Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Isavuconazonium sulfate		
Name of Active Ingredient: Isavuconazole		

SYNOPSIS

Title of Study: A Phase 1, Open-Label, Multicenter, Non-comparative Pharmacokinetics and Safety Study of Intravenous and Oral Isavuconazonium Sulfate in Pediatric Patients, Part 1. 9766-CL-0046.

Investigators/Coordinating Investigator: ▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆

Study Center(s): 11 centers in the U.S.

Publication Based on the Study: None to date

Study Period: 02 Oct 2017 to 09 May 2018 (7 months)

Study Initiation Date (Date of First Enrollment): 02 Oct 2017

Study Completion Date (Date of Last Evaluation): 09 May 2018

Phase of Development: Phase 1

Objectives: The primary objective of this study was to evaluate the pharmacokinetics, safety and tolerability of multiple doses of intravenous and oral isavuconazonium sulfate administered daily in pediatric subjects. In Part 1 of this study, only intravenous study drug was administered.

Methodology: The study was a phase 1, open-label, multicenter study to evaluate the pharmacokinetics, safety and tolerability of intravenous and oral isavuconazonium sulfate in pediatric subjects. This study was conducted in 2 sequential parts: Part 1 consisted of 3 intravenous dosing cohorts and Part 2 is to consist of 2 oral dosing cohorts. In Part 1, pediatric subjects aged 1 to < 18 years of age were enrolled into 3 age cohorts:

- Cohort 1: 1 to < 6 years of age
- Cohort 2: 6 to < 12 years of age
- Cohort 3: 12 to < 18 years of age

Eligible subjects received an intravenous loading regimen of isavuconazonium sulfate, which consisted of a dose every 8 hours (± 2 hours) on days 1 and 2 (a total of 6 doses), followed by once daily intravenous maintenance dosing for up to 26 additional days (for a maximum of 28 days of dosing). The first maintenance dose was to start 12 to 24 hours after the administration of the last loading dose. Subsequent maintenance doses were to be administered once a day (24 hours ± 2 hours from the previous maintenance dose).

The 24-hour intravenous pharmacokinetic profile of isavuconazole, the active moiety of isavuconazonium sulfate, included blood samples collected on days 3 (+ 1 day), 7 (± 1 day), and at the day 28 or EOT visit.

Number of Subjects (Planned, Enrolled and Analyzed): A total of 29 pediatric subjects were enrolled into the 3 age cohorts, ensuring there would be at least 8 subjects evaluable for the primary analysis in each cohort.

Diagnosis and Main Criteria for Inclusion: The study population consisted of subjects who, in the opinion of the treating physician, could benefit from isavuconazonium sulfate in the prophylactic setting. These included those at high risk for invasive fungal disease, such as children with hematological malignancy including HSCT recipients.

Test Product, Dose and Mode of Administration, Batch Numbers: Commercial isavuconazonium sulfate for injection, batch number 929942.

Duration of Treatment (or Duration of Study, if applicable): The maximum period of dosing was to be 28 days.

Reference Product, Dose and Mode of Administration, Batch Numbers: There was no reference product.

Criteria for Evaluation:
Efficacy: No formal prospectively defined efficacy assessments were planned in this study. In cases of breakthrough fungal infection, the site of infection, causative organism, start/stop dates, and any follow-up information available regarding resolution and therapies used to treat the infection was recorded.

Pharmacokinetics: The pharmacokinetic endpoints were as follows:

- C_{max}, AUC_{tau}, t_{max}: day 3 and day 7 (iv only)
- C_{trough}: days 3 and 7, and if applicable, days 14, 21, 28 (iv only):
- Model-derived parameters: CL, V_{ss}, AUC_{ss}, $t_{1/2}$

A preliminary pediatric population pharmacokinetics model was developed based on isavuconazole plasma concentration data obtained from 8 subjects irrespective of age cohort who received intravenous doses of isavuconazonium sulfate, with 24-hour pharmacokinetic profiles from both day 3 and day 7. This model was used to estimate pharmacokinetic parameters to determine if any modification to the intravenous dosing regimen was warranted. Enrollment was not interrupted during the preliminary modeling. After all subjects in Part 1 had completed the study, all subjects with at least one isavuconazole plasma concentration were included in the development of the final intravenous pediatric population pharmacokinetics model. The 24-hour pharmacokinetics profile included blood samples collected on days 3 (+ 1 day), 7 (± 1 day), and at the day 28 or EOT visit (or within 2 days prior to the last dose). If the subject was able to provide pharmacokinetics samples beyond day 7, trough sampling was performed weekly (± 1 day), approximately 24 hours after prior day's infusion (i.e., within 15 minutes prior to start of next infusion) through day 28 or EOT.

Statistical Methods: Observed plasma concentration data for isavuconazole were listed. Individual subject concentration-time profiles (linear and semi-log scale), as well as overlay (spaghetti plots) for each day by age cohort were produced. For the analysis of pharmacokinetics, descriptive statistics included number of subjects (n), mean, SD, CV, geometric mean, geometric CV, median, minimum and maximum. For the t_{max}, only n, median, minimum and maximum was calculated.

Pharmacokinetics parameters (C_{max}, AUC_{tau}, and t_{max}) were listed and summarized using descriptive statistics by age cohort and overall. A pediatric population pharmacokinetics model was developed with intravenous data based on the already established adult population pharmacokinetics model whereby model-derived pharmacokinetics parameters (CL, V_{ss}, AUC_{ss} and $t_{1/2}$) were estimated.

Summary of Results/Conclusions:

Population: A total of 29 subjects were enrolled in this study, and 2 enrolled subjects were not given study drug. Twenty-seven subjects were given at least one dose of study drug (constituting the safety analysis set [SAF]). Of the SAF, 26 subjects provided at least one valid pharmacokinetics measurement (constituting the pharmacokinetic analysis set [PKAS]), and 24 subjects completed the study [Table 1].

The demographic characteristics of the subjects are described in [Table 2]. The subjects were predominately male (21 subjects, 72%) and white (18 subjects, 62%), with ages ranging from 1 to 17 years.

The primary underlying diagnoses of the subjects are shown in [Table 3]. Acute myelogenous leukemia was the most common diagnosis (10 subjects, 37%), followed by neuroblastoma (4 subjects, 14.8%) and aplastic anemia (3 subjects, 11.1%).

All (9/9) subjects in Cohort 1 and all but 2 (6/8) subjects in Cohort 2 were ≤ 40 kg in weight and were dosed at 10 mg/kg; all (10/10) subjects in Cohort 3 weighed more than 40 kg and were dosed at 372 mg.

Efficacy/Pharmacokinetic Results:

Efficacy: No breakthrough infections were observed.

Pharmacokinetics: A summary of C_{trough} values on days 3 and 7 are shown in [Table 4]. A summary of plasma pharmacokinetic parameters of isavuconazole after multiple dosing is presented by age group and day in [Table 5]. Within each age cohort, there was a tendency for C_{max} and AUC_{tau} values to be slightly higher at day 3 than at day 7. The median t_{max} was similar across all age groups. When comparing across age cohorts, on day 3 the mean AUC_{tau} and C_{max} were comparable for Cohorts 1 and 2 and were approximately 30% to 35% lower for Cohort 3. On day 7 the mean AUC_{tau} and C_{max} decreased as age increased.

A population pharmacokinetic model was developed from Part 1 of Study 9766-CL-0046 for the intravenous administration of isavuconazonium sulfate. Due to limited number of pharmacokinetic samples, the data from Study 9766-CL-0046 were combined with that of 16 subjects from Part 2 of Study 9766-CL-0018 who were administered a single dose of 372 mg of isavuconazonium sulfate (iv), including 8 adult subjects with varying degrees of renal impairment and 8 adult healthy subjects.

Based on modeling and simulation results, the proposed daily dose for the clinical study in pediatric patients is:

- 10 mg/kg isavuconazonium sulfate for patients weighing ≤ 37 kg (the maximum loading and daily maintenance doses to be administered to any patient are 372 mg),

OR

- 372 mg isavuconazonium sulfate for patients weighing > 37 kg.

Details of the modeling and simulation procedure and results are available in a separate population pharmacokinetic modeling report.

Based on noncompartmental analysis of parameters on day 3 and day 7, Cohort 3 appears to have lower C_{max} and AUC as compared to Cohorts 1 and 2, however these parameters might not be at steady state. Plasma concentration data from this study will be used to support a population pharmacokinetic model developed for isavuconazole and for pharmacokinetic pharmacodynamic modeling. The results and the model development will be described in detail in the population pharmacokinetic report issued separately from this CSR.

Safety Results: Events from EOT visits that occurred on scheduled visit days were displayed under Day 28/EOT rather than the scheduled visit day.

An overview of TEAEs is shown in [Table 6]. The TEAEs occurring at the frequency of at least 20% of subjects (i.e., 2) at the PT level in any single treatment cohort is shown in [Table 7]. The TEAEs with the highest frequencies were pyrexia (51.9%), mucosal inflammation (44.4%), diarrhea (33.3%), thrombocytopenia, anemia, abdominal pain, epistaxis and pain in extremity (22.2% each). Only subjects in Cohort 1 experienced AEs in the SOC of Injury, poisoning and procedural complications. Otherwise, there were no obvious differences between the age groups.

TEAEs in 37% of subjects (10/27) were considered at least possibly related to study drug [Table 8]. The drug-related TEAEs occurring most frequently were infusion related reaction, procedural nausea, and procedural vomiting, each reported for 2 (22.2%) subjects in Cohort 1. In the other cohorts, no TEAE was seen in more than 1 subject. Study drug-related TEAEs were low in all cohorts.

Overall, 44.4% (12/27) of subjects experienced an SAE. Overall, the most frequent SAEs were diarrhea and pyrexia (3 [11.1%] subjects each), followed by febrile neutropenia, abdominal pain, mucosal inflammation, and cytomegalovirus infection (2 [7.4%] subjects each). The number of SAEs for individual events was very low.

Only 1 SAE (electrocardiogram QT prolonged) was considered at least possibly related to study drug. This SAE resulted in discontinuation of study drug on day 8.

AEs resulting in discontinuation were reported for 2 subjects [Table 9].

In this study, multiple intravenous doses of isavuconazole were generally safe and well tolerated by male and female subjects in all age cohorts, with a safety profile which was similar to adults.

CONCLUSIONS:

- This was the first study in which the safety and pharmacokinetics of isavuconazonium sulfate was formally investigated in children.
- On day 3, C_{max} and AUC_{tau} were comparable for Cohorts 1 and 2, but were lower for Cohort 3. On day 7, AUC_{tau} and C_{max} decreased with increasing age. A population pharmacokinetic model was developed to determine appropriate dosing regimen in children.
- Isavuconazonium sulfate was generally safe and well-tolerated in this study, with an overall AE frequency that was similar to what was observed in adults. The frequency and type of AEs observed was expected based on the underlying medical conditions of the study population.
- No obvious difference in overall and individual-type AEs was observed between the 3 age cohorts.
- Study drug was withdrawn in 1 subject due to liver toxicity, and in 1 subject due to QT prolongation. Two subjects experienced mild IRR events but study drug was not withdrawn by the principal investigator.

Date of Report: 17 Dec 2019

Table 1   Subject Disposition and Analysis Sets, Part 1

Analysis Set	Cohort 1 1 to < 6 years (n = 11) n (%)	Cohort 2 6 to < 12 years (n = 8) n (%)	Cohort 3 12 to < 18 years (n = 10) n (%)	Total (n = 29) n (%)
Registered	11 (100)	8 (100)	10 (100)	29 (100)
Safety analysis set	9 (81.8)	8 (100)	10 (100)	27 (93.1)
Pharmacokinetic analysis set	9 (81.8)	8 (100)	9 (90.0)	26 (89.7)
Treatment discontinuation	2 (18.2)	1 (12.5)	2 (20.0)	5 (17.2)
Adverse event	0	1 (12.5)	1 (10.0)	2 (6.9)
Withdrawal by subject	1 (9.1)†	0	1 (10.0)	2 (6.9)
Other‡	1 (9.1)	0	0	1 (3.4)

All registered subjects.

Safety analysis set: all registered subjects who received at least 1 dose of study drug. Pharmacokinetic analysis set: all registered subjects who took at least one dose of study drug and who had at least one plasma concentration measurement.

† Prior to dosing.
‡ Consent disputed between parents prior to dosing.
Source: End-of-Text Tables 12.1.1.1 and 12.1.1.2, Appendix 13.2.1.1

Table 2   Summary of Demographics and Baseline Characteristics, Part 1

Parameter Category/ Statistics	Cohort 1 1 to < 6 years (n = 11)	Cohort 2 6 to < 12 years (n = 8)	Cohort 3 12 to < 18 years (n = 10)	Total (n = 29) n (%)
Sex, n (%)				
Male	7 (63.6)	6 (75.0)	8 (80.0)	21 (72.4)
Female	4 (36.4)	2 (25.0)	2 (20.0)	8 (27.6)
Ethnicity, n (%)				
Not Hispanic or Latino	4 (36.4)	2 (25.0)	4 (44.4)	10 (35.7)
Hispanic or Latino	7 (63.6)	6 (75.0)	5 (55.6)	18 (64.3)
Missing	0	0	1	1
Race, n (%)				
White	5 (45.5)	7 (87.5)	6 (60.0)	18 (62.1)
Black or African American	3 (27.3)	1 (12.5)	1 (10.0)	5 (17.2)
Asian	1 (9.1)	0	1 (10.0)	2 (6.9)
American Indian or Alaska Native	0	0	0	0
Native Hawaiian or Pacific Islander	1 (9.1)	0	0	1 (3.4)
Other	1 (9.1)	0	2 (20.0)	3 (10.3)
Age, years				
Mean (SD)	3.2 (1.3)	9.0 (1.7)	14.6 (1.8)	8.7 (5.2)
Median	3.0	9.5	14.5	9.0
Min - Max	1–5	6–11	12–17	1–17
Weight, (kg)				
Mean (SD)	15.18 (3.11)	33.81 (16.06)	69.13 (19.15)	38.92 (27.21)
Median	15.60	32.73	65.85	31.80
Min - Max	9.0–19.1	18.6–67.4	42.4–103.5	9.0–103.5
Table continued on next page				

Parameter Category/ Statistics	Cohort 1 1 to < 6 years (n = 11)	Cohort 2 6 to < 12 years (n = 8)	Cohort 3 12 to < 18 years (n = 10)	Total (n = 29) n (%)
Height, (cm)				
Mean (SD)	97.23 (11.76)	136.05 (17.52)	167.06 (9.51)	134.6 (32.34)
Median	96.50	134.75	162.75	139.00
Min - Max	77.0–111.0	116.0–167.9	157.4–181.0	77.0–181.0
BMI, (kg/m^2)				
Mean (SD)	16.92 (2.58)	17.27 (3.59)	24.39 (4.52)	19.79 (5.05)
Median	16.32	17.07	24.34	18.67
Min - Max	13.8–21.6	13.7–23.9	16.3–31.6	13.7–31.6

All registered subjects.

BMI: body mass index (weight [kg]/height [m^2]); Max: maximum; Min: minimum

Source: End-of-Text Table 12.1.2.1

Table 3   Primary Underlying Disease Diagnosis or Event, Part 1

	Cohort 1 1 to < 6 years (n = 11) n (%)	Cohort 2 6 to < 12 years (n = 8) n (%)	Cohort 3 12 to < 18 years (n = 10) n (%)	Total (n = 29) n (%)
Acute lymphocytic leukemia	0	1 (12.5)	1 (10.0)	2 (7.4)
Acute myelogenous leukemia	4 (44.4)	2 (25.0)	4 (40.0)	10 (37.0)
Aplastic anemia	0	2 (25.0)	1 (10.0)	3 (11.1)
Immune disorder	1 (11.1)	0	0	1 (3.7)
Neuroblastoma	3 (33.3)	1 (12.5)	0	4 (14.8)
Other†	1 (11.1)	2 (25.0)	3 (30.0)	6 (22.2)
Other solid tumor‡	0	0	1 (10.0)	1 (3.7)
Missing	2	0	0	2

All registered subjects.

† Idiopathic aplastic anemia, X-linked adrenoleukodystrophy, hemophagocytic lymphohistiocytosis, acute lymphocytic leukemia relapse, acute myeloblastic leukemia, severe combined immunodeficiency disease.
‡ Metastatic Ewing's sarcoma.

Source: End-of-Text Table 12.1.2.1, Appendix 13.2.4.1

Table 4   Summary of Plasma Trough Concentrations (ng/mL) for Intravenous Isavuconazole (PKAS)

Observed Parameter Statistic	Cohort 1 1 to < 6 years	Cohort 2 6 to < 12 years	Cohort 3 12 to < 18 years
C$_{trough}$ (ng/mL)			
Day 3			
n	9	8	9
Mean (SD)	4200 (1440)	4310 (2120)	2520 (1120)
%CV	34.3	49.1	44.6
Median	4460	4190	2720
Min – Max	2210 – 6110	1700 – 8020	1120 – 4420
Day 7			
n	9	8	8
Mean (SD)	3320 (1710)	2970 (1680)	2730 (1140)

Table continued on next page

Observed Parameter Statistic	Cohort 1 1 to < 6 years	Cohort 2 6 to < 12 years	Cohort 3 12 to < 18 years
%CV	51.5	56.7	41.6
Median	3610	2400	2380
Min – Max	1140 – 5950	770 – 5230	1710 – 4960

PKAS: all subjects who took at least 1 dose of study drug and who have at least 1 plasma concentration. Patients received 6 loading doses of isavuconazonium sulfate at 10 mg/kg (if weight ≤ 40 kg) or at 372 mg (if weight > 40 kg) on days 1 and 2, and on days 3 to 28 received 10 mg/kg or 372 mg, respectively, once daily.

CV: coefficient of variation; Geo: geometric; Min: minimum; Max: maximum; PKAS: pharmacokinetic analysis set.

Source: End-of-Text Table 12.4.1

Table 5   Summary of Plasma Pharmacokinetic Parameters for Intravenous Isavuconazole by Cohort and Day (PKAS)

Parameter Statistic	Cohort 1 1 to < 6 years	Cohort 2 6 to < 12 years	Cohort 3 12 to < 18 years
Day 3 (± 1)			
C_{max} (ng/mL)			
n	8	6	8
Mean (SD)	7810 (830)	7800 (1640)	5530 (2320)
%CV	10.6	21.0	41.9
Median	7960	8110	5200
Min – Max	6520 – 8930	5020 – 9420	2970 – 9730
AUC_{tau} (h·ng/mL)			
n	8	6	8
Mean (SD)	112000 (25000)	102000 (35000)	70100 (29600)
%CV	22.2	34.5	42.2
Median	105000	107000	61600
Min – Max	79900 – 157000	58800 – 156000	41800 – 132000
t_{max} (h)			
n		6	8
Median	1.11	1.08	1.11
Min – Max	0.883 – 1.17	1.02 – 4.37	0.900 – 1.17
Day 7 (± 1)			
C_{max} (ng/mL)			
n	9	8	7
Mean (SD)	7310 (1210)	6780 (2110)	5020 (1200)
%CV	16.6	31.1	23.8
Median	7310	6970	5650
Min – Max	5840 – 9960	4440 – 9910	3440 – 6120
AUC_{tau} (h·ng/mL)			
n	8	8	6
Mean (SD)	96800 (47300)	87200 (33200)	76800 (20500)
%CV	48.9	38.1	26.6
Median	102000	78200	77800
Min – Max	43000 – 179000	56000 – 144000	54100 – 103000
Table continued on next page			

Parameter Statistic	Cohort 1 1 to < 6 years	Cohort 2 6 to < 12 years	Cohort 3 12 to < 18 years
t_{max} (h)			
n	9	8	7
Median	1.08	1.08	1.07
Min – Max	1.03 – 1.35	1.02 – 1.22	1.02 – 1.20

PKAS: all subjects who took at least 1 dose of study drug and who have at least 1 plasma concentration. Subjects received 6 loading doses of isavuconazonium sulfate at 10 mg/kg (if weight ≤ 40 kg) or at 372 mg (if weight > 40 kg) on days 1 and 2, and on days 3 to 28 received 10 mg/kg or 372 mg, respectively, once daily.

CV: coefficient of variation; Geo: geometric; Min: minimum; Max: maximum; PKAS: pharmacokinetic analysis set.

Source: End-of-Text Table 12.4.2

Table 6   Overview of Treatment-emergent Adverse Events (SAF)

Number and Percentage of Subjects	Cohort 1 1 to < 6 years (n = 9) n (%)	Cohort 2 6 to < 12 years (n = 8) n (%)	Cohort 3 12 to < 18 years (n = 10) n (%)	Total (n = 27) n (%)
Any TEAE	7 (77.8)	8 (100.0)	10 (100.0)	25 (92.6)
Drug-related† TEAEs	3 (33.3)	3 (37.5)	4 (40.0)	10 (37.0)
Serious TEAE‡s	3 (33.3)	4 (50.0)	5 (50.0)	12 (44.4)
Drug-related† Serious TEAEs‡	0	0	1 (10.0)	1 (3.7)
TEAEs Leading to Withdrawal of Treatment	0	1 (12.5)	1 (10.0)	2 (7.4)
Drug-related† TEAEs Leading to Withdrawal of Treatment		1 (12.5)	1 (10.0)	2 (7.4)
Deaths§	0	0	0	0

SAF: all registered subjects who received at least 1 dose of study drug. A TEAE was defined as an AE observed after starting administration of the study drug through follow-up. AE: adverse event; SAE: serious adverse event; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

† A reasonable possibility that the event may have been caused by the study drug as assessed by the investigator. If relationship is missing then it is considered as drug-related.
‡ Includes SAEs upgraded by the sponsor based on review of the sponsor's list of Always Serious terms, if any upgrade was done.
§ All reported deaths after the first study drug administration.

Source: End-of-Text Table 12.6.1.1

Table 7   Frequency of Treatment-emergent Adverse Events Occurring in ≥ 20% of Subjects in Any Treatment Cohort (SAF)

MedDRA (v19.1) System Organ Class Preferred term	Cohort 1 1 to < 6 years (n = 9) n (%)	Cohort 2 6 to < 12 years (n = 8) n (%)	Cohort 3 12 to < 18 years (n = 10) n (%)	Total (n = 27) n (%)
Overall	**7 (77.8)**	**8 (100.0)**	**10 (100.0)**	**25 (92.6)**
Blood and lymphatic system disorders				
Thrombocytopenia	3 (33.3)	1 (12.5)	2 (20.0)	6 (22.2)
Anaemia	2 (22.2)	1 (12.5)	3 (30.0)	6 (22.2)
Neutropenia	1 (11.1)	2 (25.0)	1 (10.0)	4 (14.8)
Febrile neutropenia	2 (22.2)	0	1 (10.0)	3 (11.1)
Table continued on next page				

MedDRA (v19.1) System Organ Class Preferred term	Cohort 1 1 to < 6 years (n = 9) n (%)	Cohort 2 6 to < 12 years (n = 8) n (%)	Cohort 3 12 to < 18 years (n = 10) n (%)	Total (n = 27) n (%)
Cardiac disorders				
Tachycardia	1 (11.1)	2 (25.0)	2 (20.0)	5 (18.5)
Gastrointestinal disorders				
Diarrhoea	2 (22.2)	4 (50.0)	3 (30.0)	9 (33.3)
Abdominal pain	1 (11.1)	2 (25.0)	3 (30.0)	6 (22.2)
Constipation	0	0	2 (20.0)	2 (7.4)
General disorders and administration site conditions				
Pyrexia	4 (44.4)	5 (62.5)	5 (50.0)	14 (51.9)
Mucosal inflammation	5 (55.6)	4 (50.0)	3 (30.0)	12 (44.4)
Fatigue	1 (11.1)	1 (12.5)	3 (30.0)	5 (18.5)
Immune system disorders				
Graft versus host disease in skin	0	2 (25.0)	3 (30.0)	5 (18.5)
Graft versus host disease	2 (22.2)	1 (12.5)	1 (10.0)	4 (14.8)
Engraftment syndrome	0	1 (12.5)	2 (20.0)	3 (11.1)
Infections and infestations				
Clostridium difficile infection	1 (11.1)	1 (12.5)	2 (20.0)	4 (14.8)
BK virus infection	1 (11.1)	2 (25.0)	0	3 (11.1)
Human herpesvirus 6 infection	0	1 (12.5)	2 (20.0)	3 (11.1)
Cytomegalovirus infection	0	0	2 (20.0)	2 (7.4)
Injury, poisoning and procedural complications				
Infusion related reaction	2 (22.2)	0	0	2 (7.4)
Procedural nausea	2 (22.2)	0	0	2 (7.4)
Procedural vomiting	2 (22.2)	0	0	2 (7.4)
Investigations				
Electrocardiogram QT prolonged	0	0	2 (20.0)	2 (7.4)
White blood cell count decreased	1 (11.1)	0	2 (20.0)	3 (11.1)
Activated partial thromboplastin time prolonged	0	0	2 (20.0)	2 (7.4)
Prothrombin time prolonged	0	0	2 (20.0)	2 (7.4)
Metabolism and nutrition disorders				
Hypomagnesaemia	1 (11.1)	1 (12.5)	3 (30.0)	5 (18.5)
Hyperglycaemia	1 (11.1)	0	2 (20.0)	3 (11.1)
Hypoalbuminaemia	2 (22.2)	0	1 (10.0)	3 (11.1)
Musculoskeletal and connective tissue disorders				
Pain in extremity	1 (11.1)	1 (12.5)	4 (40.0)	6 (22.2)
Arthralgia	0	0	3 (30.0)	3 (11.1)
Back pain	0	0	2 (20.0)	2 (7.4)
Nervous system disorders				
Headache	2 (22.2)	1 (12.5)	0	3 (11.1)
Table continued on next page				

MedDRA (v19.1) System Organ Class Preferred term	Cohort 1 1 to < 6 years (n = 9) n (%)	Cohort 2 6 to < 12 years (n = 8) n (%)	Cohort 3 12 to < 18 years (n = 10) n (%)	Total (n = 27) n (%)
Psychiatric disorders				
Irritability	2 (22.2)	0	1 (10.0)	3 (11.1)
Renal and urinary disorders				
Dysuria	0	3 (37.5)	1 (10.0)	4 (14.8)
Respiratory, thoracic and mediastinal disorders				
Epistaxis	3 (33.3)	2 (25.0)	1 (10.0)	6 (22.2)
Skin and subcutaneous tissue disorders				
Pruritus	2 (22.2)	0	2 (20.0)	4 (14.8)
Rash	0	0	2 (20.0)	2 (7.4)
Urticaria	2 (22.2)	0	0	2 (7.4)
Surgical and medical procedures				
Central venous catheter removal	0	2 (25.0)	0	2 (7.4)
Vascular disorders				
Hypertension	1 (11.1)	2 (25.0)	0	3 (11.1)

SAF: all registered subjects who received at least 1 dose of study drug. A TEAE was defined as an AE observed after starting administration of the study drug through follow-up. Within a system organ class, subjects may have reported more than 1 preferred term.

AE: adverse event; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

Source: End-of-Text Table 12.6.1.2

Table 8   Frequency of Drug-related Treatment-emergent Adverse Events (SAF)

MedDRA (v19.1) System Organ Class Preferred term	Cohort 1 1 to < 6 years (n = 9) n (%)	Cohort 2 6 to < 12 years (n = 8) n (%)	Cohort 3 12 to < 18 years (n = 10) n (%)	Total (n = 27) n (%)
Overall	**3 (33.3)**	**3 (37.5)**	**4 (40.0)**	**10 (37.0)**
Gastrointestinal disorders	**1 (11.1)**	**0**	**1 (10.0)**	**2 (7.4)**
Diarrhoea	1 (11.1)	0	0	1 (3.7)
Nausea	0	0	1 (10.0)	1 (3.7)
Immune system disorders	**0**	**1 (12.5)**	**0**	**1 (3.7)**
Graft versus host disease	0	1 (12.5)	0	1 (3.7)
Injury, poisoning and procedural complications	**2 (22.2)**	**0**	**0**	**2 (7.4)**
Infusion related reaction	2 (22.2)	0	0	2 (7.4)
Procedural nausea	2 (22.2)	0	0	2 (7.4)
Procedural vomiting	2 (22.2)	0	0	2 (7.4)
Investigations	**0**	**2 (25.0)**	**1 (10.0)**	**3 (11.1)**
Electrocardiogram QT prolonged	0	0	1 (10.0)	1 (3.7)
Cardiac murmur	0	1 (12.5)	0	1 (3.7)
Hepatic enzyme increased	0	1 (12.5)	0	1 (3.7)
Metabolism and nutrition disorders	**0**	**1 (12.5)**	**0**	**1 (3.7)**
Fluid imbalance	0	1 (12.5)	0	1 (3.7)
Table continued on next page				

MedDRA (v19.1) System Organ Class Preferred term	Cohort 1 1 to < 6 years (n = 9) n (%)	Cohort 2 6 to < 12 years (n = 8) n (%)	Cohort 3 12 to < 18 years (n = 10) n (%)	Total (n = 27) n (%)
Skin and subcutaneous tissue disorders	**1 (11.1)**	**0**	**3 (30.0)**	**4 (14.8)**
Pruritus generalised	0	0	1 (10.0)	1 (3.7)
Rash	0	0	1 (10.0)	1 (3.7)
Rash follicular	0	0	1 (10.0)	1 (3.7)
Urticaria	1 (11.1)	0	0	1 (3.7)

SAF: all registered subjects who received at least 1 dose of study drug. A TEAE was defined as an AE observed after starting administration of the study drug through follow-up. Within a system organ class, subjects may have reported more than 1 preferred term.

AE: adverse event; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

Source: End-of-Text Table 12.6.1.3

Table 9   Adverse Events Resulting in Discontinuation (SAF)

Treatment Group n Dose	MedDRA (v 19.1) Preferred Term	Onset/Stop Day (Last Dose Day)	Outcome	Relationship to Study Drug
Cohort 2 (n = 1) 185.5 mg	Hepatic enzyme increased	11/15 (13)	Recovered/Resolved	Probable
Cohort 3 (n = 1) 372 mg	Electrocardiogram QT prolonged	7/15 (8)	Recovered/Resolved	Possible

SAF: all registered subjects who received at least 1 dose of study drug. Cohort 1: age group 1 to < 6 years; Cohort 2: age group 6 to < 12 years; Cohort 3: age group 12 years to < 18 years. A treatment-emergent adverse event was defined as an AE observed after starting administration of the study drug through follow-up.

AE: adverse event; SAF: safety analysis set.

Source: Appendices 13.2.1.1, 13.2.5.1, 13.2.7.5

Name of Sponsor/Company: Astellas Pharma Global Development, Inc.		
Name of Finished Product: Isavuconazonium sulfate		
Name of Active Ingredient: Isavuconazole		

SYNOPSIS

Title of Study: A Phase 1, Open-Label, Multicenter, Non-comparative Pharmacokinetics and Safety Study of Intravenous and Oral Isavuconazonium Sulfate in Pediatric Patients, Part 2. 9766-CL-0046.

Investigators/Coordinating Investigator: ███████████████████████████

Study Center(s): 12 centers in the U.S.

Publication Based on the Study: None to date.

Study Period: 01 Oct 2018 to 05 Jul 2019 (8 months)

Study Initiation Date (Date of First Enrollment): 01 Oct 2018

Study Completion Date (Date of Last Evaluation): 05 Jul 2019

Phase of Development: Phase 1

Objectives: The primary objective of this study was to evaluate the pharmacokinetics, safety and tolerability of multiple doses of intravenous and oral isavuconazonium sulfate administered daily in pediatric subjects. In Part 2 of this study, oral study drug was administered.

Methodology: The study was a phase 1, open-label, multicenter study to evaluate the pharmacokinetics, safety and tolerability of intravenous and oral isavuconazonium sulfate in pediatric subjects. This study was conducted in 2 sequential parts: Part 1 consisted of 3 intravenous dosing cohorts and Part 2 consisted of 2 oral dosing cohorts. Subjects younger than 6 years of age were excluded from Part 2 due to the size of the oral capsule. Thus there was no oral treatment cohort corresponding to Cohort 1 (subjects aged 1 to < 6 years) as found in Part 1 of the study. In Part 2, pediatric subjects aged 6 to < 18 years of age were enrolled into 2 age cohorts:

- Cohort 4: 6 to < 12 years of age

- Cohort 5: 12 to < 18 years of age

Eligible subjects in cohorts 4 and 5 received a loading regimen of isavuconazonium sulfate by oral administration, comprising one dose every 8 hours (± 2 hours) on day 1 and day 2 (a total of 6 doses), followed by once daily oral maintenance dosing for up to 26 additional days (a maximum of 28 days of dosing). The first maintenance dose started 12 to 24 hours after the administration of the last loading dose; and subsequent maintenance doses were administered once daily, 24 hours ± 2 hours from the previous maintenance dose.

The 24-hour pharmacokinetic profile of isavuconazole included blood samples collected on day 7 (± 1 day) predose, ± 10 min at 1 hour, 2 hours, 3 hours and 4 hours, ± 30 min at 6 hours and 8 hours and 24 hours (within 1h before next study drug administration) after study drug administration.

Number of Subjects (Planned, Enrolled and Analyzed): A total of 20 subjects were enrolled in Part 2 oral cohorts 4 and 5, ensuring there would be at least 8 subjects evaluable for the primary analysis in each cohort.

Diagnosis and Main Criteria for Inclusion: The study population consisted of subjects who, in the opinion of the treating physician, could benefit from isavuconazonium sulfate in the prophylactic setting. These included those at high risk for invasive fungal disease, such as children with hematological malignancy including hematopoietic stem cell transplantation recipients.

Test Product, Dose and Mode of Administration, Batch Numbers: Isavuconazonium sulfate capsules, drug product batch number 17CH03SD.HQ00059.

Duration of Treatment (or Duration of Study, if applicable): The maximum period of dosing was to be 28 days.

Reference Product, Dose and Mode of Administration, Batch Numbers: There was no reference product.

Criteria for Evaluation:

Efficacy: No formal prospectively defined efficacy assessments were planned in this study. In cases of breakthrough fungal infection, the site of infection, causative organism, start/stop dates, and any follow-up information available regarding resolution and therapies used to treat the infection was recorded.

Pharmacokinetics: For Part 2, the 24-hour pharmacokinetics profile included blood samples collected on day 7 (± 1 day). In addition, blood samples were collected before the first dose on days 2, 3, 5, 14 (± 2 days), 21 (± 2 days), and day 28 (± 2 days).

The pharmacokinetic endpoints were as follows:

- C_{max}, AUC_{tau}, t_{max}: day 7
- C_{trough}: days 2, 3 5 and 7
- Model-derived parameters: CL, V_{ss}, AUC_{ss}, $t_{1/2}$

A preliminary pediatric population pharmacokinetic model was developed by adding plasma concentration data obtained from 8 subjects who received the oral formulation with 24-hour pharmacokinetic profiles, irrespective of age cohort, to the existing pharmacokinetic model developed for the intravenous dosing. These data were used to estimate pharmacokinetic parameters to determine if any modification to the dosing regimen was warranted. After all subjects in Part 2 had completed the study, all subjects from both Part 1 and Part 2 with at least one isavuconazole plasma concentration measurement were included in the final pediatric population pharmacokinetic model. Doses for intravenous and oral administration were proposed based on modeling and simulations in the population pharmacokinetics reports.

Statistical Methods: Observed plasma concentration data for isavuconazole were listed. Individual subject concentration-time profiles (linear and semi-log scale), as well as overlay (spaghetti plots) for each day by age cohort were produced. For the analysis of pharmacokinetics, descriptive statistics included number of subjects (n), mean, SD, CV, geometric mean, geometric CV, median, minimum and maximum. For the t_{max}, only n, median, minimum and maximum were calculated.

Pharmacokinetic parameters (C_{max}, AUC_{tau}, and t_{max}) were listed and summarized using descriptive statistics by age cohort and overall. A pediatric population pharmacokinetic model was developed with intravenous data based on the already established adult population pharmacokinetic model whereby model-derived pharmacokinetic parameters (CL, V_{ss}, AUC_{ss} and $t_{1/2}$) were estimated.

Summary of Results/Conclusions: A total of 20 subjects were enrolled in Part 2 of this study, and 1 enrolled subject was not given study drug. Nineteen subjects were given at least one dose of study drug (constituting the safety analysis set [SAF]). Of these, 19 subjects provided at least one valid pharmacokinetic measurement (constituting the pharmacokinetic analysis set [PKAS]), and 14 subjects completed the study [Table 1].

The demographic characteristics of the subjects are described in [Table 2]. The subjects were predominately female (11 subjects, 55%) and white (16 subjects, 80%), with ages ranging from 6 to 17 years.

The primary underlying diagnoses of the subjects are shown in [Table 3]. Acute myelogenous leukemia was the most common diagnosis (6 subjects, 30%), followed by acute lymphocytic leukemia (5 subjects, 25%).

Most (6/10) subjects in Cohort 4 were ≤ 32 kg in weight and were dosed at 10 mg/kg. All subjects in Cohort 5 weighed more than 32 kg and were dosed at 372 mg. Four (4/10) subjects in Cohort 4 weighed more than 32 kg, and 3 were dosed at 372 mg (1 was not dosed) [Appendices 13.2.4.1 and 13.2.5.1].

Efficacy/Pharmacokinetic/Pharmacodynamic Results:

Efficacy: No breakthrough infections were observed.

Pharmacokinetics: A summary of C_{trough} values at days 2, 3, 5 and 7 is shown in [Table 4]. A summary of plasma pharmacokinetic parameters of isavuconazole after multiple dosing is presented by age group for day 7 in [Table 5]. Within each age cohort, there was a tendency for C_{max} and AUC_{tau} values on day 7 to be slightly higher in the younger cohort. The median t_{max} was similar across both age groups.

Calculated pharmacokinetic parameters from the final population pharmacokinetic model incorporating data from both intravenous and oral dosing (Astellas Study A9766-PK-0008) [Appendix 13.3.1] are shown in [Table 6].

Based on the final simulation, the proposed daily dose administered either intravenously (1 to < 18 years) or orally (6 to < 18 years, with minimum weight of 12 kg) is:

> 10 mg/kg isavuconazonium sulfate for subjects weighing ≤ 37 kg (the maximum loading and daily maintenance doses to be administered to any subject are 372 mg)
>
> OR
>
> 372 mg isavuconazonium sulfate for subjects weighing > 37 kg

Due to similarity in exposures attained after either intravenous or oral administration in pediatric patients, and also to the similarity with the exposures in adult patients after receiving the clinical recommended dosage, the route of administration in pediatric patients can be switched between intravenous and oral as needed. Currently this interchangeability of administration routes is allowed in adults.

Safety Results: Events from EOT visits that occurred on scheduled visit days were displayed under Day 28/EOT rather than the scheduled visit day.

An overview of treatment-emergent adverse events (TEAEs) is shown in [Table 7]. The TEAEs occurring at the frequency of at least 20% of subjects (i.e., 2) at the preferred term level in any single treatment cohort is shown in [Table 8]. The TEAEs with the highest frequencies within a cohort were pyrexia (55.6%), vomiting (40%) and abdominal pain (33.3%). There were no obvious differences between the age groups.

TEAEs in 52.6% of subjects (10/19) were considered at least possibly related to study drug [Table 9]. The drug-related TEAEs occurring most frequently were vomiting and nausea each reported for 2 (22.2%) subjects in Cohort 4. In Cohort 5, no related TEAE was seen in more than 1 subject. Overall, vomiting (15.8%), diarrhea, headache and nausea (10.5% each) were the most common related TEAEs, but study drug-related TEAEs were low in both cohorts.

Overall, 42.1% (8/19) of subjects experienced a serious adverse event (SAE). The most frequent SAE in any single treatment cohort was pyrexia (2 [22.2%] subjects); all other SAEs were experienced by 1 subject each. The number of SAEs for individual events was very low.

One subject reported treatment-related SAEs. Four SAEs (tachycardia, nausea, vomiting and pyrexia) occurred on day 18 in a 10-year-old girl in Cohort 4, and were considered at least possibly related to study drug. The SAE of pyrexia was mild in severity; the SAEs of tachycardia, nausea and vomiting were considered severe. The SAEs of nausea, vomiting and pyrexia resulted in discontinuation of study drug on day 20. The subject recovered and all events were considered resolved. This subject was also noted in regard to a protocol deviation.

Adverse events (AEs) resulting in discontinuation were reported for 4 subjects, 3 in Cohort 4 and 1 in Cohort 5 [Table 10]. One subject in Cohort 4 experienced 4 SAEs on day 18, 3 of which resulted in discontinuation of study drug. The events were considered possibly related to study drug, which was withdrawn on day 20. Another subject in Cohort 4, a 7-year-old-girl, had alanine aminotransferase and aspartate aminotransferase increased on day 23. The events were both of moderate severity and considered to be probably related to study drug, which was withdrawn on the same day. The events were considered to be resolving at the end of the study. A 10-year-old girl subject in Cohort 4 experienced abdominal pain upper of moderate severity on day 9 that was considered to be possibly related to study drug, which was withdrawn on day 10. The event was considered resolved on day 10. In Cohort 5, a 14-year-old girl subject experienced severe mucosal inflammation (oral mucositis) on day 8 that was considered not related to study drug, which was withdrawn on day 7. The event was considered resolved on day 24

CONCLUSIONS:

- This was the first study in which the safety and pharmacokinetics of oral isavuconazonium sulfate was formally investigated in children.
- On day 7, mean AUC_{tau} and C_{max} were numerically higher in the younger subjects (aged 6 to < 12 years), based on noncompartmental pharmacokinetic analysis. A similar trend with age in these parameters was seen in Part 1 of this study following intravenous dosing. The population pharmacokinetic model confirmed that the oral formulation and dosage utilized in present study provided exposures similar to exposures in adults and are adequate to be used in future safety and efficacy clinial trials.
- Isavuconazonium sulfate was generally safe and well-tolerated in this study. There is no new safety information specific to the pediatric population that can be derived from these data. The frequency and type of AEs observed was expected based on the underlying medical conditions of the study population.

- No obvious difference in overall and individual-type AEs was observed between the 2 age cohorts in this part of the study, nor between subjects given intravenous or oral drug in this study.

Date of Report: 19 Dec 2019

Table 1   Subject Disposition and Analysis Sets, Part 2

Analysis Set	Cohort 4 6 to < 12 years (n = 10) n (%)	Cohort 5 12 to < 18 years (n = 10) n (%)	Total (n = 20) n (%)
Registered	10 (100)	10 (100)	20 (100)
Safety analysis set	9 (90.0)	10 (100)	19 (95.0)
Pharmacokinetic analysis set	9 (90.0)	10 (100)	19 (95.0)
Treatment discontinuation	4 (40.0)	2 (20.0)	6 (30.0)
Adverse event	3 (30)	1 (10.0)	4 (20.0)
Withdrawal by subject	1 (10.0)†	0	1 (5.0)
Other	0	1 (10.0)‡	1 (5.0)

All registered subjects.

Safety analysis set: all registered subjects who received at least 1 dose of study drug. Pharmacokinetic analysis set: all registered subjects who took at least one dose of study drug and who had at least one plasma concentration measurement.
† Prior to dosing.
‡ Concomitant medication use.

Source: End-of-Text Tables 12.1.1.1 and 12.1.1.2, Appendix 13.2.1.1

Table 2   Summary of Demographics and Baseline Characteristics, Part 2

Parameter Category/ Statistics	Cohort 4 6 to < 12 years (n = 10)	Cohort 5 12 to < 18 years (n = 10)	Total (n = 20)
Sex, n (%)			
Male	5 (50.0)	4 (40.0)	9 (45.0)
Female	5 (50.0)	6 (60.0)	11 (55.0)
Ethnicity, n (%)			
Not Hispanic or Latino	2 (20.0)	8 (80.0)	10 (50.0)
Hispanic or Latino	8 (80.0)	2 (20.0)	10 (50.0)
Race, n (%)			
White	9 (90.0)	7 (70.0)	16 (80.0)
Black or African-American	0	1 (10.0)	1 (5.0)
Asian	0	1 (10.0)	1 (5.0)
American Indian or Alaska Native	1 (10.0)	0	1 (5.0)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	0	1 (10.0)	1 (5.0)
Age, years			
Mean (SD)	9.0 (1.8)	14.5 (1.4)	11.8 (3.2)
Median	9.5	14.5	11.5
Min - Max	6 - 11	12 - 17	6 - 17
Table continued on next page			

Parameter Category/ Statistics	Cohort 4 6 to < 12 years (n = 10)	Cohort 5 12 to < 18 years (n = 10)	Total (n = 20)
Weight, (kg) Mean (SD) Median Min - Max	32.26 (11.34) 28.6 18.3 – 50.1	55.42 (19.15) 50.35 37.9 – 92.8	43.84 (19.39) 42.45 18.3 – 92.8
Height, (cm) Mean (SD) Median Min - Max	134.60 (12.60) 137.40 114.5 – 153.0	156.81 (8.37) 153.80 147.0 – 173.8	145.71 (15.43) 149.0 114.5- 173.8
BMI, (kg/m^2) Mean (SD) Median Min - Max	17.34 (3.75) 16.69 13.6 – 23.2	22.15 (5.51) 19.83 16.6 – 31.1	19.74 (5.21) 18.42 13.6 – 31.1

All registered subjects.

BMI: body mass index (weight [kg]/height [m^2]); Max: maximum; Min: minimum

Source: End-of-Text Table 12.1.2.1

Table 3   Primary Underlying Disease Diagnosis or Event

Condition	Cohort 4 6 to < 12 years (n = 10) n (%)	Cohort 5 12 to < 18 years (n = 10) n (%)	Total (n = 20) n (%)
Acute lymphocytic leukemia	2 (20.0)	3 (30.0)	5 (25.0)
Acute myelogenous leukemia	4 (40.0)	2 (20.0)	6 (30.0)
Aplastic anemia	1 (10.0)	0	1 (5.0)
Chronic granulomatous disease	0	1 (10.0)	1 (5.0)
Other†	3 (30.0)	4 (40.0)	7 (35.0)

All registered subjects.

FAB: French-American-British classification.

† Acute osteomyelitis, acute myeloid leukemia FAB M5, cystic fibrosis, Fanconi anemia, myelodysplastic syndrome, myelodysplastic syndrome with 5q deletion, myeloid sarcoma.

Source: End-of-Text Table 12.1.2.1, Appendix 13.2.4.1

Table 4   Summary of Plasma Trough Concentrations (ng/mL) for Oral Isavuconazole (PKAS)

Observed Parameter Statistic	Cohort 4 6 to < 12 years	Cohort 5 12 to < 18 years
C$_{trough}$ (ng/mL)		
Day 2		
n	9	10
Mean (SD)	3690 (2070)	2550 (1420)
%CV	56.2	55.8
Median	2700	2270
Min – Max	1210 – 6660	819 – 4930
Table continued on next page		

Observed Parameter Statistic	Cohort 4 6 to < 12 years	Cohort 5 12 to < 18 years
Day 3		
n	9	10
Mean (SD)	4660 (2420)	3690 (1900)
%CV	52.0	51.5
Median	4520	3510
Min – Max	1450 – 8390	1130 – 6960
Day 5		
n	8	9
Mean (SD)	4400 (1750)	3250 (1420)
%CV	39.9	43.7
Median	4920	3450
Min – Max	1560 – 6800	1200 – 5130
Day 7		
n	9	8
Mean (SD)	3970 (1840)	3100 (1620)
%CV	46.3	52.2
Median	3780	2910
Min – Max	1440 – 6350	1230 – 6230

PKAS: all subjects who took at least 1 dose of study drug and who have at least 1 plasma concentration measurement. Subjects received 6 loading doses of isavuconazonium sulfate at 10 mg/kg (if weight $\leq$ 32 kg) or at 372 mg (if weight > 32 kg) on days 1 and 2, and on days 3 to 28 received 10 mg/kg or 372 mg, respectively, once daily.
CV: coefficient of variation; Geo: geometric; min: minimum; max: maximum; PKAS: pharmacokinetic analysis set.
Source: End-of-Text Table 12.4.1

Table 5 **Summary of Observed Plasma Pharmacokinetic Parameters for Oral Isavuconazole by Cohort, Day 7 (PKAS)**

Observed Parameter Statistic	Cohort 4 6 to < 12 years	Cohort 5 12 to < 18 years
Day 7 (± 1)		
C_{max} (ng/mL)		
n	9	8
Mean (SD)	6040 (2240)	5030 (2170)
%CV	37.1	43.1
Median	5780	5430
Min – Max	2870 – 8930	1950 – 7750
AUC_{tau} (ng·h/mL)		
n	7	5
Mean (SD)	111000 (50200)	83300 (33400)
%CV	45.2	40.1
Median	121000	76700
Min – Max	48600 – 185000	37600 – 127000
Table continued on next page		

Observed Parameter Statistic	Cohort 4 6 to < 12 years	Cohort 5 12 to < 18 years
t_{max} (h)		
n	9	8
Median	4.00	3.98
Min – Max	1.98 – 6.08	3.05 – 8.03

PKAS: all subjects who took at least 1 dose of study drug and who have at least 1 plasma concentration measurement. Subjects received 6 loading doses of isavuconazonium sulfate at 10 mg/kg (if weight ≤ 32 kg) or at 372 mg (if weight > 32 kg) on days 1 and 2, and on days 3 to 28 received 10 mg/kg or 372 mg, respectively, once daily.

CV: coefficient of variation; Geo: geometric; min: minimum; max: maximum; PKAS: pharmacokinetic analysis set.

End-of-Text Tables 12.4.1 and 12.4.2

Table 6   **Summary of Calculated Plasma Pharmacokinetic Parameters for Isavuconazole (Intravenous and Oral Dosing) (PKAS)**

Calculated Parameter Statistic	Cohorts 1, 2, 3, 4 and 5 (from Parts 1 and 2)
CL (L/h)	
n	36
Mean (SD)	2.01 (1.16)
V_{ss} (L) †	
n	36
Mean (SD)	207.35 (169.34)
AUC_{ss} (ng·h/mL)	
n	36
Mean (SD)	95180.54 (38734.64)
$t_{1/2}$ (h)	
n	36
Mean (SD)	80.48 (52.28)

PKAS: all subjects who took at least 1 dose of study drug and who have at least 1 plasma concentration measurement.

PKAS: pharmacokinetic analysis set.

† V_{ss} = v2 (volume of central compartment) + v3 (volume of first peripheral compartment) + v4 (volume of second peripheral compartment).

Source: Study A9766-PK-0008 Appendix 10.5

Table 7   Overview of Treatment-emergent Adverse Events (SAF)

Number and Percentage of Subjects	Cohort 4 6 to < 12 years (n = 9) n (%)	Cohort 5 12 to < 18 years (n = 10) n (%)	Total (n = 19) n (%)
Any TEAE	9 (100.0)	9 (90.0)	18 (94.7)
Drug-related† TEAEs	4 (44.4)	6 (60.0)	10 (52.6)
Serious TEAE‡s	5 (55.6)	3 (30.0)	8 (42.1)
Drug-related† Serious TEAEs‡	1 (11.1)	0	1 (5.3)
TEAEs Leading to Withdrawal of Treatment	3 (33.3)	1 (10.0)	4 (21.1)
Drug-related† TEAEs Leading to Withdrawal of Treatment	3 (33.3)	0	3 (15.8)
Deaths§	0	0	0

SAF: all registered subjects who received at least 1 dose of study drug. A TEAE was defined as an AE observed after starting administration of the study drug through follow-up.

AE: adverse event; SAE: serious adverse event; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

† A reasonable possibility that the event may have been caused by the study drug as assessed by the investigator. If relationship is missing then it is considered as drug-related.
‡ Includes SAEs upgraded by the sponsor based on review of the sponsor's list of Always Serious terms, if any upgrade was done.
§ All reported deaths after the first study drug administration.

Source: End-of-Text Table 12.6.1.1

Table 8   Frequency of Treatment-emergent Adverse Events Occurring in ≥ 20% of Subjects in Any Treatment Cohort (SAF)

MedDRA (v19.1) System Organ Class Preferred term	Cohort 4 6 to < 12 years (n = 9) n (%)	Cohort 5 12 to < 18 years (n = 10) n (%)	Total (n = 19) n (%)
Overall	**9 (100.0)**	**9 (90.0)**	**18 (94.7)**
Blood and lymphatic system disorders			
Anaemia	0	2 (20.0)	2 (10.5)
Febrile neutropenia	0	2 (20.0)	2 (10.5)
Cardiac disorders			
Tachycardia	2 (22.2)	0	2 (10.5)
Gastrointestinal disorders			
Vomiting	3 (33.3)	4 (40.0)	7 (36.8)
Abdominal pain	3 (33.3)	2 (20.0)	5 (26.3)
Nausea	2 (22.2)	2 (20.0)	4 (21.1)
Diarrhoea	2 (22.2)	1 (10.0)	3 (15.8)
General disorders and administration site conditions			
Pyrexia	5 (55.6)	2 (20.0)	7 (36.8)
Investigations			
Weight decreased	1 (11.1)	2 (20.0)	3 (15.8)
Nervous system disorders			
Headache	2 (22.2)	1 (10.0)	3 (15.8)
Table continued on next page			

MedDRA (v19.1) System Organ Class Preferred term	Cohort 4 6 to < 12 years (n = 9) n (%)	Cohort 5 12 to < 18 years (n = 10) n (%)	Total (n = 19) n (%)
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	2 (22.2)	0	2 (10.5)
Skin and subcutaneous tissue disorder			
Rash	1 (11.1)	2 (20.0)	3 (15.8)

SAF: all registered subjects who received at least 1 dose of study drug. A TEAE was defined as an AE observed after starting administration of the study drug through follow-up.

AE: adverse event; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

Source: End-of-Text Table 12.6.1.2

Table 9   Frequency of Drug-related Treatment-emergent Adverse Events (SAF)

MedDRA (v19.1) System Organ Class Preferred term	Cohort 4 6 to < 12 years (n = 9) n (%)	Cohort 5 12 to < 18 years (n = 10) n (%)	Total (n = 19) n (%)
Overall	**4 (44.4%)**	**6 (60.0%)**	**10 (52.6%)**
Cardiac disorders	**2 (22.2%)**	**0**	**2 (10.5%)**
Conduction disorder	1 (11.1%)	0	1 (5.3%)
Tachycardia	1 (11.1%)	0	1 (5.3%)
Gastrointestinal disorders	**3 (33.3%)**	**2 (20.0%)**	**5 (26.3%)**
Vomiting	2 (22.2%)	1 (10.0%)	3 (15.8%)
Diarrhoea	1 (11.1%)	1 (10.0%)	2 (10.5%)
Nausea	2 (22.2%)	0	2 (10.5%)
Abdominal pain upper	1 (11.1%)	0	1 (5.3%)
General disorders and administration site conditions	**1 (11.1%)**	**0**	**1 (5.3%)**
Pyrexia	1 (11.1%)	0	1 (5.3%)
Investigations	**1 (11.1%)**	**1 (10.0%)**	**2 (10.5%)**
Alanine aminotransferase increased	1 (11.1%)	0	1 (5.3%)
Aspartate aminotransferase increased	1 (11.1%)	0	1 (5.3%)
Weight decreased	0	1 (10.0%)	1 (5.3%)
Nervous system disorders	**1 (11.1%)**	**1 (10.0%)**	**2 (10.5%)**
Headache	1 (11.1%)	1 (10.0%)	2 (10.5%)
Psychiatric disorders	**1 (11.1%)**	**0**	**1 (5.3%)**
Depression	1 (11.1%)	0	1 (5.3%)
Skin and subcutaneous tissue disorders	**0**	**2 (20.0%)**	**2 (10.5%)**
Pruritus allergic	0	1 (10.0%)	1 (5.3%)
Rash erythematous	0	1 (10.0%)	1 (5.3%)

SAF: all registered subjects who received at least 1 dose of study drug. A TEAE was defined as an AE observed after starting administration of the study drug through follow-up.

AE: adverse event; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

Source: End-of-Text Table 12.6.1.3

Table 10   Adverse Events Resulting in Discontinuation (SAF)

Treatment Group n Age, Sex, Dose	MedDRA (v 19.1) Preferred Term	Onset/Stop Day (Last Dose Day)	Outcome	Relationship to Study Drug
Cohort 4 (n = 3)				
10 years Female 372.5 mg	Nausea	18/39 (20)	Recovered/Resolved	Possible
	Vomiting	18/39	Recovered/Resolved	Possible
	Pyrexia	18/22	Recovered/Resolved	Possible
7 years Female 223.5 mg	Alanine aminotransferase increased	23 – (23)	Recovering/Resolving	Probable
	Aspartate aminotransferase increased	23 –	Recovering/Resolving	Probable
10 years Female 298 mg	Abdominal pain upper	9/10 (10)	Recovered/Resolved	Possible
Cohort 5 (n = 1)				
14 years Female 372.5 mg	Mucosal inflammation	8/24 (7)	Recovered/Resolved	Not related

SAF: all registered subjects who received at least 1 dose of study drug. Cohort 4: age group 6 to < 12 years; Cohort 5: age group 12 to < 18 years. A treatment-emergent adverse event was defined as an AE observed after starting administration of the study drug through follow-up.

AE: adverse event; SAF: safety analysis set.

Source: Appendices 13.2.1.1, 13.2.5.1, 13.2.7.5