Amsterdam, 30 April 2020
EMA/CHMP/304783/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Cresemba

International non-proprietary name: isavuconazonium sulfate

Procedure no.: EMA/H/C/002734/P46/006

Marketing authorisation holder (MAH): Basilea Pharmaceutica Deutschland GmbH

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On January 2020, the MAH submitted a completed paediatric study for Cresemba (study 9766-CL-0046), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure(s) P46. The study is part of the agreed paediatric investigation plan EMEA-001301-PIP02-12-M03 (P/0100/2019).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Description

Isavuconazonium sulfate is a water-soluble triazole antifungal agent and the prodrug of the active moiety isavuconazole. Isavuconazole demonstrates a fungicidal effect by blocking the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14 alpha demethylase responsible for the conversion of lanosterol to ergosterol. This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane, thus weakening the structure and function of the fungal cell membrane.

Isavuconazonium sulfate is indicated in adults for the treatment of

- invasive aspergillosis
- mucormycosis in patients for whom amphotericin B is inappropriate

The current adult posology:

Loading dose

The recommended loading dose is one vial after reconstitution and dilution (equivalent to 200 mg of isavuconazole) every 8 hours for the first 48 hours (6 administrations in total).

Maintenance dose

The recommended maintenance dose is one vial after reconstitution and dilution (equivalent to 200 mg of isavuconazole) once daily, starting 12 to 24 hours after the last loading dose.

Duration of therapy should be determined by the clinical response. For long-term treatment beyond 6 months, the benefit-risk balance should be carefully considered.

Switch to oral isavuconazole

CRESEMBA is also available as hard capsules containing 100 mg isavuconazole, equivalent to 186 mg isavuconazonium sulfate. On the basis of the high oral bioavailability (98%), switching between intravenous and oral administration is appropriate when clinically indicated.

2.2. Information on the development programme

The MAH stated that study 9766-CL-0046 (A phase 1, open-label, multicenter, non-comparative pharmacokinetics and safety study of intravenous and oral isavuconazonium sulfate in paediatric patients) is part of a clinical development program. The variation application consisting of the full relevant data package (i.e. containing several studies) is expected to be submitted by 07/2022.
A listing of all the concerned studies is annexed (Figure 1).

Figure 1. Overview of concerned studies

Non clinical studies

Product Name: Cresemba Active substance: Isavuconazole (as isavuconazonium sulfate)

Study title	Study number	Date of completion	Date of submission of final study report
Thirteen-week, oral gavage repeated-dose study to evaluate safety and toxicokinetics in four groups of juvenile rats treated with isavuconazonium (sulfate) followed by a 4-week recovery period	9766-TX-0066	10 September 2015 (final report signed)	To be submitted in a variation application consisting of the full relevant data package once the paediatric development plan is finalised

Clinical studies

Product Name: Cresemba Active substance: Isavuconazole (as isavuconazonium sulfate)

Study title	Study number	Date of completion	Date of submission of final study report
Open-label, multi-center, noncomparative study to evaluate pharmacokinetics and safety of intravenous and oral isavuconazonium (sulfate) in children from 1 year to less than 18 years of age with haematologic malignancy	9766-CL-0046	5 July 2019 (LPLV) with database lock on 26 July 2019	24 January 2020
Open-label, multi-center, noncomparative study to evaluate safety and tolerability of isavuconazonium (sulfate) in children from 1 year to less than 18 years of age with invasive aspergillosis and infections caused by rare moulds and yeasts (e.g., zygomycetes/mucormycetes, non-candida yeasts or dimorphic fungi)	9766-CL-0107	31 December 2021	Not applicable

The MAH explains that the purpose of study 9766-CL-0046 is to provide an understanding of the pharmacokinetics of intravenous and oral treatment regimens in paediatric subjects of different age groups, but that it does not allow any definitive conclusion regarding the safety and the efficacy of isavuconazole in paediatric patients with invasive aspergillosis/mucormycosis.

Moreover, the MAH does not seek an update of the isavuconazole product information until all studies as outlined in the PIP (in particular Study 9766-CL-0107) are completed.

2.3. Information on the pharmaceutical formulations used in the study

In **part 1** of the study, the *intravenous* drug was administered using the formulation marketed for adult patients (200 mg isavuconazole, powder for concentrate for solution for infusion).

In **part 2** of the study, the *oral* drug was administered. A 74.5 mg size 3 capsule of isavuconazonium sulfate (corresponding to 40 mg isavuconazole) developed for paediatric use was administered to paediatric subjects aged 6 to < 18 years of age.

2.4. Clinical aspects

2.4.1. Introduction

The MAH submitted a final report for:

- A phase 1, open-label, multicenter, non-comparative pharmacokinetics and safety study of intravenous and oral isavuconazonium sulfate in paediatric patients **(9766-CL-0046)**
    - Part 1: The currently approved intravenous formulation (Cresemba for injection) was administered to intravenous cohorts 1 (1 to <6 years), 2 (6 to <12 years, and cohort 3 (12 < 18 years).
    - Part 2: A 74.5 mg oral formulation of isavuconazonium sulfate (corresponding to 40mg isavuconazole) developed for paediatric use was administered orally to cohorts 4 (6 to <12 years) and 5 (12 to < 18 years) in Part 2 of this study. Subjects younger than 6 years of age were excluded from Part 2 due to the size of the oral capsule.

2.4.2. Clinical study (9766-CL-0046)

Methods

Objective(s)

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 paediatric subjects.

Study design

In **part 1**, eleven centres in the US enrolled 29 paediatric subjects aged 1 to < 18 years of age into the following three intravenous 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).

In **part 2**, twelve centres in the US enrolled 24 subjects aged 6 to 18 years old into the following oral cohorts.

- Cohort 4: 6 to < 12 years of age
- Cohort 5: 12 to < 18 years of age

Subjects younger than 6 years of age were excluded from Part 2 due to the size of the oral capsule.

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).

In all cohorts, 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).

For the IV administration, the 24-hour 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. If the subject was able to provide pharmacokinetics samples beyond day 7, trough sampling was performed weekly (± 1 day), approximately 24 hours after the prior day's infusion (i.e., within 15 minutes prior to the start of next infusion) through day 28 or EOT.

For the oral administration, the 24-hour pharmacokinetic profile of isavuconazole was based on blood samples collected on day 7 (± 1 day) pre-dose, ± 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. In addition, blood samples were collected within 1 hour before the (first) dose on each of days 2, 3, 5, 14 (± 2 days), 21 (± 2 days), and day 28 (± 2 days).

For IV, the average duration of treatment in this study was to be approximately 14 days and for oral approximately 7 days (± 1 day); however, for subjects deriving benefit from the prophylactic regimen as deemed by the investigator, treatment could continue for up to a maximum of 28 days.

Study population / Sample size

Inclusion criteria

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 transplant (HSCT) recipients.

Exclusion criteria (major)

One subject had familial short QT syndrome, was receiving medications that are known to shorten the QT interval, or had a clinically significant abnormal ECG.

One subject had evidence of hepatic dysfunction (TBL ≥3 ULN, ALT or AST ≥5 ULN), cirrhosis or chronic hepatic failure

In part 1 and 2, subjects whose pharmacokinetics were not evaluable were assessed and replaced as appropriate. Up to 36 subjects (Part 1) or 24 subjects (Part 2) were to be enrolled to ensure that in each age cohort at least 8 subjects had evaluable pharmacokinetics (see table 2 to 5 in the results section).

Treatments

The adult clinical dosing regimen used to establish the safety and efficacy was 372 mg isavuconazonium sulfate (equivalent to 200 mg isavuconazole) every 8 hours for the first 2 days followed by 372 mg once daily thereafter.

In **part 1**, for children weighing ≤ 40 kg:

- Loading regimen of 10.0 mg/kg isavuconazonium sulfate infusions every 8 hours (± 2 hours), for 6 doses total over the course of days 1 and 2, followed by;
- Maintenance doses of 10.0 mg/kg isavuconazonium sulfate administered once daily for up to a maximum of 26 additional days, starting 12 to 24 hours after the last loading dose.

The maximum loading and daily maintenance doses administered to any subject was to be 372 mg.

For children weighing > 40 kg:

- Loading regimen of 372 mg isavuconazonium sulfate infusions (1 vial) every 8 hours (± 2 hours), for 6 doses total over the course of days 1 and 2, followed by;
- Maintenance doses of 372 mg isavuconazonium sulfate (1 vial) administered once daily for up to a maximum of 26 additional days, starting 12 to 24 hours after the last loading dose.

In **part 2**, the daily oral dose was based on body weight, as shown in table 1.

Table 1. Body weight based dosing for the oral cohorts 4 and 5 (part II).

Body weight (kg)	Loading (Day 1 and Day 2)/Total Daily Isavuconazonium Sulfate Dose (mg)	Maintenance (up to 26 days)/Total Daily Isavuconazonium Sulfate Dose (mg)
16 – 17	3 × 2 capsules (size 3)/447 mg	1 × 2 capsules (size 3)/149 mg
18 – 24	3 × 3 capsules (size 3)/670.5 mg	1 × 3 capsules (size 3)/223.5 mg
25 – 31	3 × 4 capsules (size 3)/894 mg	1 × 4 capsules (size 3)/298 mg
≥ 32 †	3 × 5 capsules (size 3)/1117.5 mg	1 × 5 capsules (size 3)/372.5 mg

† In both Part 1 and Part 2, dosing was 10 mg/kg to maximum dose of 372.5 mg. The cut-off weight of 40 kg used in Part 1 was changed to 32 kg for more dosing accuracy.

Prohibited Therapies:
Treatment with concomitant drugs that are strong inhibitors or inducers of CYP3A4 were prohibited. Use of systemic azole-type antifungals was prohibited during study drug administration. Treatment with concurrent drugs that are CYP3A4 substrates and have a narrow therapeutic range were prohibited or reduced in dose, as determined by the investigator.

Outcomes/endpoints

While dosing is reflected as milligrams of the administered prodrug (isavuconazonium sulfate), this compound is converted by plasma esterases within seconds to the active moiety (isavuconazole), and thus exposure is represented as milligrams of isavuconazole. The pharmacokinetic endpoints of isavuconazole 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}, $t_{1/2}$

Efficacy: no formal prospectively defined efficacy assessments were planned in this study.

The safety endpoints were:

- Nature, frequency, and severity of treatment-emergent adverse events (TEAEs)
- Vital sign measurements (temperature, pulse rate and blood pressure)
- Laboratory assessments (hematology and chemistry)
- Routine 12-lead ECGs

Pharmacokinetic and statistical methods

Pharmacokinetic parameters of isavuconazole were calculated by non-compartmental analysis and by popPK analysis. Pharmacokinetic parameters are presented as geometric mean values with geometric coefficients of variation [%] and/or ranges. Descriptive statistical analyses were applied.

Population pharmacokinetic analyses

A paediatric population pharmacokinetics model was developed with intravenous data (**part 1**) based on the already established adult population pharmacokinetics model, based on **study 9766-CL-0018**, whereby model-derived pharmacokinetics parameters (CL, Vss, AUCss and t1/2) were estimated. The IV model was then updated, adding available PK data from part 2 of the study.

The aim of the population pharmacokinetic analysis was to confirm the appropriate dosing regimens in paediatric population 6 to <12 years of age.

A base paediatric population pharmacokinetic model built on adult IV data (9766-CL-0018) and data from the IV and first PO part (12 to <18 years) of the 9766-CL-0046 study was a 3-compartment model with combined zero and first order absorption and linear elimination. The base model also included allometric scaling based on body weight to scale size-related changes in clearance and volume of distribution. All random effects were treated as log-normally distributed. The Ln-Ln transformation of both the model and the data was used to stabilize the residual variance. The residual variance of the Ln-Ln transformed model was additive. The above-mentioned base model was utilized as an initial model for further development and finalization after the addition of data from the second PO part (6 to <12 years) from the 9766-CL-0046 study.

Serum creatinine, age, liver chemistry, sex and race were explored as covariates in the model. Only statistically significant covariates were included in the model. In addition, the covariates that were included in the best model were required to have clinical significance, which might alter dosing recommendations.

For the best model, population and individual PK parameters were estimated and the precision of the population model parameters (e.g. asymptotic standard errors or bootstrap 95% CIs) were generated. Nonparametric bootstrapping with replacement using 1000 replications was used to provide further validation of the model parameter estimates.

Monte Carlo simulations were performed in NONMEM to confirm the paediatric dosing regimen. Individual and population profiles were simulated to steady-state. The area under the isavuconazole concentration-time curve at steady-state (AUCs) was calculated for each simulated subject. Predicted exposures from the simulated patients were compared against observed exposures from adult patients at the therapeutic dose (372 mg) enrolled in the SECURE study, which was conducted in adult patients with invasive aspergillosis and other filamentous fungi.

The analyses were performed using NONMEM software version 7.3 (Icon Development Solutions, Ellicott City, MD, USA).

Results

Recruitment/ Number analysed

Pharmacokinetic parameters were determined for 26 (part 1) and 19 (part 2) paediatric patients, see table 2 and 3 below. For safety, 27 (part 1) and 19 (part 2) paediatric patients were taken into account.

Table 2. Disposition and analysis sets, part I

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.

Table 3. Disposition and analysis sets, part II

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.

Baseline data

Baseline characteristics are displayed in table 4 and 5.

Table 4. 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)
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 Other 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
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/m²)				
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

Table 5. 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
Weight (kg)			
Mean (SD)	32.26 (11.34)	55.42 (19.15)	43.84 (19.39)
Median	28.6	50.35	42.45
Min - Max	18.3 – 50.1	37.9 – 92.8	18.3 – 92.8
Height (cm)			
Mean (SD)	134.60 (12.60)	156.81 (8.37)	145.71 (15.43)
Median	137.40	153.80	149.0
Min - Max	114.5 – 153.0	147.0 – 173.8	114.5- 173.8
BMI (kg/m²)			
Mean (SD)	17.34 (3.75)	22.15 (5.51)	19.74 (5.21)
Median	16.69	19.83	18.42
Min - Max	13.6 – 23.2	16.6 – 31.1	13.6 – 31.1

Primary underlying diagnoses of the subjects in Part 1 and Part 2 are shown in table 6 and 7

Table 6. 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.

Table 7. Primary Underlying Disease Diagnosis or Event, Part 2

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.

Observed Pharmacokinetic results

The observed pharmacokinetic parameters, based on non-compartmental analysis, are displayed in table 8 to 11.

When comparing across age cohorts, on day 3, the mean AUC_{tau}, C_{trough} 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.

Table 8. Summary of Observed Plasma Pharmacokinetic Parameters for IV Isavuconazole in the maintenance setting dosed 10 mg/kg QD with maximal dose of 372 mg isavuconazonium sulfate by Cohort

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)
%CV	51.5	56.7	41.6
Median	3610	2400	2380
Min – Max	1140 – 5950	770 – 5230	1710 – 4960

Table 9. Summary of Observed Plasma Pharmacokinetic Parameters for IV Isavuconazole in the maintenance setting dosed 10 mg/kg QD with maximal dose of 372 mg isavuconazonium sulfate by Cohort

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
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

Table 10. Summary of Observed Plasma Pharmacokinetic Parameters for Oral Isavuconazole in the maintenance setting dosed 149 to 372.5 mg QD isavuconazonium sulfate by Cohort

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
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

Table 11. Summary of Observed Plasma Pharmacokinetic Parameters for Oral Isavuconazole in the maintenance setting dosed 149 to 372.5 mg QD isavuconazonium sulfate by Cohort

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
t_{max} (h)		
n	9	8
Median	4.00	3.98
Min – Max	1.98 – 6.08	3.05 – 8.03

Population pharmacokinetic analyses

The base model developed for the IV and first PO part (12 to <18 years) of the study, which was a 3 compartment model with combined zero and first-order absorption and linear elimination, was utilized as an initial model for the final dataset. The updated structural base model included an additional inter-individual variability on volume of distribution of peripheral compartment (V3) in addition to inter-individual variability that was previously included on clearance (CL), volume of distribution of

peripheral compartments (V4), and on inter-compartmental clearance (Q4) in the previous base model. Allometric scaling using fixed exponents was applied in this model on clearance and volume of distribution parameters.

Race was statistically significant in adult population, but visual inspection did not find any correlation of race against clearance in paediatric population. No other significant covariates were identified. Goodness-of-fit plots and model parameters are displayed in figure 2 and table 10.

Figure 2. Goodness-of-fit plots. (A) Log of individual predicted concentrations versus log of observed concentrations. (B) Log of predicted concentrations versus log of observed concentrations. (C) Plot of individual weighted residual versus time. (D) Plot of individual weighted residual versus log of predicted concentrations. Black circles represent adult data, red circles represent paediatric data

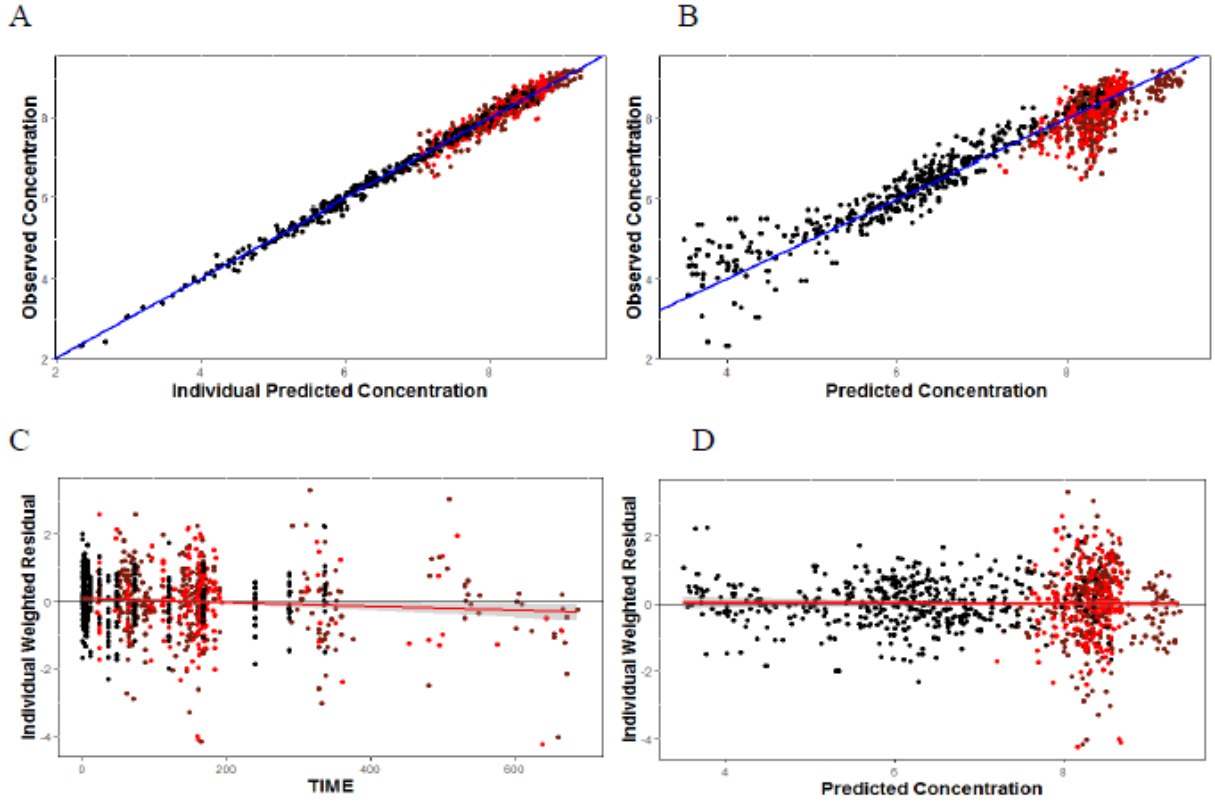


Table 6. Model parameters of the best model

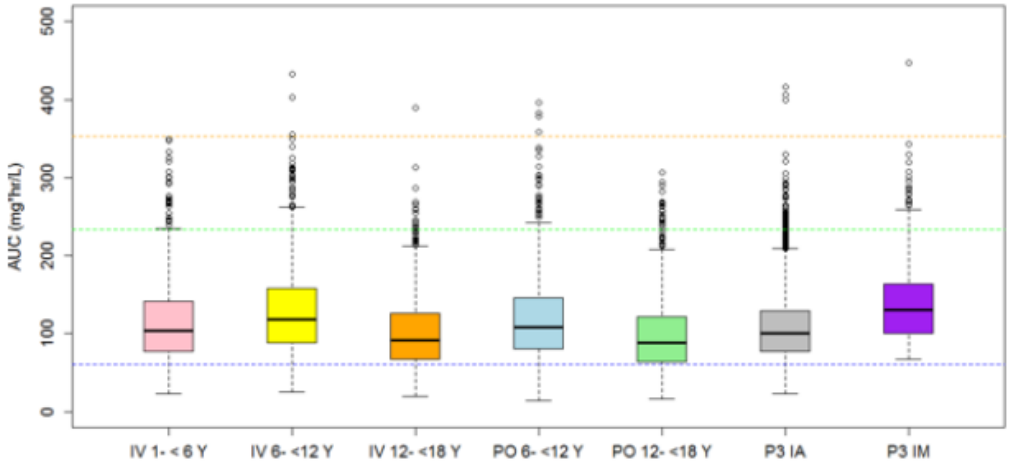
Parameter	Units	Value	SE	% RSE	Bootstrap Mean	Bootstrap 95 % CI
CL	L/hr	2.55	0.156	6	2.55	2.26 - 2.83
V_2	L	17.80	1.33	7	17.49	12.95 – 21.23
Q_3	L/hr	30.30	2.81	9	31.81	25.04 – 45.07
V_3	L	26.00	2.60	10	26.67	20.83 – 34.67
Q_4	L/hr	24.50	2.58	11	24.41	20.11 – 28.69
V_4	L	254.0	15.5	6	252.9	225.10 – 280.78
KA	hr	0.162	0.023	14	0.162	0.122 – 0.217
F1		0.95	0.071	7	0.942	0.804 – 1.08
Variability (%)						
CL		45.16	0.034	17	44.60	36.6 – 51.9
V_4		68.11	0.128	28	67.82	36.4 – 83.6
Q_4		45.71	0.052	25	45.49	36.6 – 54.77
V_3		43.24	0.141	61	42.54	14.14 – 65.95
Residual Error σ^2		40.86	0.00934	6	40.62	38.47 – 42.77

All values are rounded to nearest decimal. Population parameter estimates, standard errors of the estimates (SE), percent relative standard errors (%RSE), Bootstrap mean and Bootstrap 95% confidence intervals. CL= clearance, V2= volume of distribution of central compartment, Q3 and Q4= inter-compartmental clearance values, V3 and V4= volume of distribution of peripheral compartments, KA = absorption rate constant, F1= bioavailability

Simulations

Simulations were performed to estimate the percentage of children with isavuconazonium exposures in the target range. The applicant considered the target range for paediatric patients that isavuconazonium exposure should be higher than lowest quartile isavuconazonium exposure (60 mg*hr/L)) in adults treated with 372 mg QD and lower than the minimim isavuconazonium exposure (233 mg*hr/L) in adults treated with 1116 mg, where toxicities were observed.

Figure 3. Box plot of comparison of AUC values from simulated paediatric patients to observed AUC values from SECURE (P3 IA) study and VITAL (P3 IM) study.



Box-and-whisker plots of drug exposure AUCss in pediatric age groups (1 < 6y, 6- < 12y, 12 - <18y) and adult population (SECURE data). Boxes represent the median and 25th and 75th percentiles, whiskers represent the range of maximum and minimum values within 1.5× the interquartile range, and outliers are shown as circles. Red dots are the means. Dashed blue line is the mean AUCss from SECURE study. Dashed green and orange line are the minimum (233 mg*hr/L) and mean (353 mg*hr/L) AUCss values in a high dose adult study (1116 mg) with increased toxicity. Dashed blue line is the lowest targeted value (25th percentile, with AUCss of 60 mg*hr/L) based on exposures from SECURE study. P3 IA is the SECURE study and P3 IM is the VITAL study

For PO, 6 to < 12 years, an isavuconazonium sulfate dose of 10 mg/kg with a maximum dose of 372.5 mg provided mean exposures that were similar to and/or above the 372 mg adult dose and significantly below the 1116 mg dose group,.

In IV, across all age groups, > 99% of the predicted AUCss values were below the mean AUC24 values and > 94% of the predicted AUCss values were below the minimum adult AUC24 values for the adult population administered the supratherapeutic clinical dose (1116 mg). Greater than 82% of the predicted AUCss values were above the 25th percentile from the SECURE study.

In PO, across all age groups, > 99% of the predicted AUCss values were below the mean AUC24 values and > 96% of the predicted AUCss values were below the minimum adult AUC24 values for the adult population administered the supratherapeutic clinical dose (1116 mg).Approximately 80% of the predicted AUCss values were above the 25th percentile from SECURE study.

Table 12. Percentage of Paediatric Patients with Predicted AUCss Values Below or Above the Specified Adult AUC values (Using simulations of the model presented above)

Route	Age Group	% of Subjects Below Mean Adult AUC24 1116 mg Dose	% of Subjects Below Minimum Adult AUC24 1116 mg Dose	% of Subjects Above the 25th Percentile Adults AUCss 372 mg Dose
Intravenous	1 to < 6 years	100 %	97.0 %	88.6 %
	6 to < 12 years	99.7 %	94. 0%	92.7%
	12 to <18 years	99.9 %	98.2 %	82.1%
Oral	6 to 11 years	99.6 %	96.4 %	90.7 %
	12 to < 18 years	100%	98.2 %	78.8%

AUC24: area under the isavuconazole concentration-time curve at 24 hours (observed values); AUCss: area under the isavuconazole concentration-time curve at steady state (predicted values).

[a] Doses are expressed as isavuconazonium sulfate.

Efficacy results

No formal prospectively defined efficacy assessments were planned in this study.

In cases of breakthrough fungal infection, the site of infection, causative organism (including susceptibility testing of isolates), start/stop dates, and any follow-up information available regarding resolution and therapies used to treat the infection were recorded.

However, since no breakthrough infections were observed (neither in Part 1, nor in Part 2 of the study) no efficacy results were to report here.

Safety results

Adverse events

An overview of TEAEs is shown in [Table 13 (Part 1) and Table 14 (Part 2)].

Table 13 Overview of Treatment-emergent Adverse Events (SAF) (Part 1, IV)

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.

Table 14 Overview of Treatment-emergent Adverse Events (SAF) (Part 2, PO)

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.

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 15, Part 1, IV]. 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).

Table 15 Frequency of Treatment-emergent Adverse Events Occurring in ≥20% of Subjects in Any Treatment Cohort (SAF) (Part 1, IV)

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)
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)

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 (%)
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)
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.

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.

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 16, Part 2, PO]. The TEAEs with the highest frequencies within a cohort were pyrexia (55.6%), vomiting (40%) and abdominal pain (33.3%).

Table 16 Frequency of Treatment-emergent Adverse Events Occurring in ≥20% of Subjects in Any Treatment Cohort (SAF) (Part 2, PO)

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)
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.

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 17, Part 1, IV]. 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.

Table 17 Frequency of Drug-related Treatment-emergent AEs (SAF) (Part 1, IV)

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)
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.

TEAEs in 52.6% of subjects (10/19) were considered at least possibly related to study drug [Table 18. Part 2, PO]. The drug-related TEAEs occurring most frequently in Cohort 4 were vomiting and nausea each reported for 2 (22.2%) subjects. In Cohort 5, no related TEAE was seen in more than 1 subject. Overall, vomiting (15.8%), diarrhea nausea and headache (10.5% each) were the most common related TEAEs, but study drug-related TEAEs were low in both cohorts.

Table 18 Frequency of Drug-related Treatment-emergent AEs (SAF) (Part 2, PO)

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.

Deaths

There were no deaths in this study (Part 1 and Part 2).

Serious Adverse Events

Part 1

Overall, 44.4% (12/27) of subjects experienced an SAE. Overall, the most frequent SAEs were diarrhea and pyrexia (3 [11.1%] 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.

One SAE (electrocardiogram QT prolonged) was considered at least possibly related to study drug [End-of-Text Table 12.6.1.5], which was experienced on day 7 by a 16-year-old girl in Cohort 3 diagnosed with acute myelogenous leukemia. The AE was moderate in severity, a single episode, and was recovered from by day 15, when it was considered resolved [Appendix 13.2.7.4]. The concomitant medications of famotidine, diphenhydramine and promethazine hydrochloride were discontinued as the investigator felt they could possibly affect QTc values. This SAE resulted in discontinuation of study drug on day 8 (see *Adverse Events Resulting in Discontinuation*).

Part 2

Overall, 42.1% (8/19) of subjects experienced an 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.

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 (see *Adverse Events Resulting in Discontinuation*). The subject recovered, and all events were considered resolved. This subject was also noted in regard to a protocol deviation.

Adverse Events Resulting in Discontinuation

Part 1

AEs resulting in discontinuation were reported for 2 subjects [Table 19]

Table 19 Adverse Events Resulting in Discontinuation (SAF) (Part 1, IV)

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.

One subject, a 6-year-old girl in Cohort 2 diagnosed with aplastic anemia, experienced a severe TEAE of hepatic enzyme increased on day 11, considered probably related to study drug and resulting of withdrawal of study drug on day 15. The TEAE was associated with levels of ALT that were 476 U/L and levels of AST that were 196 U/L on day 14. ALT and AST remained elevated (352 U/L and 92 U/L, respectively) at day 15 (EOT). Alkaline phosphatase and TBL levels remained low and unaffected. At the time of the event the subject was also receiving acyclovir, aminocaproic acid, amlodipine, amphotericin B (day 14 only), clonidine, diphenhydramine, macrogol, methylphenidate, ondansetron, pentamidine, promethazine, risperidone, scopolamine melatonin, esomeprazole and ursodeoxycholic acid. The TEAE was considered resolved on day 24 (no liver enzyme results available).

Study drug was also discontinued due to a moderate SAE of electrocardiogram QT prolonged, experienced on day 7 by a 16-year-old girl in Cohort 3. The event was considered possibly related to study drug, which was withdrawn on day 8. At the time of the event, the subject was also receiving

acyclovir, diphenhydramine, famotidine, morphine, pantaprazole and tacrolimus. The event was considered resolved on day 15.

Part 2

AEs resulting in discontinuation were reported for 4 subjects, 3 in Cohort 4 and 1 in Cohort 5 [Table 20]. 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 ALT and AST 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.

Table 20 Adverse Events Resulting in Discontinuation (SAF) (Part 2, PO)

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 Vomiting Pyrexia	18/39 (20) 18/39 18/22	Recovered/Resolved Recovered/Resolved Recovered/Resolved	Possible Possible Possible
7 years Female 223.5 mg	Alanine aminotransferase increased Aspartate aminotransferase increased	23 – (23) 23 –	Recovering/Resolving Recovering/Resolving	Probable 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

Adverse Events of Special Interest

Part 1

Possible cases of drug-induced liver injury (DILI) include the 6-year-old girl subject in Cohort 2 discussed above and a 10-year-old boy in Cohort 2 receiving 336.5 mg isavuconazonium sulfate who had elevated ALT (169 U/L) and AST (90 U/L) levels on day 15. ALT was 109 U/L on day 29 (EOT),

while AST had declined to 44 U/L by that time. There were no significant changes in TBL or alkaline phosphatase levels.

Infusion-related reactions (IRRs) were reported for 2 subjects. The first subject, a 4-year-old girl in Cohort 1 receiving 168 mg study drug, experienced the TEAE of infusion related reaction (reported by the investigator as chills) during infusion of the study drug on day 1.

This TEAE was accompanied by the TEAE of procedural nausea. On day 3, the subject experienced another TEAE of infusion related reaction (reported by the investigator as chills). This TEAE was accompanied by the TEAEs of diarrhea and of procedural vomiting during the infusion. Each of these events was mild and possibly related to study drug. Study drug dosing was not changed for any event, and the subject continued to receive daily infusions until EOT on day 16. This subject met the criteria for discontinuation, but was not discontinued.

The second subject was a 3-year-old boy in Cohort 1 receiving 152 mg study drug who experienced the TEAE of infusion-related abdominal pain during infusion on day 1. This event was mild, considered possibly related to study drug. It was accompanied by the TEAE of procedural nausea (mild) and procedural vomiting (mild) which were considered possibly related to study drug. It was noted that the infusion line occluded several times during administration (the site confirmed that in-line filters were used for the infusion), and the total time of infusion was extended by 10 minutes. Study drug dosing was not changed, and the events were recovered from and considered resolved on day 1. The subject continued to receive daily infusions until EOT on day 14.

Part 2

Possible cases of drug-induced liver injury (DILI) comprise the 7-year-old girl subject in Cohort 4 discussed above. This subject received 223.5 mg study drug, and had elevated ALT (140 U/L) and AST (121 U/L) on day 22, which rose to 181 U/L and 146 U/L at the end-of-trial visit the next day. These events were considered to be probably related to study drug. By day 71 both values had resolved. There were no significant changes in TBL or alkaline phosphatase levels.

Clinical Laboratory Evaluations

Part 1

No clinically relevant changes from baseline were observed. No important changes in laboratory shift analyses were observed. Liver enzymes and TBL values for the majority of subjects tended to be within the normal laboratory ranges during the study. ALT was elevated beyond 3 x ULN in 2 of 8 (25.0%) subjects in Cohort 2, and was elevated beyond 3 x ULN in 1 subject (12.5%). AST was elevated > 3 x ULN in 1 subject in Cohort 2. A value of AST or ALT > 3 x ULN coupled with TBL > 2 x ULN in the same sample was not observed in any subject.

Part 2

No clinically relevant changes from baseline were observed. No important changes in laboratory shift analyses were observed. Liver enzymes and TBL values for the majority of subjects tended to be within the normal laboratory ranges during the study. In 1 of 9 (11.1%) subjects in Cohort 4, ALT was elevated beyond 3 x ULN (at 181 U/L [3.29 xULN]). This event was considered to be probably related to study drug. A value of AST or ALT > 3 x ULN coupled with TBL > 2 x ULN in the same sample was not observed in any subject.

Vital signs *(Part and Part 2)*

No clinically relevant changes from baseline were observed for any of the vital sign measurements. No changes in vital sign measurements were reported as an AE.

Electrocardiograms

Part 1

One subject experienced a clinically significant ECG abnormality (SAE of electrocardiogram QT prolonged on day 7). ECGs at baseline and day 8/EOT were considered abnormal but not clinically significant.

Part 2

One subject experienced a clinically significant ECG abnormality (ST abnormality and T wave inversion) reported at the day 14 visit, and a TEAE was reported (conduction disorder of mild severity, possibly related to study drug). This event was not resolved, and no action was taken.

2.4.3. Discussion on clinical aspects

Study 9766-CL-0046 is a phase 1, open-label, multicenter, non-comparative pharmacokinetics and safety study of intravenous and oral isavuconazonium sulfate in paediatric subjects of different age groups. It does not allow any definitive conclusion regarding the safety and efficacy of isavuconazole in paediatric patients with invasive aspergillosis/mucormycosis. Moreover, the MAH does not seek an update of the isavuconazole product information until all studies as outlined in the PIP (in particular Study 9766-CL-0107) are completed.

Pharmacokinetics

The aim of the current study and population pharmacokinetic analyses was to determine appropriate dosing regimens for paediatric populations receiving either IV or oral isavuconazonium sulfate. Overall, pharmacokinetic parameters were determined for 26 (part I) and 19 (part II) paediatric patients. Subsequently, exposure, defined as the AUC at steady state, was compared with the adult data using model simulations with the developed population pharmacokinetic analyses. In general, the population pharmacokinetic analyses is adequately conducted and described. Nonetheless, it would be valuable in future applications to include at least ETA versus Age and Body weight plots as the current correlation matrix cannot be assessed. Furthermore, VPCs should be provided per age group, per bodyweight group and per route of administration on a linear and log-linear scale as there appears to be a structural deviation with age in the goodness-of-fit plots. This could potentially indicate a difference in PK in the paediatric population as compared to the adult population.

When comparing across age cohorts, mean AUC_{tau}, C_{trough} and C_{max} were comparable for paediatric patients 1 to <6 years and 6 to < 12 years. In children aged < 12 years, mean AUC_{tau}, C_{trough} and C_{max} were approximately 30% to 35% higher as compared to children aged 12 to <18 years. Exposure in paediatric patients 12 to <18 years appears to be comparable to adults. Since this does not apply for the younger paediatric patients in which exposure is higher with the currently used dosing regimen as compared to adults, this should be discussed in future applications.

Currently, the target range for efficacy is 25% percentile of the AUCss and for safety, the minimum exposure of the 1116 mg dose group, in which toxicity was observed. These target ranges should be appropriately justified in future applications.

Further, it would be valuable to evaluate the relationship between pharmacokinetic parameters, in particular C_{max}, and safety effects in the paediatric population as the current analysis focusses mainly on efficacy.

Efficacy

No formal prospectively defined efficacy assessments were planned in this study.

In cases of breakthrough fungal infection, the site of infection, causative organism (including susceptibility testing of isolates), start/stop dates, and any follow-up information available regarding resolution and therapies used to treat the infection were recorded. However, since no breakthrough infections were observed (neither in Part 1, nor in Part 2 of the study) no efficacy results were to report here.

Safety

As could be expected in this severily-ill study population (due to the underlying medical disease/condition) and the extensive use of accompanying medication like oncolytics and immunosuppressants, the frequency and type of TEAEs observed was very high: 25/27 (92.6%) of patients that were treated intravenously (Part1) and 18/19 (94.7%) of patients treated orally (Part 2), respectively. The overall AE frequency was similar to what was observed in adults.

Following *intravenous* use (Part 1), 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).
Following *oral* use (Part 2), the TEAEs with the highest frequencies within a cohort were pyrexia (55.6%), vomiting (40%) and abdominal pain (33.3%).

Drug-related TEAEs attributed to bedaquiline were also reported frequently: 10/27 (37.0%) of subjects treated intravenously (Part 1) and 10/19 (52.6%) of subjects treated per os (Part 2):

> Part 1, IV: 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 (Part 1, IV).
>
> Part 2, PO: The drug-related TEAEs occurring most frequently in Cohort 4 were vomiting and nausea each reported for 2 (22.2%) subjects. In Cohort 5, no related TEAE was seen in more than 1 subject. Overall, vomiting (15.8%), diarrhea nausea and headache (10.5% each) were the most common related TEAEs, but study drug-related TEAEs were low in both cohorts (Part 2).

No obvious difference in overall and individual-type AEs was observed between the 3 age cohorts, although numbers of patients per cohort were very low and definitive conclusions can not be drawn.

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. Liver toxicity and QT changes are well known adverse events described with the use of isavuconazole.

3. CHMP overall conclusion and recommendation

The pharmacokinetic profile of isavuconazonium administered as IV or oral administration was characterised using non-compartmental analaysis and a population pharmacokinetic analyses, partly based on adult data. Overall, the analyses appear to be adequately conducted. It is advised to include some additional diagnostic plots in future applications as there appears to be a deviation in the population predicted concentrations versus observed concentrations goodness-of-fit plot, which could indicate differences in PK in the paediatric population as compared to the adult population.

Furthermore, higher exposure is observed in paediatric patients <12 years as compared to adults. The currently used target ranges and the higher exposure should be discussed in future applications. The implications for the safety of use in these children should be discussed in depth.

Currently, no change in the SmPC has been proposed, which is considered acceptable.

☒ **Fulfilled:**

No regulatory action required.

4. Additional clarification requested

Not applicable