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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Vfend®/Voriconazole

PROTOCOL NO.: A1501096

PROTOCOL TITLE: A multicenter, open-label, non-controlled, intravenous to oral switch, phase 2 study to evaluate the pharmacokinetics, safety and tolerability of voriconazole in immunocompromised children aged 2 to <15 years who are at high risk for systemic fungal infection

Study Center(s): 6 centers in Japan

Study Initiation Date and Primary Completion or Final Completion Dates:
20 September 2011 to 11 May 2013

Phase of Development: Phase 2

Study Objective(s): Primary: To characterize the pharmacokinetics, safety, and tolerability of voriconazole following an intravenous (IV) to oral switch regimen in immunocompromised children aged 2 to <15 years who are at high risk for systemic fungal infection.

Secondary: To explore the effect of potential covariates (eg, cytochrome P450 [CYP] 2C19 genotype status, age, body weight, gender) on the systemic exposure of voriconazole.

METHODS

Study Design: This was a multi-center, open-label, non-controlled Phase 2 study to evaluate the pharmacokinetics, safety, and tolerability of voriconazole following an IV to oral switch regimen in immunocompromised children aged 2 to <15 years who were at high risk for systemic fungal infection.

The study consisted of the pharmacokinetic period (IV and oral treatments), post-pharmacokinetic period, and follow-up period (Figure 1).

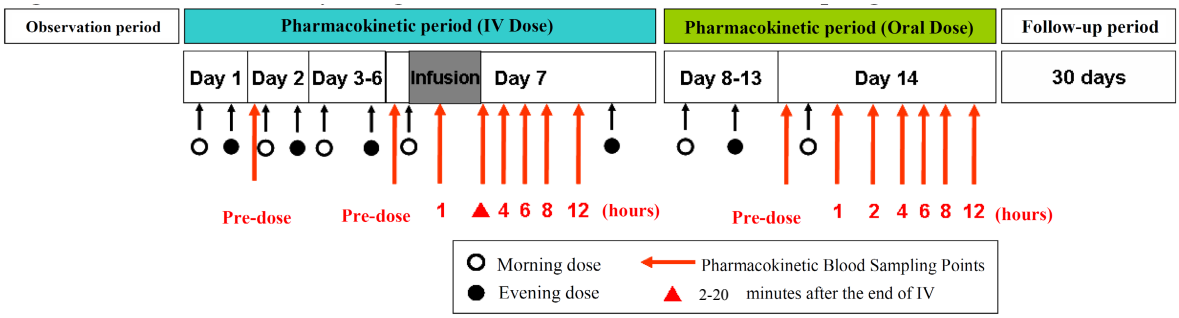
Pharmacokinetic period: a period from the start of IV treatment through the 7th day of oral treatment (7-day IV treatment and 6.5-day oral treatment with the powder for oral suspension [Day14, only the morning dose]; however, if the subject was unable to take oral medication on the 1st day of oral treatment [Day 8], IV treatment could be continued for a maximum of 20 days [up to Day 20] before switching to the oral treatment).

Post-pharmacokinetic period: an optional period based on a clinical need (if neutropenia [absolute neutrophil count <500 cells/μL] persisted and the risk for development of systemic

fungal infections was still high) to continue treatment (a treatment period which lasted beyond the end of the pharmacokinetic period [up to the 7th day of IV or oral treatment] for a total of up to 30 days [up to Day 30] including the pharmacokinetic period).

Follow-up period: 30 days (±7 days) after the last dose of voriconazole.

Figure 1. Overview of Study Design and Pharmacokinetic Blood Sampling Points



Voriconazole was administered according to the dosing regimens listed in Table 1.

Table 1. Voriconazole Dosing Schedule

	Loading dose	Maintenance dose	
	IV dose	IV dose	Oral dose[a]
Administration timing	Day 1	Day 2-7	Day 8[b]-14[c]
• Patients aged 2 to <12 years • Patients aged 12 to <15 years (weighing <50 kg)	9 mg/kg IV q12 h (for the first 24 hours of treatment)	8 mg/kg IV q12 h	9 mg/kg PO q12 h (up to a maximum of 350 mg PO q12 h)
• Patients aged 12 to <15 years (weighing ≥50 kg)	6 mg/kg IV q12 h (for the first 24 hours of treatment)	4 mg/kg IV q12 h	200 mg PO q12 h

q12h = twice daily at 12-hour intervals; IV = intravenous/intravenous dose, PO = powder for oral suspension/oral dose

a. The oral regimen was administered at least 1 hour before or 1 hour following a meal. An allowance time for twice daily dosing at 12-hour intervals was ±1 hour.
b. If subjects were unable to switch to the oral regimen on the 1st day of oral treatment (Day 8), the IV regimen could be continued up to 20 days (Day 20) before switching to the oral regimen.
c. On the 7th day of oral treatment (Day 14), only the morning oral dose was given. If clinically indicated, voriconazole treatment could be continued for a total of up to 30 days (Day 30) including the pharmacokinetic period.

Number of Subjects (Planned and Analyzed): 20 subjects were planned as targeted number of subjects and 21 subjects were analyzed.

Diagnosis and Main Criteria for Inclusion: Male or female subjects, 2 to <15 years of age, who required treatment for the prevention of systemic fungal infection, who was expected to develop neutropenia (absolute neutrophil count <500 cells/µL) lasting more than 10 days, and who could tolerate being switched to oral therapy after 7 to 20 days of voriconazole IV therapy.

Study Treatment: All voriconazole IV doses were administered at an infusion rate of 3 mg/kg/h, ie, the 9, 8, 6, or 4 mg/kg dose was administered intravenously over 180, 160, 120, or 80 minutes, respectively. If another drug was administered at the same time of

voriconazole infusion, a different line was used. Voriconazole oral doses were taken between meals, at least 1 hour before or 1 hour following a meal. An allowance time for twice daily dosing at 12-hour intervals was ± 1 hour.

Pharmacokinetic and Pharmacogenomic Endpoints: The primary endpoints of the pharmacokinetic evaluations were as follows:

- Steady-state pharmacokinetic parameters of voriconazole following IV or oral administration: area under the curve over dosing interval at steady state ($AUC_{12,ss}$), peak plasma concentration at steady state ($C_{max,ss}$), and time to reach C_{max} (T_{max})

- Plasma voriconazole concentrations (The 2nd day of IV treatment [Day 2]: just prior to the start of morning dosing; The 7th day of IV treatment [Day 7]: just prior to the start of morning dosing, 1 hour after the start of infusion, 2-20 minutes after the end of infusion, and 4, 6, 8, and 12 hours after the start of infusion; The 7th day of oral treatment [Day 14]: just prior to the start of morning dosing, and 1, 2, 4, 6, 8, and 12 hours after dosing)

The secondary endpoints were as follows:

- The ratio of $AUC_{12,ss}$ following oral treatment relative to $AUC_{12,ss}$ following IV treatment

- Steady-state pharmacokinetic parameters of the major metabolite UK-121,265 (N-oxide-voriconazole) following IV and oral treatment: $AUC_{12,ss}$, $C_{max,ss}$, and T_{max} (if plasma concentration data allowing to calculate the parameters were obtained)

Plasma voriconazole and UK-121,265 concentrations were analyzed using a validated liquid chromatography/tandem mass spectrometry method.

In the pharmacogenomic evaluation, CYP2C19 genotyping was performed in all subjects.

Safety Evaluations: Adverse events were recorded on the case report form from the time of the first IV treatment (Day 1) through the last subject visit of the 30-day follow-up period. Serious adverse events were reported from the time that the signed informed consent was provided through and including 28 calendar days after the last administration of the investigational product or the last visit day during the 30-day follow-up period (the latest allowance date being 37 days) whichever the latest date. However, serious treatment-related adverse events were to be reported promptly even after completion of the reporting period. The clinical laboratory tests, near-distance visual acuity test, color vision test, and assessment of visual symptoms were performed once each at screening, on the 7th day of IV treatment (Day 7), on the 1st day of oral treatment (Day 8, near-distance visual acuity test, color vision test, and assessment of visual symptoms only), on the 7th day (Day 14) of oral treatment, and at the 30-day follow-up visit. The body temperature, pulse rate, blood pressure, and 12-lead electrocardiograms were measured once each at screening, on the 1st day of IV treatment (Day 1) just prior to the morning dose, on the 7th day of IV treatment (Day 7) at 15 minutes before the end of morning dosing, on the 1st day (Day 8) and the 7th day (Day 14) of oral treatment at 2 hours post morning dosing, and at the 30-day follow-up visit.

Statistical Methods: The pharmacokinetic concentration analysis was performed on all subjects treated who had at least 1 concentration in either IV or oral treatment period. Descriptive statistics of plasma concentrations of voriconazole and the major metabolite UK-121,265 (N-oxide-voriconazole) were calculated by specified sampling timepoints after the administration.

The pharmacokinetic parameter analysis was performed on all subjects treated who had at least 1 of the pharmacokinetic parameters of interest. Descriptive statistics of $AUC_{12,ss}$, $C_{max,ss}$ and T_{max} on the 7th day of IV and oral treatments were calculated. Descriptive statistics of the ratio of $AUC_{12,ss}$ following oral treatment relative to $AUC_{12,ss}$ following IV treatment were calculated.

The safety analysis was performed on all subjects who received at least 1 dose of study medication.

The safety endpoints were summarized in accordance with the Pfizer Data Standards, which specifies Pfizer's standard methods for reporting clinical study data. Adverse events were coded to the system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) version 16.0.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table 2. A total of 21 subjects were assigned to and received study treatment in this study. A total of 16 subjects completed and 5 subjects discontinued the study. Two of the 5 subjects discontinued before switching to the oral treatment. The reasons for discontinuations were treatment related adverse event in 2 subjects (hepatic function abnormal and liver function test abnormal), other (because a treatment with commercial voriconazole was required during the follow-up) in 2 subjects, and no longer willing to participate in study in 1 subject.

All the 21 subjects who received study treatment were analyzed for safety and pharmacokinetic concentration. One subject (aged 11 years and extensive metabolizer [EM]) was excluded from the pharmacokinetic parameter analysis because the subject discontinued the study on Day 7 and blood sampling for drug concentration was performed at only 1 timepoint on Day 7. Consequently, 20 subjects were analyzed for pharmacokinetic parameter.

Table 2. Subject Disposition

Number (%) of Subjects	All
Assigned to study treatment	21
Treated	21
Completed	16 (76.2)
Discontinued	5 (23.8)
Treatment related adverse event	2 (9.5)
No longer willing to participate in study	1 (4.8)
Other	2 (9.5)[a]
Analyzed for pharmacokinetics	
Pharmacokinetic concentration	21 (100.0)
Pharmacokinetic parameter	20 (95.2)
Analyzed for safety	
Adverse events	21 (100.0)
Laboratory data	21 (100.0)

a. Because a treatment with commercial voriconazole was required during the follow-up.

Of the 21 subjects, 9 subjects (42.9%) were male and 12 subjects (57.1%) were female. The mean age was 9.2 years (range: 3 to 14 years), the mean weight was 30.4 kg (range: 11.5 to 55.2 kg), and the mean Body Mass Index was 16.6 kg/m^2 (range: 11.9 to 22.9 kg/m^2) (Table 3).

Table 3. Demographic Characteristics

Number (%) of Subjects	N=21
Gender	
Male	9 (42.9)
Female	12 (57.1)
Race	
Asian	21 (100.0)
Age (years)	
2～6	5 (23.8)
7～11	10 (47.6)
12～14	6 (28.6)
Mean ± Standard Deviation	9.2±3.4
Range	3～14
Weight (kg)	
Mean ± Standard Deviation	30.4±12.7
Range	11.5～55.2
BMI (kg/m^2)	
Mean ± Standard Deviation	16.6±3.0
Range	11.9～22.9
Height (cm)	
Mean ± Standard Deviation	132.3±22.6
Range	89.0～166.1

BMI = Body Mass Index
BMI = Weight / (Height × 0.01)^2

The diseases or procedures that caused immunocompromised status were acute lymphocytic leukaemia in 8 subjects, acute myeloid leukaemia in 7 subjects, Ewing's sarcoma in 2

subjects, and neuroblastoma, osteosarcoma, bone marrow transplant, and stem cell transplant in 1 subject each.

Pharmacokinetic and Pharmacogenomic Results: Voriconazole pharmacokinetic parameters are summarized descriptively for all subjects and by age-weight group in Table 4. $C_{max,ss}$ were generally observed at the end of IV administration and about 1 hour postdose following oral administration. Individual T_{max} values of 1 to 4 hours were observed for both IV and oral dosing. For all subjects included in the pharmacokinetic parameter analysis, the mean $AUC_{12,ss}$ following IV administration was 51.13 µg•hr/mL and the mean $AUC_{12,ss}$ following oral administration was 45.76 µg•hr/mL. The largest group of subjects (N=14) was the younger age group of 2 to <12 years. The mean $AUC_{12,ss}$ for this age group was 51.92 µg•hr/mL following IV administration, and 48.23 µg•hr/mL following oral dosing. The 4 subjects in the older age group with lower body weight (12 to <15 years and <50 kg) had higher average exposure than the younger subjects with the same dosing regimen, especially following IV administration. These average values reflect 1 of the 4 subjects who had the highest $AUC_{12,ss}$ value (for IV dosing, 177 µg•hr/mL; for oral dosing, 117 µg•hr/mL); the values of the 3 other subjects were comparable with the younger age group. The 2 subjects in the 12 to <15 years age group with ≥50 kg body weight, with lower voriconazole doses (the same regimen as for adults), both had a lower $AUC_{12,ss}$ than other groups for both IV dosing and oral dosing. The results for voriconazole $C_{max,ss}$ were consistent with those observed for $AUC_{12,ss}$.

Table 4. Pharmacokinetic Parameters for Plasma Voriconazole Concentration by Age-Weight

Route	Parameter (Units)	Age-Weight	N	Geometric Mean (Coefficient of Variation%)	Median[a] (Range)
IV	$AUC_{12,ss}$ (µg•hr/mL)	All	20	51.13 (68)	59.25 (14.2-177)
		2≤ age (years) <12	14	51.92 (51)	60.15 (23.0-103)
		12≤ age (years) <15 and weight (kg) <50	4	83.39 (56)	70.45 (55.7-177)
		12≤ age (years) <15 and weight (kg) ≥50	2	17.27 (28)	17.60 (14.2-21.0)
	$C_{max,ss}$ (µg/mL)	All	20	7.323 (51)	7.715 (2.32-19.6)
		2≤ age (years) <12	14	7.753 (38)	8.205 (4.62-12.6)
		12≤ age (years) <15 and weight (kg) <50	4	9.233 (55)	7.715 (6.24-19.6)
		12≤ age (years) <15 and weight (kg) ≥50	2	3.092 (42)	3.220 (2.32-4.12)
	T_{max} (hr)	All	20	NA	2.96 (0.950-4.20)
		2≤ age (years) <12	14	NA	2.96 (0.950-4.00)
		12≤ age (years) <15 and weight (kg) <50	4	NA	4.00 (2.92-4.20)
		12≤ age (years) <15 and weight (kg) ≥50	2	NA	1.34 (1.00-1.67)
PO	$AUC_{12,ss}$ (µg•hr/mL)	All	18	45.76 (90)	45.60 (10.0-156)
		2≤ age (years) <12	14	48.23 (83)	45.60 (12.4-156)
		12≤ age (years) <15 and weight (kg) <50	3	59.42 (67)	49.40 (36.3-117)
		12≤ age (years) <15 and weight (kg) ≥50	1	NA	10.00[a]
	$C_{max,ss}$ (µg/mL)	All	18	7.222 (59)	6.475 (2.03-18.3)
		2≤ age (years) <12	14	7.755 (50)	6.695 (3.58-18.3)
		12≤ age (years) <15 and weight (kg) <50	3	7.910 (45)	6.210 (6.13-13.0)
		12≤ age (years) <15 and weight (kg) ≥50	1	NA	2.03[a]
	T_{max} (hr)	All	18	NA	1.04 (0.917-3.78)
		2≤ age (years) <12	14	NA	1.09 (0.917-3.78)
		12≤ age (years) <15 and weight (kg) <50	3	NA	1.00 (0.950-2.03)
		12≤ age (years) <15 and weight (kg) ≥50	1	NA	1.00[a]

N = number of subjects contributing to the summary statistics. Only median (range) is presented for T_{max}. Summary statistics were not calculated if N=1.
NA = not applicable; IV = intravenous administration; PO = oral administration; $AUC_{12,ss}$ = area under the curve over dosing interval at steady state; $C_{max,ss}$ = peak plasma concentration at steady state; T_{max} = time to reach C_{max}
a. Individual value if N=1

Voriconazole pharmacokinetic results by CYP2C19 genotype are summarized in Table 5. The CYP2C19 genotype status was categorized as EM in 8 subjects, heterozygous extensive metabolizer (HEM) in 10 subjects, and poor metabolizer (PM) in 2 subjects. Of the 2 PM subjects, 1 subject had the highest observed $AUC_{12,ss}$ and $C_{max,ss}$ values for IV dosing; and the other subject had among the highest observed $AUC_{12,ss}$ and $C_{max,ss}$ values for both IV and oral dosing.

Table 5. Pharmacokinetic Parameters for Plasma Voriconazole Concentration by Genotype of CYP2C19

Route	Parameter (Units)	Genotype of CYP2C19	N	Geometric Mean (Coefficient of Variation%)	Median (Range)
IV	$AUC_{12,ss}$ (µg•hr/mL)	EM	8	35.96 (61)	37.60 (14.2-70.0)
		HEM	10	56.44 (50)	66.55 (23.0-103)
		PM	2	127.5 (49)	134.4 (91.8-177)
	$C_{max,ss}$ (µg/mL)	EM	8	5.321 (42)	5.965 (2.32-8.31)
		HEM	10	8.116 (37)	8.745 (4.62-12.5)
		PM	2	15.71 (32)	16.10 (12.6-19.6)
	T_{max} (hr)	EM	8	NA	3.49 (1.00-4.20)
		HEM	10	NA	2.88 (0.950-4.00)
		PM	2	NA	2.95 (2.92-2.97)
PO	$AUC_{12,ss}$ (µg•hr/mL)	EM	6	31.19 (102)	39.60 (10.0-80.8)
		HEM	10	49.34 (79)	45.60 (14.5-156)
		PM	2	99.14 (24)	100.5 (84.0-117)
	$C_{max,ss}$ (µg/mL)	EM	6	5.489 (70)	5.925 (2.03-11.0)
		HEM	10	7.657 (49)	6.475 (4.45-18.3)
		PM	2	12.28 (8)	12.30 (11.6-13.0)
	T_{max} (hr)	EM	6	NA	1.50 (0.950-3.78)
		HEM	10	NA	1.05 (0.917-2.17)
		PM	2	NA	1.02 (0.950-1.08)

N = number of subjects contributing to the summary statistics. Only median (range) is presented for T_{max}.
CYP = cytochrome P450; NA = not applicable; IV = intravenous administration; PO = oral administration; $AUC_{12,ss}$ = area under the curve over dosing interval at steady state; $C_{max,ss}$ = peak plasma concentration at steady state; T_{max} = time to reach C_{max}; EM = extensive metabolizer; HEM = heterozygous extensive metabolizer; PM = poor metabolizer

Inter-individual variability in voriconazole exposure was high, based on a more than 10-fold range in individual $AUC_{12,ss}$ values following either IV administration (14.2 to 177 µg•hr/mL) or oral administration (10.0 to 156 µg•hr/mL).

The average ratios of oral to IV $AUC_{12,ss}$ were about 1.0 for the 14 younger subjects (2 to <12 years), about 0.6 for 3 subjects aged 12 to <15 years and <50 kg, and about 0.5 for 1 subject aged 12 to <15 years and ≥50 kg. Based on the CYP2C19 genotype, the average ratio of oral/IV $AUC_{12,ss}$ was about 1.0 for 6 EM subjects and 10 HEM subjects, and about 0.8 for 2 PM subjects. Individual values for the ratio of $AUC_{12,ss}$ ranged from 0.21 to 2.15 (Table 6).

Table 6. Ratio of oral to IV $AUC_{12,ss}$ for Plasma Voriconazole Concentration

		N	Ratio of oral to IV AUC12,ss	
			Arithmetical Mean ±Standard Deviation	Median[a] (Range)
All		18	0.972 ± 0.521	0.814 (0.21～2.15)
Age-Weight	2≤ age (years) <12	14	1.077 ± 0.547	1.037 (0.21～2.15)
	12≤ age (years) <15 and weight (kg) <50	3	0.648 ± 0.015	0.652 (0.63～0.66)
	12≤ age (years) <15 and weight (kg) ≥50	1	NA	0.476[a]
Genotype of CYP2C19	EM	6	0.929 ± 0.536	0.819 (0.45～1.86)
	HEM	10	1.035 ± 0.579	0.900 (0.21～2.15)
	PM	2	0.788 ± 0.180	0.788 (0.66～0.92)

N = number of subjects contributing to the summary statistics.
IV = intravenous administration; PO = oral administration; $AUC_{12,ss}$ = area under the curve over dosing interval at steady state; NA = not applicable (summary statistics were not calculated if N=1); CYP = cytochrome P450; EM = extensive metabolizer; HEM = heterozygous extensive metabolizer; PM = poor metabolizer
a. Individual value if N=1

The median T_{max} of UK-121,265 (N-oxide-voriconazole) concentration was longer after IV administration (4 to 5 hours) than after oral administration (2 hours), while the time course of the plasma concentration of UK-121,265 was relatively flat throughout the dosing interval of 12 hours, with individual T_{max} values ranging from 0 to 11.8 hours. The exposure to UK-121,265 ($AUC_{12,ss}$ and $C_{max,ss}$) was generally similar to the results of exposure to voriconazole described earlier (Table 7).

Table 7. Pharmacokinetic Parameters for Plasma UK-121265 Concentration

Route	Parameter (Units)	N	Geometric Mean (Coefficient of Variation%)	Median[a] (Range)
IV	$AUC_{12,ss}$ (μg•hr/mL)	20	65.74 (35)	68.25 (32.1～135)
	$C_{max,ss}$ (μg/mL)	20	6.356 (34)	6.650 (3.12～12.9)
	T_{max} (hr)	20	NA	5.05 (1.00～11.8)
PO	$AUC_{12,ss}$ (μg•hr/mL)	18	77.86 (39)	77.00 (34.4～158)
	$C_{max,ss}$ (μg/mL)	18	7.784 (34)	7.490 (3.72～14.1)
	T_{max} (hr)	18	NA	2.07 (0.00～7.78)

N = number of subjects contributing to the summary statistics. Only median (range) is presented for T_{max}. Summary statistics were not calculated if N=1.
NA = not applicable; IV = intravenous administration; PO = oral administration; $AUC_{12,ss}$ = area under the curve over dosing interval at steady state; $C_{max,ss}$ = peak plasma concentration at steady state; T_{max} = time to reach C_{max}
a. Individual value if N=1

Safety Results: Overview of adverse events is provided in Table 8 (by age- weight) and Table 9 (by genotype of CYP2C19).

Table 8. Overview of Adverse Events by Age-Weight

Number (%) of Subjects	All N=21		2≤ Age (years) <12 N=15		12≤ Age (years) <15 and Weight (kg) <50 N=4		12≤ Age (years) <15 and Weight (kg) ≥50 N=2	
	All Causalities	Treatment Related	All Causalities	Treatment Related	All Causalities	Treatment Related	All Causalities	Treatment Related
Number of adverse events	80	19	50	11	26	6	4	2
Subjects with adverse events	18 (85.7)	12 (57.1)	13 (86.7)	8 (53.3)	4 (100.0)	3 (75.0)	1 (50.0)	1 (50.0)
Subjects with serious adverse events	0	0	0	0	0	0	0	0
Subjects with severe adverse events	4 (19.0)	1 (4.8)	2 (13.3)	0	2 (50.0)	1 (25.0)	0	0
Subjects discontinued due to adverse events	2 (9.5)	2 (9.5)	1 (6.7)	1 (6.7)	1 (25.0)	1 (25.0)	0	0
Subjects with dose reduced or temporary discontinuation due to adverse events	0	0	0	0	0	0	0	0

Table 9. Overview of Adverse Events by Genotype of CYP2C19

Number (%) of Subjects	EM N=9		HEM N=10		PM N=2	
	All Causalities	Treatment Related	All Causalities	Treatment Related	All Causalities	Treatment Related
Number of adverse events	42	13	29	6	9	0
Subjects with adverse events	7 (77.8)	6 (66.7)	9 (90.0)	6 (60.0)	2 (100.0)	0
Subjects with serious adverse events	0	0	0	0	0	0
Subjects with severe adverse events	3 (33.3)	1 (11.1)	1 (10.0)	0	0	0
Subjects discontinued due to adverse events	2 (22.2)	2 (22.2)	0	0	0	0
Subjects with dose reduced or temporary discontinuation due to adverse events	0	0	0	0	0	0

EM = extensive metabolizer; HEM = heterozygous extensive metabolizer; PM = poor metabolizer

In total, all-causality adverse events were reported 80 cases in 18 subjects (85.7%) and treatment-related adverse events were reported 19 cases in 12 subjects (57.1%). No apparent trend was observed in the incidences of adverse events by age-weight, by genotype of CYP2C19. The incidence of adverse events related to liver disorder was lower following IV administration compared to the overall period.

No deaths or serious adverse events were reported in this study. Discontinuations due to adverse events were reported in 2 subjects (hepatic function abnormal and liver function test abnormal in 1 subject each). Both events were considered as treatment-related. Both events required treatment but were confirmed to have resolved after the discontinuation of study treatment (Table 10).

Table 10. Discontinuations Due to Adverse Events

MedDRA version 16.0 Preferred term	Severity	Outcome	Causality
Hepatic function abnormal	Severe	Resolved	Treatment-related
Liver function test abnormal	Moderate	Resolved	Treatment-related

MedDRA = Medical Dictionary for Regulatory Activities

Common adverse events were shown in Table 11. Frequently reported all-causality adverse events (incidence ≥10% in total) were febrile neutropenia in 13 subjects (61.9%), photophobia in 9 subjects (42.9%), rash in 4 subjects (19.0%), hepatic function abnormal in 3 subjects (14.3%), alanine aminotransferase increased in 3 subjects (14.3%), and aspartate aminotransferase increased in 3 subjects (14.3%). Frequently reported treatment-related adverse events (incidence ≥10% in total) were photophobia in 9 subjects (42.9%) and hepatic function abnormal in 3 subjects (14.3%).

The majority of adverse events were mild or moderate in severity. Severe all-causality adverse events were reported in 4 subjects (abdominal pain, alanine aminotransferase increased and oropharyngeal pain in 1 subject; febrile neutropenia and epistaxis in 1 subject; hepatic function abnormal in 1 subject; sepsis in 1 subject). Severe treatment-related adverse events were reported in 1 subject (hepatic function abnormal). Except for alanine aminotransferase increased in 1 subject, severe adverse events were confirmed to have resolved.

Table 11. Adverse Events (Reported for ≥2 Subjects)

System organ class Preferred term MedDRA/ version16.0	N=21	
	All causalities	Treatment-related
Blood and lymphatic system disorders		
Febrile neutropenia	13 (61.9)	0
Eye disorders		
Photophobia	9 (42.9)	9 (42.9)
Gastrointestinal disorders		
Vomiting	2 (9.5)	0
General disorders and administration site conditions		
Pyrexia	2 (9.5)	0
Hepatobiliary disorders		
Hepatic function abnormal	3 (14.3)	3 (14.3)
Infections and infestations		
Sepsis	2 (9.5)	0
Investigations		
Alanine aminotransferase increased	3 (14.3)	0
Aspartate aminotransferase increased	3 (14.3)	0
Gamma-glutamyltransferase increased	2 (9.5)	0
Skin and subcutaneous tissue disorders		
Dermatitis	2 (9.5)	2 (9.5)
Rash	4 (19.0)	1 (4.8)

MedDRA = Medical Dictionary for Regulatory Activities

As expected from the underlying disease and its treatment of subjects, the incidence of hematology test abnormalities was high. Frequently observed non-hematology test abnormalities (incidence ≥20%) were increases of C-reactive protein (76.2%), gamma-glutamyltransferase increased (38.1%), aspartate aminotransferase increased (28.6%), and alanine aminotransferase increased (28.6%). Since most of the subjects of this study had received prior chemotherapy for the treatment of the underlying disease, the abnormalities in liver function tests may have been a consequent of the chemotherapy. There were no vital sign or electrocardiogram abnormalities reported as adverse events in this study.

CONCLUSION(S):

- Voriconazole at the dosing regimens in this study provided average steady-state exposure ($AUC_{12,ss}$) of 51.13 µg•hr/mL for IV treatment and 45.76 µg•hr/mL for oral treatment in immunocompromised children aged 2 to <15 years at high risk for systemic fungal infection.

- Systemic exposure in 2 subjects with CYP2C19 PM genotype in this study appeared to be higher than that in subjects categorized as EM or HEM. No apparent difference of exposure was observed between the groups based on age and weight.

- The IV and IV to oral switch regimen of voriconazole were safe and well tolerated, showing no obvious difference from the existing safety profile. The majority of adverse

events were mild or moderate in severity. Frequently reported treatment-related adverse events were photophobia and hepatic function abnormal. Discontinuations due to adverse events were reported in 2 subjects and both events were confirmed to have resolved. No subject experienced a serious adverse event.