fit voriconazole trough concentrations well although the absorption phase was poorly estimated, which was not unexpected as limited concentration data were available (particularly at absorption phase). On the basis of the totality of the model performance metrics, the simplified model was deemed acceptable to provide individual voriconazole exposure estimates.

Typical voriconazole clearance in these pediatric patients was greater than that in adults with IA (7.79 versus 5.30 L/h/70 kg, respectively).[24] Estimated oral bioavailability in pediatric patients was greater than that reported previously for immunocompromised pediatric patients and adults with IA (85% versus 64%, respectively).[21,24] The oral bioavailability of voriconazole in healthy adults has been estimated to be greater than 90%.[12,25] The large interindividual variability in oral bioavailability and voriconazole exposure seen in these patients may be because of them receiving many concomitant medications and having various serious underlying conditions, which could affect the oral absorption and disposition processes and could not be easily delineated.
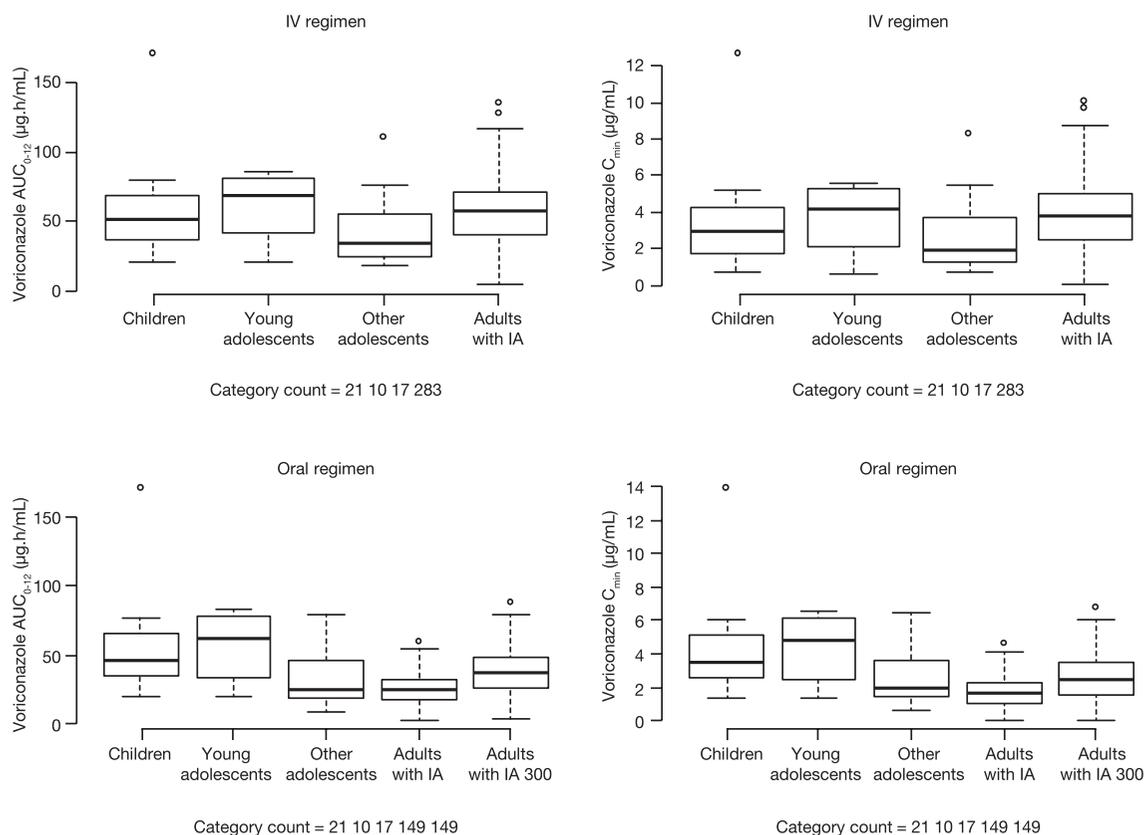

FIGURE 6. Comparison of estimated steady-state voriconazole AUC_{0-12} and C_{min} by age group at matching IV and oral doses in patients with IA. Horizontal center line represents the median; box represents the interquartile distance; whiskers represent ≤1.5 × interquartile range; outliers are represented by open circles beyond whiskers. Intravenous regimen: 8 mg/kg q12h for children (aged 2–<12 years) and young adolescents (aged 12–14 years weighing <50 kg); 4 mg/kg q12h for all other adolescents and adults with IA. Oral regimen: 9 mg/kg (max 350 mg) q12h for children (aged 2–<12 years) and young adolescents (aged 12–14 years weighing <50 kg); 200 mg q12h for all other adolescents and adults with IA. Note that data from adults with IA at 300 mg oral q12h are also included here and denoted as "Adults with IA 300". This figure was created for easy comparison across different age groups. AUC_{0-12} indicates area under the curve from 0 to 12 h; C_{min}, minimum plasma concentration (trough); IA, invasive aspergillosis; IV, intravenous; q12h, every 12 h.

The current analysis is consistent with previous findings in adults with IA where CYP2C19 genotyping status did not have a clinically relevant effect on voriconazole exposure.[24] A recently published article concluded that a CYP2C19 genotype-directed dosing algorithm (ie, 5, 6 or 7 mg/kg q12h stratified by CYP2C19 status) allowed pediatric patients (n = 20) to reach target voriconazole concentration significantly sooner than pediatric patients with a standard dosing regimen (5 mg/kg q12h, n = 25).[26] Of note, the doses evaluated in that publication are lower than those investigated in our studies. It is possible that the use of lower doses in these pediatric patients might be an important factor in the delay of reaching target concentration, in addition to the CYP2C19 polymorphism. CYP2C19 is known to be the major pathway for voriconazole metabolism, but notably other pathways, such as CYP3A4 and CYP2C9, are also involved and consequently CYP2C19 genotype alone does not explain the variability in voriconazole exposure. The impact of genotype on voriconazole exposure can be influenced by a patient's demographic characteristics, underlying disease and concomitant medications. Hence, voriconazole dose adjustment solely based on CYP2C19 genotype is not currently recommended.

Approximately 42% of pediatric patients received omeprazole or esomeprazole (CYP2C19 inhibitors known to increase voriconazole exposure in healthy subjects[27]). Although no trend was identified in our assessment, the impact of these concomitant medications on voriconazole exposure cannot be ruled out. Similarly, approximately 30% of adults with IA for comparison also received concomitant omeprazole or esomeprazole.[24] At matching IV doses, average exposure values and distributions were similar in these pediatric patients and adult patients with IA (Fig. 6). At matching oral doses, average exposures in pediatric patients were greater than that in adult patients with IA; however, substantial overlap in exposure distributions was observed between groups (Fig. 6). Considering that treatment is being provided for potentially life-threatening infections, it is preferred to start with a dose with relatively high exposure to ensure sufficient coverage and then reduce to lower doses if needed.

Although an association between increased voriconazole exposure and hepatic AEs was established (with multiple-panel data only), voriconazole concentrations could not be used to accurately predict hepatic AE occurrence given the large uncertainty of prediction (Fig. 4A and B). Note that the multiple-panel data analysis may have overestimated the AE occurrence probability, as a patient with multiple AEs would be counted several times.

The lack of association of voriconazole exposure with efficacy and other safety end points may be because of an insufficient sample size. These findings are consistent with what has previously been reported in adult patients with IA.[24] These patients typically had multiple comorbidities and received multiple medications. In addition, treatment effect is just one of the contributing factors leading to successful clinical outcomes for life-threatening fungal infections. Patients' underlying conditions and ability to respond to the treatment are also important factors influencing the clinical outcomes. No consensus regarding correlations of voriconazole exposure with clinical outcomes and treatment-related toxicity has been established because of the complexity of fungal infections in the clinical setting, despite substantial efforts to do so.[9,10,28–37] Therefore, the clinical response and tolerability of individual patients should continue to be the primary consideration for dose adjustment, and voriconazole C_{min} (if available) should be considered as a secondary marker for the purpose of dose adjustment.

In our studies, most pediatric patients (64%; n = 34) did not require dose adjustments; 26% (n = 14) had dose reductions and 11% (n = 6) had dose escalations. One patient had dose reduction and dose escalation during the treatment period. Among them, 9 patients had dose reductions because of high voriconazole concentrations, whereas 3 had dose escalations because of low concentrations based on predefined provisional instructions. Dose adjustment with 1 mg/kg (50 mg oral) was sufficient for all but 3 patients with IA, indicating that slight adjustment of the initial dose was generally adequate. Taken together, the proposed dosing regimens were deemed acceptable as the initial recommendation for pediatric patients.

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