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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Cresemba

isavuconazole

Procedure no: EMEA/H/C/002734/P46/007

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Submission	26.05.2023	26.05.2023	☐
☐	Start	19.06.2023	19.06.2023	☐
☐	CHMP Rapporteur Assessment Report	24.07.2023	24.07.2023	☐
☐	CHMP members comments	07.08.2023	07.08.2023	☐
☐	Updated CHMP Rapporteur Assessment Report	10.08.2023	10.08.2023	☐
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☐	Submission	04.09.2023	04.09.2023	☐
☐	Re-start	13.09.2023	13.09.2023	☐
☐	CHMP Rapporteur Assessment Report	27.09.2023	28.09.2023	☐
☐	CHMP members comments	02.10.2023	02.10.2023	☐
☐	Updated CHMP Rapporteur Assessment Report	05.10.2023	05.10.2023	☐
☒	CHMP adoption of conclusions:	12.10.2023	12.10.2023	☐

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1. Introduction

On 26 May 2023, the MAH submitted a completed paediatric study (Study 9766-CL-0107) for Cresemba (isavuconazonium sulfate), 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-M04. A short critical expert overview (4 pages, dated 17-05-2023) was also provided.

1.1. Information on the product

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. Scientific discussion

2.1. Information on the development program

Study 9766-CL-0107, a phase 2, open-label, non-comparative, multicenter study to evaluate the safety and tolerability, efficacy and pharmacokinetics of isavuconazonium sulfate for the treatment of invasive aspergillosis (IA) or invasive mucormycosis (IM) in paediatric subjects, is part of the agreed paediatric investigation plan (PIP) EMEA-001301-PIP02-12-M04.

A line listing of all the concerned studies is shown in **Figure 1**.

Figure 1. Overview of concerned studies

Nonclinical 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	Exp. submission September 2023

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	24 January 2020
Phase 2, open-label, non-comparative, multicenter study to evaluate the safety and tolerability, efficacy and pharmacokinetics of isavuconazonium sulfate for the treatment of invasive aspergillosis (IA) or invasive mucormycosis (IM) in pediatric subjects	9766-CL-0107	14 December 2022	26 May 2023

The primary objective of study 9766-CL-0107 was to assess the pharmacokinetics, efficacy and safety of isavuconazonium sulfate for the treatment of IA or IM in pediatric participants.

On the basis of these studies the MAH regards all elements of the agreed PIP now as completed but does not seek an update of the isavuconazole product information with this submission.
The MAH rather proposes to discuss label updates in a planned application to obtain approval for the use of isavuconazole in paediatric patients from 1 to < 18 years of age, and to obtain marketing authorisation approval of a new capsule formulation (corresponding to 40 mg isavuconazole) specifically developed for use in paediatric patients. Expected submission of the relevant application is September 2023. The application will comprise the full relevant data package containing quality, nonclinical and clinical data.

2.2. Information on the pharmaceutical formulations used in the study

In study 9766-CL-0107 all participants were assigned to open-label treatment via intravenous and/or oral administration with isavuconazole.

Intravenous isavuconazonium sulfate for injection was supplied in a single-dose vial as a sterile lyophilized white to yellow powder containing 372.6 mg isavuconazonium sulfate (corresponding to 200 mg isavuconazole) as currently marketed for adult patients.

Oral isavuconazonium sulfate was supplied as oral capsules (size 3) containing 74.5 mg of isavuconazonium sulfate (corresponding to 40 mg isavuconazole). These size 3 capsules [smaller than the size 0 elongated capsule containing 186.3 mg isavuconazonium sulfate corresponding to 100 mg isavuconazole as being used in adults] were developed specifically for paediatric use following the agreed PIP and evaluated in PIP study 2, 9766-CL-0046, assessed under EMA/H/C/002734/P46/006.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted the final study report for **Study 9766-CL-0107** (dated 09-05-2023).

2.3.2. Clinical study (9766-CL-0107)

This paediatric study was a phase 2, open-label, non-comparative, multicenter study to assess the safety and tolerability, efficacy and pharmacokinetics of isavuconazonium sulphate in paediatric participants aged 1 to <18 years in the treatment of Invasive Aspergillosis or Invasive mucormycosis.

Methods

Objective(s)

Pharmacokinetics

The objective was to evaluate the pharmacokinetics of isavuconazole by monitoring the plasma concentrations in paediatric participants during treatment with isavuconazonium sulfate.

Efficacy

The efficacy objective was to assess the efficacy of isavuconazonium sulfate for the treatment of IA or IM in pediatric participants.

Safety

The safety objective was to evaluate the safety and tolerability of isavuconazonium sulfate in pediatric participants.

Palatability

To assess the initial experience with the new oral formulation after receiving the first dose of oral capsules.

Outcomes/endpoints

Pharmacokinetics

Pharmacokinetic endpoints included plasma trough (predose) levels on days 7, 14, 21, 42 and 84 or end of treatment.

Efficacy

The *primary efficacy endpoint* was "All-cause mortality through day 42".

Note: Any death that occurred after first dose of study drug through day 42 was included. Participants who died on or before day 42, as well as those who were lost to follow-up before day 42 were counted as deaths. The crude all-cause mortality rate was calculated by dividing the number of deaths by the number of FAS subjects, and a 2-sided exact 95% CI was calculated.

The key secondary efficacy endpoints were "all-cause mortality through day 84 and EOT" and "Overall, clinical, radiological and mycological response through days 42 and 84 and EOT". Response was assessed by the investigator using the criteria in **Table 1**.

Table 1. *Investigator Guidance for Successful Outcome*

	Clinical Response	Mycological Response	Radiological Response
Success	• Resolution of all attributable signs and symptoms OR • Resolution of attributable clinical symptoms and physical findings	• Eradicated • Presumed eradication	• ≥ 90% improvement • ≥ 50% to < 90% improvement • ≥ 25% to < 50% improvement (for day 42 only)

An Adjudication Committee (AC) was set up to confirm the diagnosis and overall, clinical, mycological and radiological response.

Safety

Safety outcomes include AEs, vital signs, ECGs and laboratory parameters.

Study design

The study activated 30 centers in Belgium, Spain, United Kingdom, Germany and the US, from which 10 centers enrolled participants from the US, Spain, and Belgium.

All participants were diagnosed with at least possible IFD requiring systemic antifungal therapy, and entered into screening anytime between days -5 to 1 (predose). All participants were assigned to

open-label treatment via IV or oral administration at the discretion of the investigator. The oral formulation could only be given to participants aged 6 to < 18 years and with a body weight of at least 12 kg. The route of administration could change at the investigator's discretion as needed for treatment purposes since the resulting exposure from the 2 routes of administration is considered equivalent on a mg:mg basis.

Treatment began on day 1, and participants were followed for up to 60 days post-last dose for safety.

Treatment was administered until the participant had a successful outcome as judged by the investigator or for a maximum duration of 84 days (IA) or 180 days (IM), whichever occurred first.

Participants who were discharged from the hospital with oral capsules for at-home administration were required to return weekly for study drug accountability and to receive new oral dosing supplies. Participants who began oral administration were to complete the oral dosing acceptability assessment after ingesting their first oral dose. Isavuconazonium sulfate oral capsules could be administered with or without food.

Pharmacokinetic endpoints included plasma trough (predose) levels on days 7, 14, 21, 42 and 84 or EOT. In addition, 24-hour PK samples were obtained on any 1 day between days 14 and 42 while the participant was still receiving study drug. The 24-hour PK samples were obtained for IV dosing as follows: 1 hour prior to start of infusion, within 5 minutes after the end of infusion, 4 to 10 hours and 16 to 24 hours after start of infusion. The 24-hour PK samples were obtained for oral dosing as follows: a sample 1 hour prior to next oral dose, and a sample at 1, 3, 4, hours, between 6 to 8 hours and at 24 hours post-dosing. No samples were to be taken from IM participants after day 84.

Throughout the study, safety and tolerability were assessed by the continuous recording of AEs, vital signs, ECGs and safety laboratory evaluations.

Study participants

Thirty pediatric participants aged 1 to < 18 years who met the following criteria were planned to be enrolled into the study.

Key inclusion criteria were:

- Proven, probable, or possible IFI per the [EORTC/MSG 2008] criteria.

  Note 1: Subjects with "possible" IFI were eligible for enrolment; however, diagnostic tests to confirm the invasive fungal disease as "probable" or "proven" according to the EORTC/MSG criteria were to be completed within 10 calendar days after the first dose of study drug.

  Note 2: In addition to the criteria set for mycological criteria by the EORTC/MSG in 2008, and only for subjects with an underlying hematologic malignancy or recipients of HSCT who also have clinical and radiologic features consistent with invasive fungal infection, the following are acceptable:

  Galactomannan (GM) levels (optical density index) meeting the below criteria are acceptable mycological evidence for enrolment or upgrading the diagnosis to probable IA:

  1. A single value for serum or bronchoalveolar lavage (BAL) fluid of ≥ 1.0 or
  2. Two serum GM values of ≥ 0.5 from 2 separate samples

Key exclusion criteria were:

- Participant had another IFD other than possible, probable or proven IA or IM.
- Participant had chronic aspergillosis, aspergilloma or allergic bronchopulmonary aspergillosis.
- Participant had received mold-active systemic antifungal therapy, effective against the primary IMI, for more than 4 days during the 7 days preceding the first dose.
  Note: Prior use of prophylactic antifungal therapy was considered acceptable.
- Participant was unlikely to survive 30 days in the investigator's opinion

Treatments

Intravenous Dosing:

Subjects weighing ≤ 37 kg:

- Loading regimen of 10.0 mg/kg isavuconazonium sulfate infusions every 8 hours (± 2) for 6 doses (days 1 and 2)
- Maintenance dose of 10.0 mg/kg isavuconazonium sulfate administered once daily starting 12 to 24 hours after the last loading dose

Subjects weighing > 37 kg:

- Loading regimen of 372 mg isavuconazonium sulfate infusions (1 vial) every 8 hours (± 2) for 6 doses (days 1 and 2)
- Maintenance dose of 372 mg isavuconazonium sulfate (1 vial) administered once daily starting 12 to 24 hours after the last loading dose

The maximum loading and daily maintenance doses to be administered to any subject are 372 mg per individual dose.

The first maintenance dose started 12 to 24 hours after the administration of the last loading dose. Subsequent maintenance doses were administered once daily (24 hours ± 2 hours from the previous maintenance dose).

Oral dosing:

Oral administration is only for subjects aged 6 to < 18 years and with a body weight of at least 12 kg. The daily dose is based on body weight and intended to deliver a dose approximately equal to 10 mg/kg. The oral and intravenous formulations are equivalent on a mg:mg basis (see Table 2):

Table 2. *Oral Dosing Regimen by Body Weight*

Body weight (kg)	Loading (Day 1 and Day 2)/Total Daily Isavuconazonium Sulfate Dose (mg)	Maintenance (up to 84 days [IA] or 180 days [IM])/Total Daily Isavuconazonium Sulfate Dose (mg)
12 to < 18	3 × 2 capsules/447 mg	1 × 2 capsules/149 mg
18 to < 25	3 × 3 capsules/670.5 mg	1 × 3 capsules/223.5 mg
25 to < 32	3 × 4 capsules/894 mg	1 × 4 capsules/298 mg
≥ 32	3 × 5 capsules/1117.5 mg	1 × 5 capsules/372.5 mg

The first maintenance dose started 12 to 24 hours after the administration of the last loading dose. Subsequent maintenance doses were administered once daily (24 hours ± 2 hours from the previous maintenance dose).

Due to the similarity in exposure (AUC) between IV and oral in paediatric participants established in Study 9766-CL-0046, the investigator could change dosing between the 2 routes (IV vs oral) throughout treatment as needed for treatment purposes.

Prohibited therapies:

Treatments with concomitant drugs that are strong inhibitors or inducers of CYP3A4 and use of other systemic antifungals was prohibited during study drug administration.

Note: Subjects taking prohibited medications who were willing to discontinue these medications, as clinically indicated and based upon the investigator's recommendation, were allowed to washout over a period of 5 half-lives on a schedule determined by the investigator.

Sample size

No formal sample size calculation was performed. A sample size of approximately 30 participants was planned, including at least 5 evaluable participants per age cohort: 1 to <12 years of age and 12 to <18 years of age. Evaluable subjects are subjects who have received at least 1 dose of study drug.

Randomisation and blinding (masking)

Study 9766-CL-0107 was a phase 2, open-label, non-comparative study.

Statistical Methods

Pharmacokinetics

The pharmacokinetic analysis set (PKAS) consists of all subjects who took at least 1 dose of study drug and who have at least 1 plasma concentration. Sampling times along with plasma concentrations of isavuconazonium sulfate levels will be displayed in listings. Descriptive statistics (e.g. n, mean, SD, minimum, median, maximum, coefficient of variation (CV), geometric mean and geometric CV will be provided for plasma concentrations of isavuconazole.

Plasma concentration data from this study will be used to support a population pharmacokinetic (PK) model developed for Isavuconazonium sulfate.

Bioanalysis

Serum concentrations in study 9766-CL-0107 were determined using a validated LC/MS/MS method (method validation report: P1131.02). This method was validated within study for within- and between-run bias and precision. Long term stability of samples was confirmed up to 1077 days at -80 °C in K_3EDTA and 1022 days in K_2EDTA. A total of 166 plasma samples were analysed and maximum duration of sample storage from collection was 984 days at -80°C. A total of 17 samples (9.94% of total number of human plasma samples) was reanalysed for the incurred sample reanalysis. Of which 100% of the samples passed the incurred sample reanalysis criteria.

Clinical

Analysis sets

- The full analysis set (FAS) consists of all subjects who are enrolled and receive at least one dose of study drug. This will be the primary analysis set for efficacy analyses.
- The modified FAS (mFAS) consists of the subset of the FAS subjects who have either probable or proven IA or IM diagnosis at baseline or up to 10 days after first dose.
- The safety analysis set (SAF) consists of all subjects who are enrolled and receive at least 1 dose of study drug. For this study, the SAF is the same as the FAS.

No formal inferential analyses were performed. The analysis was descriptive, crude success rates and 2-sided exact 95% CIs have been calculated and summarized for FAS and mFAS analysis sets.

All previous and concomitant medications are summarized for subjects in FAS and SAF analysis sets and presented in listings.

Medical history for each subject will be presented in a listing.

The Data and Safety Monitoring Board's (DSMB) primary responsibilities is safeguarding the interests of study subjects and assessing the safety of the study treatment(s) and study procedures.

The Adjudication Committee's (AC) primary responsibilities is to confirm the diagnosis and overall, clinical, radiological and mycological response of IA or IM.

Results

Participant flow / Number analysed / Recruitment

Thirty-one (31) participants with at least possible invasive fungal disease requiring systemic mold-active antifungal therapy were enrolled to receive treatment. All enrolled participants received study drug. Therefore, 31 (100.0%) participants were included in the safety analysis and in the full analysis set (FAS), 13 (41.9%) participants were included in the in the modified FAS (mFAS) and 28 (90.3%) in the pharmacokinetic analysis set (PKAS).

Treatment Discontinuation

Nineteen (61.3%) of participants completed treatment by either achieving the maximum treatment duration (12; 38.7%) or achieving a successful outcome before maximum treatment duration was reached (7; 22.6%). The proportion of participants who prematurely discontinued treatment was 38.7% (12 of 31). The 3 most common reasons for discontinuation of treatment, based on the investigator's categorization, were lack of efficacy 12.9% (4 of 31), adverse event 9.7% (3 of 31), and other 16.1% (5 of 31). Of the participants that discontinued due to "not having the fungus intended for the study or not having a definitive diagnosis of IA or IM", all met the possible IMI criteria at study entry. Of the 4 participants who discontinued as a result of lack of efficacy, 1 died as a result of progressive IFD disease 4 days after treatment discontinuation.

Twenty-eight (28; 90.3%) participants completed both the 30-day and 60-day follow-up visits (SAF). Three (3; 9.7%) participants prematurely discontinued the study due to death (all unrelated to study treatment) and thus did not complete either the EOT + 30-day or EOT + 60-day follow-up visit.

Baseline data

In the FAS population, the mean age of participants was 9.7 years, and the majority of participants were White (61.3%), 1 to < 12 years of age (61.3%) and female (80.6%), see Table 3.

Table 3. *Demographic table (FAS)*

		Categorization of IFD†‡				
Parameter	**Category/ Statistic**	**Proven or Probable IA (n = 12)**	**Proven or Probable IM (n = 1)**	**Possible IFD (n = 16)**	**Other IFD§ (n = 2)**	**Total (N = 31)**
Sex	Male	2 (16.7)	1 (100)	3 (18.8)	0	6 (19.4)
	Female	10 (83.3)	0	13 (81.3)	2 (100)	25 (80.6)
Ethnicity	Hispanic or Latino	3 (25.0)	1 (100)	4 (25.0)	2 (100)	10 (32.3)
	Not Hispanic or Latino	7 (58.3)	0	12 (75.0)	0	19 (61.3)
	Not specified	2	0	0	0	2
Race	White	4 (33.3)	1 (100)	13 (81.3)	1 (50.0)	19 (61.3)
	Black or African American	0	0	1 (6.3)	0	1 (3.2)
	Asian	4 (33.3)	0	1 (6.3)	0	5 (16.1)
	Other⁑	2 (16.7)	0	1 (6.3)	1 (50.0)	4 (12.9)
	Not specified	2	0	0	0	2
Age (years)	Mean (SD)	9.8 (5.2)	14.0 (NC)	9.2 (5.3)	12.0 (1.4)	9.7 (5.0)
	Median	10.0	14.0	9.0	12.0	10.0
	Min - max	1 – 16	14 – 14	1 – 17	11 – 13	1 – 17
Age category (years)	1 – < 12	7 (58.3)	0	11 (68.8)	1 (50.0)	19 (61.3)
	12 – < 18	5 (41.7)	1 (100)	5 (31.3)	1 (50.0)	12 (38.7)
Weight (kg)	Mean (SD)	37.01 (21.77)	50.5 (NC)	37.81 (19.21)	35.05 (8.84)	37.73 (19.16)
	Median	30.60	50.50	44.45	35.05	42.60
	Min - max	9.6 – 84.3	50.5 – 50.5	9.0 – 74.0	28.8 – 41.3	9.0 – 84.3
Height (cm)	Mean (SD)	133.11 (29.45)	NR	131.51 (32.09)	147.90 (5.80)	133.30 (29.56)
	Median	138.50		132.00	147.90	138.00
	Min - max	80.5 – 172.0		72.5 – 177.5	143.8 – 152.0	72.5 – 177.5
BMI (kg/m^2)	Mean (SD)	18.98 (4.42)	NC	19.76 (4.44)	15.90 (2.79)	19.17 (4.33)
	Median	17.77		18.82	15.90	17.84
	Min - max	14.0 – 28.5		13.5 – 28.2	13.9 – 17.9	13.5 – 28.5

BMI: body mass index; FAS: full analysis set; IA: invasive aspergillosis; IFD: invasive fungal disease; IM: invasive mucormycosis; NC: not calculated; NR: not reported

† Investigator assessment of IFD diagnosis was used.

‡ According to EORTC/MSG 2008 criteria.

§ IFDs which were confirmed to not be IA or IM by the investigator.

⁑ Included 'unknown', 'unspecified', 'White/Asian', and 'Latino and/or Hispanic'

Primary Underlying Disease or Condition

The primary underlying condition of malignancy was reported in the majority (19; 61.3%) of participants (Table 4).

Table 4. *Overview of underlying disease or condition*

	Categorization of IFD†‡				
	Proven or Probable IA (n = 12)	**Proven or Probable IM (n = 1)**	**Possible IFD (n = 16)**	**Other IFD§ (n = 2)**	**Total (N = 31)**
Malignancy	6 (50.0%)	1 (100.0%)	11 (68.8%)	1 (50.0%)	19 (61.3%)
Acute lymphocytic leukemia	3 (25.0%)	1 (100.0%)	5 (31.3%)	0	9 (29.0%)
Acute myelogenous leukemia/ relapse acute myelogenous leukemia	1 (8.3%)	0	3 (18.8%)	1 (50.0%)	5 (16.1%)
B-Lymphoblastic lymphoma	1 (8.3%)	0	0	0	1 (3.2%)
MDS transformed to acute myelogenous leukemia	0	0	1 (6.3%)	0	1 (3.2%)
Non-Hodgkin lymphoma	0	0	2 (12.5%)	0	2 (6.5%)
Other solid tumor	1 (8.3%)	0	0	0	1 (3.2%)
Non-Malignancy	6 (50.0%)	0	5 (31.3%)	1 (50.0%)	12 (38.7%)
Immune disorder	2 (16.7%)	0	1 (6.3%)	1 (50.0%)	4 (12.9%)
Other	4 (33.3%)	0	4 (25.0%)	0	8 (25.8%)

FAS: full analysis set; IA: invasive aspergillosis; IFD: invasive fungal disease; IM: invasive mucormycosis; MDS: myelodysplastic syndrome

† Investigator assessment of IFD diagnosis was used.

‡ According to EORTC/MSG 2008 criteria.

§ IFDs which were confirmed to not be IA or IM by the investigator.

The most common malignancies were acute lymphocytic leukemia (9 participants) and acute myelogenous leukemia/relapse acute myelogenous leukemia (5 participants). Nearly two-thirds of participants (64.5%) had recently resolved or ongoing neutropenia, approximately half (45.2%) were on other recognized T-cell immunosuppressants and approximately one-third (32.3%) were on prolonged use of corticosteroids. Additional medical history often included anemia (58.1%), pyrexia (58.1%), hypoalbuminemia (41.9%), hypertension (32.3%) and sepsis (29.0%).

Prior and concomitant used antifungal agents

The 3 most commonly used prior antifungal medications for the SAF population were fluconazole (32.3%, 10/31), liposomal amphotericin B (29.0%, 9/31) and micafungin (19.4%, 6/31), (Table 5.)

Table 5. *Prior Antifungal Therapy*

	Categorization of IFD[*¶]				
Therapeutic Subgroup[†] Chemical Subgroup[‡] Preferred WHO Name	**Proven or Probable IA (n = 12)**	**Proven or Probable IM (n = 1)**	**Possible IFD (n = 16)**	**Other IFD[§] (n = 2)**	**Total (N = 31)**
Overall	7 (58.3%)	1 (100.0%)	14 (87.5%)	2 (100.0%)	24 (77.4%)
Antimycotics for Systemic Use	7 (58.3%)	1 (100.0%)	14 (87.5%)	2 (100.0%)	24 (77.4%)
Antibiotics	3 (25.0%)	0	8 (50.0%)	0	11 (35.5%)
Amphotericin B	0	0	2 (12.5%)	0	2 (6.5%)
Amphotericin B, liposome	3 (25.0%)	0	6 (37.5%)	0	9 (29.0%)
Other antimycotics for systemic use	4 (33.3%)	1 (100.0%)	9 (56.3%)	0	14 (45.2%)
Caspofungin	0	0	4 (25.0%)	0	4 (12.9%)
Caspofungin acetate	2 (16.7%)	0	2 (12.5%)	0	4 (12.9%)
Micafungin	2 (16.7%)	1 (100.0%)	3 (18.8%)	0	6 (19.4%)
Triazole and tetrazole derivatives	4 (33.3%)	1 (100.0%)	6 (37.5%)	2 (100.0%)	13 (41.9%)
Fluconazole	3 (25.0%)	1 (100.0%)	4 (25.0%)	2 (100.0%)	10 (32.3%)
Fluconazole; sodium chloride	0	0	1 (6.3%)	0	1 (3.2%)
Voriconazole	2 (16.7%)	0	3 (18.8%)	0	5 (16.1%)
Stomatological Preparations	0	0	1 (6.3%)	0	1 (3.2%)
Anti-infectives and antiseptics for local oral treatment	0	0	1 (6.3%)	0	1 (3.2%)
Nystatin	0	0	1 (6.3%)	0	1 (3.2%)

IA: invasive aspergillosis; IFD: invasive fungal disease; IM: invasive mucormycosis; SAF: safety analysis set

* Investigator assessment of IFD diagnosis was used.

† ATC 2nd level.

‡ ATC 4th level.

¶ According to EORTC/MSG 2008 criteria.

§ IFDs which were confirmed to not be IA or IM by the investigator.

The 3 most commonly used antifungal medications during the study including during the follow-up period were voriconazole (35.5%, 11/31), liposomal amphotericin B (29.0%, 9/31) and micafungin (19.4%, 6/31), Table 6.

Table 6. *Antifungal medications during the study*

	Categorization of IFD*γ				
Therapeutic Subgroup† Chemical Subgroup‡ Preferred WHO Name	Proven or Probable IA (n = 12)	Proven or Probable IM (n = 1)	Possible IFD (n = 16)	Other IFD§ (n = 2)	Total (N = 31)
Overall	7 (58.3%)	1 (100.0%)	10 (62.5%)	2 (100.0%)	20 (64.5%)
Antifungals for Dermatological Use	0	1 (100.0%)	2 (12.5%)	1 (50.0%)	4 (12.9%)
Antibiotics	0	0	2 (12.5%)	0	2 (6.5%)
Amphotericin B	0	0	1 (6.3%)	0	1 (3.2%)
Nystatin	0	0	1 (6.3%)	0	1 (3.2%)
Antifungals for systemic use	0	0	0	1 (50.0%)	1 (3.2%)
Terbinafine	0	0	0	1 (50.0%)	1 (3.2%)
Imidazole and triazole derivatives	0	1 (100.0%)	0	0	1 (3.2%)
Clotrimazole	0	1 (100.0%)	0	0	1 (3.2%)
Antimycotics for Systemic Use	7 (58.3%)	1 (100.0%)	10 (62.5%)	2 (100.0%)	20 (64.5%)
Antibiotics	5 (41.7%)	1 (100.0%)	3 (18.8%)	1 (50.0%)	10 (32.3%)
Amphotericin B	1 (8.3%)	0	1 (6.3%)	0	2 (6.5%)
Amphotericin B, liposomal	5 (41.7%)	1 (100.0%)	2 (12.5%)	1 (50.0%)	9 (29.0%)
Other antimycotics for systemic use	2 (16.7%)	1 (100.0%)	5 (31.3%)	1 (50.0%)	9 (29.0%)
Caspofungin¶	0	0	3 (18.8%)	0	3 (9.7%)
Micafungin	2 (16.7%)	1 (100.0%)	2 (12.5%)	1 (50.0%)	6 (19.4%)
Triazole and tetrazole derivatives	6 (50.0%)	1 (100.0%)	6 (37.5%)	2 (100.0%)	15 (48.4%)
Fluconazole	0	0	0	1 (50.0%)	1 (3.2%)
Isavuconazonium sulfate‡‡	0	1 (100.0%)	3 (18.8%)	1 (50.0%)	5 (16.1%)
Posaconazole	1 (8.3%)	0	0	1 (50.0%)	2 (6.5%)
Voriconazole	5 (41.7%)	1 (100.0%)	4 (25.0%)	1 (50.0%)	11 (35.5%)

IA: invasive aspergillosis; IFD: invasive fungal disease; IM: invasive mucormycosis; SAF: safety analysis set

γ According to EORTC/MSG 2008 criteria.

∗ Investigator assessment of IFD diagnosis was used.

† ATC 2nd level.

‡ ATC 4th level.

¶ This group contains the terms caspofungin and caspofungin acetate.

‡‡ This group contains the terms isavuconazole, isavuconazonium and isavuconazonium sulfate (administered during the follow-up period).

§ IFDs which were confirmed to not be IA or IM by the investigator.

According to study protocol concomitant use of other systemic antifungal agents was be avoided. However, other systemic antifungal agents were used in a significant number of patients with *proven or probable* IA or IM [8 of 13, (61.5%)]. The medication included agents like posaconazole, voriconazole and amphotericin B that are known to be active against *Aspergillus* infections, while amphotericin B is the preferred first-line treatment for invasive mucormycosis. Although there may have been good clinical reasons for adding these agents to the study drug, the exact contribution of isavuconazole to the clinical success of treatment is therefore difficult to determine.

Mucormycosis

The use of isavuconazole in mucormycosis is currently only approved for "adult patients for whom amphotericin B is inappropriate".

The only pediatric patient diagnosed with *proven or probable IM* was treated with intravenous isavuconazole for 15 days, however failed on therapy and even showed progression of the disease. Inferred from the sparse available data, this patient received micafungin and fluconazole as *prior* systemic antifungal treatment (not mold-active agents) and as *concomitant* systemic antifungal therapy liposomal amphotericin B, micafungin and voriconazole (only amphotericin B has anti-mold activity). It is not clear whether this patient received isavuconazole as the initial therapy and liposomal amphotericin B was added to isavuconazole at a later stage or the other way around. It is also not clear why treatment with micafungin was continued and voriconazole was added. Did the patient have a mixed infection? This issue was not pursued in the context of this P46 procedure. However, the MAH was asked to provide details on the chosen drug regimen and its policy as part of a separate application.

Pharmacokinetic results

Isavuconazole trough concentrations were relatively lower in the 1 to < 6 years age group compared to the 6 to < 12 years and 12 to < 18 years age groups on days 7 and 14 (Table 7).

Table 7. *Isavuconazole Trough Plasma Concentrations*

Age Group (Years)	Statistic	Isavuconazole Trough Plasma Concentrations (ng/mL)	
		Day 7	Day 14
1 to < 6	n	6	6
	Mean (SD)	2965.0 (1770.5)	2286.7 (1991.3)
	%CV	59.7	87.1
	Median	2465.0	2004.0
	Min - Max	1350 – 6280	376 – 4980
	Geometric Mean	2612.6	1442.2
6 to < 12	n	10	6
	Mean (SD)	3732.7 (1855.0)	3623.3 (1878.0)
	%CV	49.7	51.8
	Median	3790.0	3625.0
	Min - Max	837 – 6320	1490 – 6270
	Geometric Mean	3162.5	3191.4
12 to < 18	n	9	6
	Mean (SD)	3862.2 (1427.1)	4380.0 (2022.4)
	%CV	36.9	46.2
	Median	3890.0	4525.0
	Min - Max	1510 – 6280	1780 – 6880
	Geometric Mean	3600.1	3937.5

%CV: coefficient of variation; LLOQ: lower limit of quantitation; PKAS: pharmacokinetic analysis set

Concentrations below LLOQ (100 ng/mL) were set to zero

Geometric mean was not calculated if 1 or more concentrations were < LLOQ. SD and %CV were not calculated if half or a majority of the concentrations at a given time point were < LLOQ

Plasma concentration data from this study has been evaluated in combination with data from other paediatric studies in a population-based pharmacokinetic model (Study 9766-PK-0009).

Duration of Exposure to study drug

The mean total study drug duration (IV and oral) was 57.7 days. The median duration of study drug administration was 55 days (range 2-181 days) for total dosing, 13 days for intravenous dosing and 64 days for oral dosing. Twenty-four (77.4%) of participants received ≥ 14 days of isavuconazonium sulfate treatment and 19 (61.3%) had ≥ 42 days of treatment.

The median duration of study drug administration was slightly longer but not inconsistent with what was observed in the adult phase 3 controlled study ([9766-CL-0104]: 45 days for total dosing, 5 days for IV dosing and 56 days for oral dosing). The exposure data in this pediatric population were consistent with what was observed in the adult phase 3 controlled study (9766-CL-0104).

Efficacy results

Primary Efficacy Endpoint - All-cause Mortality Through Day 42 (FAS)

Two participants of 31 total (6.5%) died during the first 42 days. In the subset of proven or probable IA or IM, one (8.3%) participant died. The cause of death was related to the IA infection. [Table 8].

Table 8. *All-cause Mortality Through Day 42 (FAS)*

		Categorization of IFD†‡				
Timepoint	Outcome	Proven or Probable IA (n = 12)	Proven or Probable IM (n = 1)	Possible IFD (n = 16)	Other IFD§ (n = 2)	Total (N = 31)
Day 42	All-cause mortality	1 (8.3%)	0	1 (6.3%)	0	2 (6.5%)
	95% CI (%)	(0.21, 38.48)	(0.00, 97.50)	(0.16, 30.23)	(0.00, 84.19)	(0.79, 21.42)
	Known deaths	1 (8.3%)	0	1 (6.3%)	0	2 (6.5%)

EORTC/MSG: European Organisation for Research and Treatment of Cancer/Mycoses Study Group; EOT: end of treatment; FAS: full analysis set; IA: invasive aspergillosis; IFD: invasive fungal disease; IM: invasive mucormycosis

† Investigator assessment of IFD diagnosis was used.

‡ According to EORTC/MSG 2008 criteria.

§ IFDs which were confirmed to not be IA or IM by the investigator.

Source: End-of-Text Table 12.3.1.1

One additional participant died between days 42 and 84 (as a result of pre-existing atypical Griscelli syndrome). None of the 3 deaths was considered related to study treatment by the investigator.

No participants died while on study drug treatment (all deaths occurred during the follow-up period).

Key Secondary efficacy endpoint - AC-assessed Overall Response at days 42 and 84 and at EOT

The AC-assessed overall response rates for the FAS set were 29.0%, 25.8% and 54.8% at days 42 and 84 and EOT, respectively [Table 9].

Table 9. *AC-assessed Overall Response (FAS)*

		Categorization of IFD†‡				
Timepoint	Outcome Response	Proven or Probable IA (n = 12)	Proven or Probable IM (n = 1)	Possible IFD (n = 16)	Other IFD§ (n = 2)	Total (N = 31)
EOT	Success	8 (66.7%)	0	9 (56.3%)	0	17 (54.8%)
	Complete	3 (25.0%)	0	3 (18.8%)	0	6 (19.4%)
	Partial	5 (41.7%)	0	6 (37.5%)	0	11 (35.5%)
	Failure	2 (16.7%)	1 (100.0%)	1 (6.3%)	0	4 (12.9%)
	Stable	0	0	0	0	0
	Progression	2 (16.7%)	1 (100.0%)	1 (6.3%)	0	4 (12.9%)
	Not evaluable	2 (16.7%)	0	6 (37.5%)	2 (100.0%)	10 (32.3%)
Day 42	Success	4 (33.3%)	0	5 (31.3%)	0	9 (29.0%)
	Complete	0	0	1 (6.3%)	0	1 (3.2%)
	Partial	4 (33.3%)	0	4 (25.0%)	0	8 (25.8%)
	Failure	0	0	2 (12.5%)	0	2 (6.5%)
	Stable	0	0	1 (6.3%)	0	1 (3.2%)
	Progression	0	0	1 (6.3%)	0	1 (3.2%)
	Not evaluable	1 (8.3%)	0	6 (37.5%)	0	7 (22.6%)
	No assessment by AC	7	1	3	2	13 (41.9%)
Day 84	Success	5 (41.7%)	0	3 (18.8%)	0	8 (25.8%)
	Complete	1 (8.3%)	0	1 (6.3%)	0	2 (6.5%)
	Partial	4 (33.3%)	0	2 (12.5%)	0	6 (19.4%)
	Failure	0	0	0	0	0
	Stable	0	0	0	0	0
	Progression	0	0	0	0	0
	Not evaluable	0	0	3 (18.8%)	0	3 (9.7%)
	No assessment by AC	7	1	10	2	20 (64.5%)

AC: Adjudication Committee; EORTC/MSG: European Organisation for Research and Treatment of Cancer/Mycoses Study Group; EOT: end of treatment; FAS: full analysis set; IA: invasive aspergillosis; IFD: invasive fungal disease; IM: invasive mucormycosis

If a participant did not reach days 42 or 84 of therapy, the AC did not perform these assessments.| Overall response was based on a composite of clinical, mycological and radiological responses with success criteria assessed. Overall response was considered 'Not evaluable' when one of the composite responses was 'Not Assessed'.

The frequency 'N' in a column heading represents the number of participants by the investigator assessment of IFD diagnosis.

† Investigator assessment of IFD diagnosis was used.

‡ According to EORTC/MSG 2008 criteria.

§ IFDs which were confirmed to not be IA or IM by the investigator.

Source: End-of-Text Table 12.3.2.1

Of the participants with proven or probable IA or IM, 8 participants were assessed by the AC as having a successful *overall response* at the EOT (8/13, 61.5% [IA+IM]).

The only patient diagnosed with proven or probable IM failed on isavuconazole therapy and showed progression of the disease.

Other secondary efficacy endpoints

In the FAS, at EOT, 8 of 12 (66.7%) participants with proven or probable IA and of the participants with possible IFD 11 of 16 (68.8%) were judged by the investigator to have had a successful *clinical response* to treatment.

In the FAS, successful *mycological response* (presumed eradication) at EOT occurred in 9 of 12 (75.0%) participants with proven or probable IA and in 2 of 16 (12.5%) participants with possible IFD.

No further details were provided on the mycological parameters (species, MICs etc). These details will be part of a separate application. This issue was not pursued in the context of this P46 procedure.

In the FAS, successful *radiological response* (complete or partial disappearance of radiological findings indicative of IFD at baseline) at EOT occurred in 8 of 12 (66.7%) participants with proven or probable IA and in 8 of 16 (50.0%) participants with possible IFD.

Safety results

Adverse events (Table 10)

Table 10. *Overview of Treatment-emergent Adverse Events and Deaths (SAF)*

	Categorization of IFD†‡									
	Proven or Probable IA (n = 12)		Proven or Probable IM (n = 1)		Possible IFD (n = 16)		Other IFD§ (n = 2)		Total (N = 31)	
Parameter	n (%)	#E	n (%)	#E	n (%)	#E	n (%)	#E	n (%)	#E
Overall TEAEs	11 (91.7%)	181	1 (100.0%)	12	15 (93.8%)	202	2 (100.0%)	20	29 (93.5%)	415
Drug-related¶ TEAEs	3 (25.0%)	16	1 (100.0%)	1	5 (31.3%)	7	0	0	9 (29.0%)	24
Serious TEAEs††	9 (75.0%)	22	0	0	9 (56.3%)	20	0	0	18 (58.1%)	42
Drug-related¶ Serious TEAEs††	1 (8.3%)	4	0	0	0	0	0	0	1 (3.2%)	4
TEAEs Leading to Death	2 (16.7%)	2	0	0	1 (6.3%)	1	0	0	3 (9.7%)	3
Drug-related¶ TEAEs Leading to Death	0	0	0	0	0	0	0	0	0	0
TEAEs Leading to Withdrawal of Treatment	2 (16.7%)	2	0	0	1 (6.3%)	1	0	0	3 (9.7%)	3
Drug-related¶ TEAEs Leading to Withdrawal of Treatment	1 (8.3%)	1	0	0	1 (6.3%)	1	0	0	2 (6.5%)	2
Deaths‡‡	2 (16.7%)	2	0	0	1 (6.3%)	1	0	0	3 (9.7%)	3

#E: number of events; EORTC/MSG: European Organisation for Research and Treatment of Cancer/Mycoses Study Group; IA: invasive aspergillosis; IFD: invasive fungal disease; IM: invasive mucormycosis; SAF: safety analysis set; TEAE: treatment-emergent adverse event

† Investigator assessment of IFD diagnosis was used.

‡ According to EORTC/MSG 2008 criteria.

§ IFDs which were confirmed to not be IA or IM by the investigator.

¶ A reasonable possibility that the event may have been caused by the study drug as assessed by the investigator. If relationship was missing, then it was considered drug-related.

†† Includes SAEs upgraded by the sponsor based on review of the sponsor's list of Always Serious terms, if any upgrades were done.

‡‡ All reported deaths after the first study drug administration.

Source: End-of-Text Table 12.6.1.1.1

Overall, a total of 29 (93.5%) participants experienced 415 treatment-emergent adverse events (TEAEs), 24 of which were considered treatment-related. The most common TEAEs (occurring in ≥5% of participants) were pyrexia (29.0%), diarrhea (25.8%), vomiting (22.6%), non-cardiac chest pain (16.1%), stomatitis (16.1%), nausea (12.9%) and aphthous ulcer (12.9%) [for details see CSR 9766-CL-0107 Table 11 pages 35-37].

The MAH is asked to provide more details on TEAEs chest pain, stomatitis and aphthous ulcers: When did these events emerge during isavuconazole treatment and what was their course during treatment (or thereafter)? Are these events considered to be exposure related and/or age related? Are

these events mainly related to oral or intravenous treatment with isavuconazole (for instance infusion time related)? The MAH is asked for further clarification (**OC**).

Consistent with the phase 3 study in adults, more than half (58.1%) of all participants experienced a Serious TEAE, with a total of 42 such events. The most common SAEs were septic shock (3 [9.7%] participants), febrile neutropenia (3 [9.7%] participants), and stomatitis (2 [6.5%] participants). Four of these events were considered to be treatment-related. These 4 events all occurred in a single participant and comprised infusion site pain, infusion site pruritus, injection site reaction and infusion related reaction. One of these, injection site reaction on day 2, led to withdrawal of study treatment on the same day. In this pediatric population, febrile neutropenia, septic shock and stomatitis were the most frequently observed SAEs, similar to those in the adult population.

Discontinuation of study drug

TEAEs leading to discontinuation of study drug were reported in 3 (9.7%) participants, and consisted of injection site reaction, hypotension, and hemoptysis in 1 participant each.

- Injection site reaction occurred in a 13-year-old male on day 2 and led to discontinuation on the same day. The episode was moderate in severity, categorized as serious and considered related to study drug.
- Hypotension occurred in a 16-year-old female on day 1 and was ongoing, leading to discontinuation on day 6. The episode was severe in severity, categorized as non-serious and considered related to study drug. Of note, this participant died on day 26 due to ongoing history of septic shock.
- Hemoptysis occurred in a 16-year-old female on day 16 and study drug was discontinued on the same day. The episode was severe in severity, categorized as serious and considered unrelated to study drug.

Deaths

There were 3 deaths during the study

- A 15-year-old female with probable IA and a medical history of atypical Griscelli syndrome, type II, died on day 61 as a result of cardiovascular collapse. The last day of study drug dosing was day 38; drug had been withdrawn due to worsening of clinical condition related to comorbidities.
- A second participant, a 16-year-old female with possible IFD and relevant medical history of ongoing sepsis, died as a result of septic shock on day 26. Study drug had been withdrawn on day 6 due to ongoing severe drug-related TEAE of hypotension.
- A third participant, a 16-year-old female with proven IA and relevant medical history of ongoing acute humoral rejection of lung transplant, died as a result of progressive IFD on day 15. Study drug had been withdrawn on day 10 due to lack of efficacy.

None of the deaths were considered treatment-related by the investigator.

Clinical laboratory evaluations,

Hematology and chemistry

No clinically significant changes from baseline were observed in any of the hematology or chemistry parameters

Potentially clinically significant values for liver enzymes
Three participants had concurrent ALT and/or AST > 3 x ULN and total bilirubin > 2 x ULN. These were considered by the MAH unlikely to be related to study drug and more likely to be related to the participants' complex medical conditions, underlying comorbidities, and multiple concomitant medications. *The MAH did not discuss whether these changes are related to the degree of exposure to isavuconazole (see also OC2).*

Vital signs, or 12-lead ECGs

Overall, there were no clinically significant results or trends in vital signs, or 12-lead ECGs in this study.

Palatability

Overall, the majority of the participants had a neutral or positive response ("not bad, not good", "good", or "really good") to how the oral capsule tasted, how it was to swallow, and how they would feel if they took the medication again. Only 1 participant had a negative response ("bad").

2.3.3. Discussion on clinical aspects

Pharmacokinetics

In the previous P46 procedure, where study 9766-CL-0046 was assessed, paediatric patients aged below 12 years of age appeared to have a higher exposure with the 10 mg/kg dosing regimen. Current data of study 9766-CL-0107 appear to indicate the opposite. A pooled population pharmacokinetic analysis is planned, which should provide clarity on the pharmacokinetics of isavuconazonium in the paediatric age range. Potential differences between paediatric exposure and adult exposure should be thoroughly discussed and justified by providing evidence for the expected therapeutic window (in terms of both safety and efficacy). As limited information was provided in this procedure, this issue is not pursued. However, the MAH was requested to commit to providing the results of the pooled population pharmacokinetic analysis (Study 9766-PK-0009), which may be provided at the time of marketing application authorisation for the extension of the indication. (OC)

Furthermore, the MAH was reminded of the comments already made during a previous P46 procedure on study 9766-CL-0046 (EMA/H/C/002734/P46/006) that are relevant at time of marketing application and/or submission of the population pharmacokinetic analysis results. Most importantly;

- It is advised to include additional diagnostic plots in future applications as there appears to be a deviation in the population predicted concentrations versus observed concentrations in the goodness-of-fit plot in the population pharmacokinetic model (Study 9766-PK-0008), which could indicate differences in PK in the paediatric population as compared to the adult population.

- It would be valuable to evaluate the relationship between pharmacokinetic parameters, in particular C_{max}, and safety effects in the paediatric population as the previously provided analyses focusses mainly on efficacy.

Efficacy

No formal prospectively defined efficacy assessments were planned in study 9766-CL-0107. Efficacy data were collected during the study only for descriptive purposes.

Primary Efficacy Endpoint in study 9766-CL-0107 was *All-cause Mortality Through Day 42 (FAS)*. Two of 31 total (6.5%) pediatric patients died during the first 42 days, which is a relatively low number when compared to that reported in adults (18.7%). In the most important subset of patients diagnosed with *proven or probable* Invasive Aspergillosis (IA) or Invasive Mucormycosis (IM), 1 (8.3%) participant died. The cause of death was related to IA infection.

The AC-assessed overall response rates for the FAS set at days 42 and 84 and EOT were 29.0%, 25.8% and 54.8%, respectively. Of the 12 patients diagnosed with *proven or probable IA*, 8 were assessed by the AC as having a successful overall response at the EOT (8/12, 66.7%).

The only patient diagnosed with *proven or probable IM* that was treated with intravenous isavuconazole for 15 days failed on therapy and showed progression of the disease.

The efficacy results of study 9766-CL-0107 are difficult to interpret due to several study limitations:

- This was an open-label, non-comparative trial.
- The sample size was low. A limited number of 31 pediatric patients were enrolled in study 9766-CL-0107.
- Of these, only 12 patients were diagnosed with *proven or probable* Invasive Aspergillosis and a single patient with *proven or probable* Invasive mucomycosis (subpopulation of major interest).
- Mycological details (pathogens, MICs) were not provided/discussed.
- According to study protocol concomitant use of other systemic antifungal agents was be avoided. However, these were used in a significant number of patients with *proven or probable* IA or IM [8 of 13, (61.5%)]. The medication included agents like posaconazole, voriconazole and amphotericin B that are known to be active against *Aspergillus* infections, while amphotericin B is the preferred first-line treatment for invasive mucormycosis. Although there may have been good clinical reasons for adding these agents to the study drug, the exact contribution of isavuconazole to the clinical success of the overall treatment is therefore difficult to determine.

Since the clinical data on efficacy (and safety) of isavuconazole in the paediatric population is very limited, proof of efficacy in both indications will be mainly based on adult data, it is therefore considered crucial that, based on the PK data obtained in adults and children, efficacy and safety results from trials conducted in adults can be extrapolated to the pediatric population.

The MAH does not seek an update of the isavuconazole product information with this submission, but this will be applied for as part of a separate application. Whether the use of isavuconazole in paediatric patients from 1 to < 18 years of age will be approvable is to be decided at a later stage. *The MAH*

stated that the grouped application will comprise the full relevant data package containing quality, nonclinical, and clinical data. It is assumed that microbiological data will be part of the package.

Safety

As could be expected in this severely-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 in study 9766-CL-0107 was very high: 29 (93.5%) participants experienced 415 treatment-emergent adverse events (TEAEs). The pattern, frequency and types of TEAE's (as well as SAEs) that occurred in study 9766-CL-107 were in line with those reported in pediatric study 9766-CL-0046 and generally in line with those observed in the adult population.

The most common TEAEs (occurring in ≥5% of children) were pyrexia (29.0%), diarrhea (25.8%), vomiting (22.6%), non-cardiac chest pain (16.1%), stomatitis (16.1%), nausea (12.9%) and aphthous ulcer (12.9%) [for details see CSR 9766-CL-0107 Table 11 pages 35-37]. Pyrexia, nausea, vomiting, and diarrhea occurred at similar frequencies as those in the phase 3, controlled study in adult patients with IFD (Study 9766-CL-0104), however, non-cardiac chest pain, stomatitis and aphthous ulcer were not common in the adult study population.

On request the MAH provided more details on TEAEs chest pain, stomatitis and aphthous ulcers, but from the submitted data it did not appear that these TEAEs were drug related or age related (see also Section 5 of this AR).

The most common SAEs were septic shock 3 (9.7%), febrile neutropenia 3 (9.7%), and stomatitis 2 (6.5%). Four of these events were considered to be treatment-related, all occurred in a single participant and led to withdrawal of study treatment (infusion site related adverse reactions). Infusion site related adverse reactions are well known to occur and are reported in adults as well and there appears to be no tendency that these reactions occur more in children than in adults.

The clinical laboratory evaluations did not provide new insights, although the proportion of isavuconazole-treated participants experiencing a combined increase of AST or ALT of > 3 x ULN and total bilirubin > 2 x ULN in this pediatric population was higher as compared to the adult population in Study 9766-CL-0104 (9.7% versus 3.2%). The MAH explained that in a detailed review of the data for each of the 3 participants from Study 9766-CL-0107, each had confounding factors that could also explain the combined elevations in transaminases and total bilirubin. The MAH was asked to discuss whether these events are related to the degree of isavuconazole exposure and from the MAH's response it does not appear that such an association exists (see Section 5 of this AR).

3. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

Pharmacokinetics

1. The MAH is requested to commit to providing the results of the pooled population pharmacokinetic analysis (Study 9766-PK-0009), which may be provided at the time of marketing application authorisation for the extension of the indication.

Safety

2. Pyrexia, nausea, vomiting, and diarrhea occurred at similar frequencies as those in the phase 3, controlled study in adult patients with IFD (Study 9766-CL-0104), however, non-cardiac chest pain, stomatitis and aphthous ulcer were not common in the adult study population. The MAH is asked to provide more details on TEAEs chest pain, stomatitis and aphthous ulcers: When did these events emerge during isavuconazole treatment and what was their course during treatment (or thereafter)? Are the these events considered to be exposure related and/or age related? Are these events mainly related to oral or intravenous treatment with isavuconazole (for instance infusion time related)? The MAH is asked for further clarification.

3. The proportion of isavuconazole-treated participants experiencing a combined increase of AST or ALT of > 3 x ULN and total bilirubin > 2 x ULN in this pediatric population was higher as compared to the adult population in Study 9766-CL-0104 (9.7% versus 3.2%). The MAH explained that in a detailed review of the data for each of the 3 participants from Study 9766-CL-0107, each had confounding factors that could also explain the combined elevations in transaminases and total bilirubin. The MAH is however asked to discuss whether these events are related to the degree of isavuconazole exposure.

4. MAH responses to Request for supplementary information

On 4 September 2023 the MAH responded to the questions raised by the CHMP, as follows:

Pharmacokinetics

Question 1

The MAH is requested to commit to providing the results of the pooled population pharmacokinetic analysis (Study 9766-PK-0009), which may be provided at the time of marketing application authorisation for the extension of the indication.

MAH response

The results of the pooled population pharmacokinetic analysis study have been provided with a separate application for extension of the currently-approved indications to pediatric patients, combined with a line extension to register an additional strength of the currently-approved oral formulation, isavuconazole hard capsules, submitted on 31 August 2023.

Assessment

The MAH has submitted a type II variation grouped with a line-extension (EMEA/H/C/002734/X/0042/G) with the pooled population pharmacokinetic analysis.

Issue resolved.

Safety

Question 2.

Pyrexia, nausea, vomiting, and diarrhea occurred at similar frequencies as those in the phase 3, controlled study in adult patients with IFD (Study 9766-CL-0104), however, non-cardiac chest pain, stomatitis and aphthous ulcer were not common in the adult study population. The MAH is asked to provide more details on TEAEs chest pain, stomatitis and aphthous ulcers: When did these events emerge during isavuconazole treatment and what was their course during treatment (or thereafter)? Are the these events considered to be exposure related and/or age related? Are these events mainly related to oral or intravenous treatment with isavuconazole (for instance infusion time related)? The MAH is asked for further clarification.

MAH response (in summary)

- **Patients with TEAEs of non-cardiac chest pain or chest pain in study 9766-CL-0107**

Mild to moderate TEAEs of non-cardiac chest pain or chest pain were reported in six of the 31 patients (19.4%) in study 9766-CL-0107. None of these events were considered causally related to isavuconazole.

The age range of patients reported with TEAEs of non-cardiac chest pain or chest pain was 7 to 13 years, and five of the six patients had an underlying hematologic malignancy. All six patients had invasive fungal disease (IFD) affecting the lungs, with two patients presenting with additional pleural involvement. There was no clear temporal pattern regarding the time of onset of non-cardiac chest pain. Four of the six patients were receiving oral isavuconazole at the time of onset of the TEAE, one was receiving intravenous isavuconazole, and one patient reported non-cardiac chest pain after the end of isavuconazole treatment. Four patients reported non-cardiac chest pain as medical history (within 14 days of study enrolment), which was ongoing in three patients at the time of study enrolment

Five of the six patients who were reported with TEAEs of non-cardiac chest pain or chest pain had AUC estimates. In these five patients, the median AUC was 126.2 mg*hr/L (min – max: 73.1 – 153.8). The median AUC in the remaining 23 patients in the study with AUC estimates who were not reported with TEAEs of non-cardiac chest pain or chest pain was 99.6 mg*hr/L (min – max: 35.8 – 215.6) [**Appendix 1.,** *Rapp. comm. see Annexes to this AR*].

Discussion and conclusion

The number of patients with a pre-study medical history of non-cardiac chest pain or chest pain was similar (n = 7) to the number of patients reporting TEAEs of non-cardiac chest pain or chest pain (n = 6), indicating that there was no increase in the level of non-cardiac chest pain during the study. Four of the six patients reported with TEAEs of non-cardiac chest pain or chest pain also had a medical history of non-cardiac chest pain. An additional three patients had a medical history of non-cardiac chest pain or chest pain but did not report TEAEs while enrolled in the study, and two patients had TEAEs of non-cardiac chest pain or chest pain without a medical history of either of these events (**Table 2**).

Baseline characteristics in regard to age range and underlying hematologic malignancies were consistent between patients who had both a medical history and TEAE of non-cardiac chest pain or chest pain and those who had either a medical history or TEAE only. In view of this pattern of medical history and TEAEs, together with the investigators' causality assessments that none of the TEAEs of non-cardiac chest pain or chest pain were study-drug-related, the lung and pleural involvement of IFD, and the lack of an exposure relationship, a causal effect of isavuconazole with TEAEs of non-cardiac chest pain or chest pain is considered highly unlikely.

The assumption that TEAEs of non-cardiac chest pain or chest pain reflect symptoms related to the underlying disease of pulmonary/pleural IFD, rather than a side effect of isavuconazole, is further supported by the fact that it is known that unspecific symptoms including chest pain are frequent in immunosuppressed children with pulmonary IFD (**Müller 2002**), and have been reported in eight (32%) of 25 pediatric patients with acute leukemia and IFD based on a retrospective case series (**Tüfekçi 2015**). This background rate is consistent with the percentage of non-cardiac chest pain or chest pain reported as medical history or TEAEs in study 9766-CL-0107.

Table 2 Study 0766-CL-0107: Overview of the occurrence of non-cardiac chest pain or chest pain before and after study enrolment

Patient number	Age / Gender / Race / Country	Underlying disease	Host factor	Site of infection	Medical history (Start – Stop)	TEAE (Start – Stop)	Isavuconazole treatment (days)
[redacted]	7/M/A/[redacted]	ALL	1,3,4	Lung	Day −9 – Day −9	Day 46 – 61	84
	11/F/A/[redacted]	CCAM		Lung, Pleura	Day −9 – ongoing	Day 37 – 41	61
	13/F/W[redacted]	AML	1	Lung	Day −3 – ongoing	Day 75 – 91	67
	11/F/W[redacted]	AML	1	Lung, Skin	Day −1 – ongoing	Day 6-9 and 48-49	6
	6/F/A/[redacted]	ALL	1,3,4	Lung, Pleura	Day −3 – ongoing	Not reported	84
	6/F/W[redacted]	ALL	1,3,4	Lung	Day −4 – ongoing	Not reported	51
	16/F/W[redacted]	AML	1,3	Lung	Day −4 – ongoing	Not reported	6
	9/F/A/[redacted]	BLL	1,3,4	Lung, Pleura	Not reported	Day 17 – 21	84
	7/F/W[redacted]	ALL	1	Lung	Not reported	Day 8 – 8	84

[redacted], ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; BLL = B-lymphoblastic lymphoma; CCAM = congenital cystic adenomatoid malformation; F = female; M = male; W = White.
Host factors: 1: Recently resolved or ongoing neutropenia. 2: Inherited severe immunodeficiency. 3 = Treatment with other recognized T-cell immunosuppressants. 4 = Prolonged use of corticosteroids. 5 = Receipt of an allogeneic hematopoietic stem cell transplant.

References:

Müller FM, Trusen A, Weig M. Clinical manifestations and diagnosis of invasive aspergillosis in immunocompromised children. Eur J Pediatr. 2002 Nov;161(11):563–74.

Tüfekçi Ö, Yılmaz Bengoa Ş, Demir Yenigürbüz F, et al. Management of Invasive Fungal Infections in Pediatric Acute Leukemia and the Appropriate Time for Restarting Chemotherapy. Turk J Haematol. 2015 Dec;32(4):329–37.

Assessment

The MAH conclusion that TEAEs of 'non-cardiac chest pain or chest pain' are to be related to the underlying disease of pulmonary/pleural IFD, rather than to isavuconazole therapy, is endorsed.

Issue resolved.

- **Patients with TEAEs of stomatitis and aphthous ulcers in study 9766-CL-0107**

In study 9766-CL-0107, TEAEs of stomatitis (n = 5) or aphthous ulcer (n = 4) were reported in 8/31 patients (25.8%). One patient reported episodes of both stomatitis and aphthous ulcers. The age of patients reported with TEAEs of stomatitis or aphthous ulcers was 1 to 13 years, with a median age of 7.5 years, compared to a median age of 10 years in the overall study population.

There were five patients with their first TEAEs of stomatitis or aphthous ulcer reported while the patient was receiving isavuconazole (intravenous n = 2, oral n = 3), with maximum severity mild (n = 3), moderate (n = 1), or severe (n = 1). There were three patients with their first TEAEs of stomatitis or aphthous ulcer reported after the end of isavuconazole treatment, with maximum severity mild (n = 2), or moderate (n = 1).

A summary of each patient reported with stomatitis and/or aphthous ulcers is provided in **Table 3** (*Rapp. comm. see Annexes to this AR*)

All patients with TEAEs of stomatitis or aphthous ulcers had underlying hematologic malignancies, for which all but one patient had received combination chemotherapy in close temporal relationship to the onset of the events of stomatitis or aphtous ulcers. The most commonly used intravenous chemotherapy agents in patients reported with stomatitis or aphthous ulcers were methotrexate (n = 5 intravenous) and cytarabine (n = 4), both of which are known to be a frequent cause of chemotherapy-associated stomatitis.

None of the TEAEs of stomatitis or aphthous ulcers were considered to be causally-related to isavuconazole, and no patients discontinued isavuconazole treatment due to a TEAE of stomatitis or aphthous ulcers.

Seven of the eight patients who were reported with TEAEs of stomatitis and/or aphthous ulcers had AUC data. In these patients the median AUC was 84.3 mg*hr/L (min – max: 35.8 – 126.2). The median AUC in the remaining 21 patients with AUC estimates who were not reported with TEAEs of stomatitis or aphthous ulcers was 106.3 mg*hr/L (min – max: 37.8 – 215.6).

Discussion and conclusion

Patients experiencing TEAEs of stomatitis or aphthous ulcers in study 9766-CL-0107 were characterized by underlying hematologic malignancies and the receipt of chemotherapy in close temporal relationship to the onset of stomatitis or aphthous ulcers; these TEAEs were transient and did not show a relationship to exposure.

Chemotherapy-induced oral mucositis is the main non-hematologic complication of cytotoxic chemotherapy in pediatric cancer patients. In a recent systematic review and meta-analysis, the percentage of pediatric cancer patients developing oral mucositis following chemotherapy was estimated at 53.6%, ranging from 16.7% to 91.5% across various studies (**Docimo 2022**).

In study 9766-CL-0107, 19 of 31 (61.3%) of patients had an underlying malignancy, and 15 patients received chemotherapy while enrolled in the study, of whom eight (53.3%) were reported with a TEAE of stomatitis and/or aphthous ulcer. The proportion of patients with stomatitis or aphthous ulcers was therefore consistent with literature reports on the incidence of this side effect seen with chemotherapy (**Docimo 2022**).

The pharmacokinetics of the most frequently-used chemotherapy agents in the study (methotrexate and cytarabine) have been shown to be unaffected by isavuconazole (**Yamazaki 2017**), or are not expected to show drug-drug interactions with isavuconazole.

In conclusion, the case review of patients reported with stomatitis or aphthous ulcers in study 9766-CL-0107 does not indicate a causal relationship of isavuconazole with these events.

References:

Docimo R, Anastasio MD, Bensi C. Chemotherapy-induced oral mucositis in children and adolescents: a systematic review. Eur Arch Paediatr Dent. 2022 Aug;23(4):501–511.

Yamazaki T, Desai A, Goldwater R, et al. Pharmacokinetic Interactions Between Isavuconazole and the Drug Transporter Substrates Atorvastatin, Digoxin, Metformin, and Methotrexate in Healthy Subjects. Clin Pharmacol Drug Dev. 2017 Jan;6(1):66–75.

Assessment

Mucositis and/or aphthous ulcer are complications of cytotoxic chemotherapy (incl. methotrexate and cytarabine) in pediatric cancer patients (Docimo 2022). There appears not to be a causal relationship of isavuconazole with both adverse events. From the submitted clinical data (summarized in Table 3) these events mainly occur following previous chemotherapy.

Issue resolved.

Question 3.

The proportion of isavuconazole-treated participants experiencing a combined increase of AST or ALT of > 3 x ULN and total bilirubin > 2 x ULN in this pediatric population was higher as compared to the adult population in Study 9766-CL-0104 (9.7% versus 3.2%). The MAH explained that in a detailed review of the data for each of the 3 participants from Study 9766-CL-0107, each had confounding factors that could also explain the combined elevations in transaminases and total bilirubin. The MAH is however asked to discuss whether these events are related to the degree of isavuconazole exposure.

MAH response (in summary)

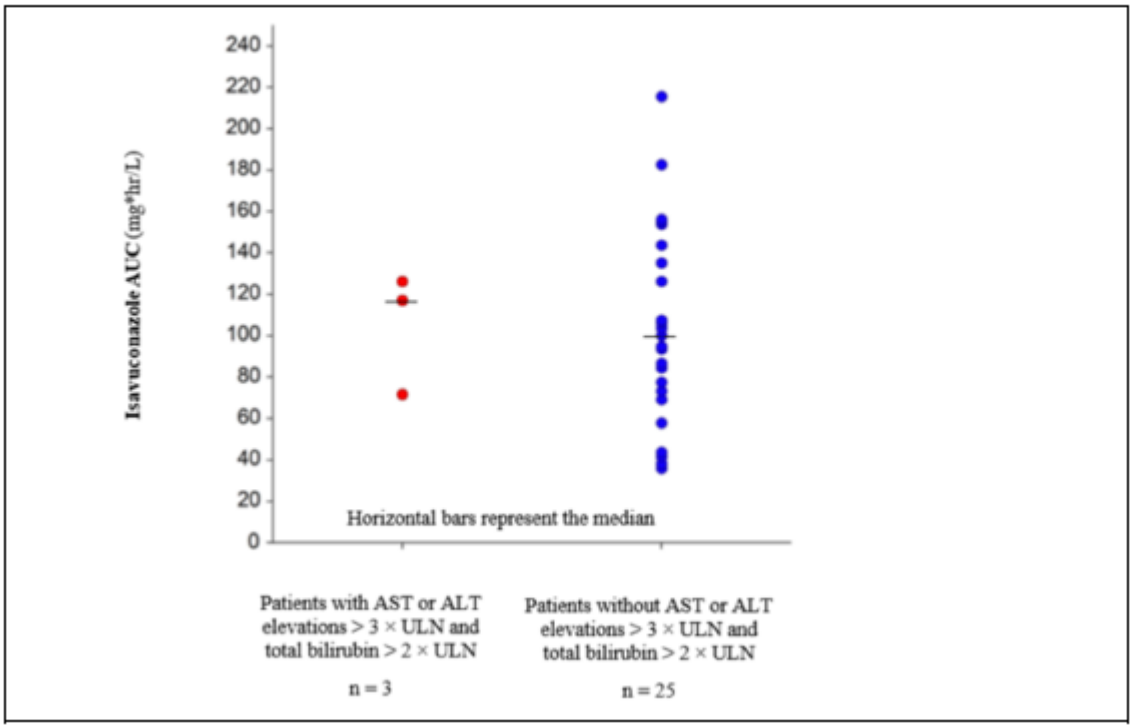
Three participants had concurrent ALT and/or AST > 3 × ULN and total bilirubin > 2 × ULN. The sponsor carefully evaluated each of these three cases, and for each participant concluded that the hepatic abnormalities were unlikely to be related to study drug, and were more likely to be related to the participants' complex medical conditions, underlying comorbidities, and multiple concomitant medications.

All three patients with ALT/AST/total bilirubin elevations had AUC estimates. In these patients, the median AUC was 117.2 mg*hr/L (min – max: 71.6 – 126.0). The median AUC in the remaining 25 patients in the study was 99.6 mg*hr/L (min – max: 35.8 – 215.6) [**Appendix 1.**].

- A 15-year-old female patient with atypical Griscelli syndrome and an ongoing medical history of Gram-negative rod bacteremia septic shock and sepsis and Cytomegalovirus viremia. She also had a history of elevated liver enzymes for 2 years before receiving the first dose of isavuconazole. Liver enzyme elevations during the study coincided with worsening of her clinical condition, and she died from circulatory collapse. Autopsy demonstrated liver findings that were consistent with sepsis. The AUC estimate at steady state in this patient was 71.55 mg mg*hr/L.
- A 16-year-old female patient diagnosed with acute myeloid leukemia and an ongoing medical history of sepsis, septic shock, and multi-organ failure. During study treatment, septic shock worsened and she developed abdominal distension and ascites, as well as veno-occlusive disease. She died from septic shock. The AUC estimate at steady state in this patient was 117.23 mg*hr/L.
- An 11-year-old female patient who was being actively treated for acute lymphocytic leukemia with multiple cytotoxic agents; relevant medical history included ongoing increased transaminases, hepatomegaly, and positive HHV-6 serology. HHV-6 is known to cause acute liver dysfunction in both immunocompetent and immunocompromised individuals. During study treatment, she suffered from sepsis and rhabdomyolysis, both of which likely further contributed to her elevated liver enzymes. The AUC estimate at steady state in this patient was 125.97 mg*hr/L.

Figure 1 provides a dot-plot of individual AUC estimates for patients in study 9766-CL-0107; the data do not suggest an association between exposure and the reported ALT/AST/total bilirubin increases.

Figure 1 Study 0766-CL-0107: AUC estimates in patients with and without AST or ALT elevations > 3 × ULN and total bilirubin > 2 × ULN



Assessment

It is agreed with the MAH that the data do not suggest an association between isavuconazole exposure and the reported ALT/AST/total bilirubin increases.

Issue resolved.

5. Overall conclusion and recommendation

The primary objective of study 9766-CL-0107 was to assess the pharmacokinetics, efficacy and safety of isavuconazonium sulfate in the treatment of Invasive Aspergillosis or Invasive Mucormycosis in the pediatric population (children aged 1 to 18 years).

The efficacy in children appears to be in line with that in adults. However, since the clinical data on the use of isavuconazole in the paediatric population are still very limited, proof of efficacy and safety will be mainly based on the existing adult data. Therefore, it is considered crucial that, based on the PK data obtained in adults and children, efficacy and safety results from trials conducted in adults can be extrapolated to the paediatric population.

The MAH regards all elements of the agreed PIP now as completed.

Currently, no changes in the SmPC have been proposed by the MAH, which is considered acceptable.

☒ PAM Fulfilled:

No further action required, however further data are expected in the context of a separate application for extension of the currently-approved indications to pediatric patients, combined with a line extension to register an additional strength of the currently-approved oral formulation, isavuconazole hard capsules. The variation and line-extension have been submitted on 31 August 2023 (EMEA/H/C/002734/X/0042/G).