27 June 2024
EMA/330882/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cresemba

International non-proprietary name: Isavuconazole

Procedure No. EMEA/H/C/002734/X/0042/G

Note

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

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List of abbreviations

AC	Adjudication Committee
AFT	Antifungal therapy
ALL	Acute Lymphatic Leukemia
ALT	Alkaline transaminase
AmB	Amphotericin B
ANC	Absolute neutrophil count
AST	Aspartate transaminase
AUC	area under the concentration time curve
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human use
CI	confidence interval
CL	clearance
Clcr	creatinine clearance
C_{max}	Maximum plasma concentration
CSR	clinical study report
CT	Computed tomography
EC	European Commission
ECG	electrocardiogram
ECMM/MSG ERC	European Confederation of Medical Mycology/ Mycoses Study Group Education & Research Consortium
EMA	European Medicines Agency
EOT	end-of-treatment visit
EORTC/MSG	European Organisation for the Research and Treatment of Cancer/Mycoses Study Group
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
ESRD	end-stage renal disease
FAS	full analysis set (FAS) consists of all subjects who are enrolled and receive at least one dose of study drug.
FU	Follow-up period
GI	Gastrointestinal
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HPLC	High performance liquid chromatography
HSCT	Hematopoietic stem cell transplant
IA	Invasive Aspergillosis
ICH	International Council for Harmonisation
IFD	Invasive Fungal Disease

ISA	Isavuconazole
ISS	integrated summary of safety
ITT	intent-to-treat population
IV	intravenous
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified full analysis set 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.
MIC	minimum inhibitory concentration
ND	Not detected
NLT	Not less than
NMT	Not more than
PD	pharmacodynamic(s)
PDCO	Paediatric Committee
	Permitted daily exposure
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	pharmacokinetic(s)
PKAS	pharmacokinetic analysis set
PL	Package leaflet
popPK	Population pharmacokinetic (model)
PT	preferred term
RMP	Risk Management Plan
SAE	serious adverse event
SAF	Safety analysis set (SAF) consists of all subjects who are enrolled and receive at least 1 dose of study drug.
SAP	Statistical analysis plan
SD	standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA query
SOC	System Organ Class
TAMC	Total Aerobic Microbial Count
TEAE	treatment-emergent adverse event
TYMC	Total Combined Yeasts/Moulds Count
ULN	Upper limit of normal

1. Background information on the procedure

1.1. Submission of the dossier

Basilea Pharmaceutica Deutschland GmbH submitted on 31 August 2023 a group of variations consisting of an extension of the marketing authorisation and the following variation:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to add a new strength of 40 mg hard capsule to be used in paediatric patients 6 years and older grouped with a type II variation (C.I.6.a) in order to extend the indication to include treatment of paediatric patients aged 1 year and older for CRESEMBA 200 mg powder, based on final results from studies 9766-CL-0107 and 9766-CL-0046. Study 9766-CL-0046 is a Phase 1, open-label, multicenter study to evaluate the PK, safety and tolerability of intravenous and oral isavuconazonium sulfate in paediatric patients. This study was conducted in two sequential parts: Part 1 with three intravenous dosing cohorts, and Part 2 with two oral dosing cohorts. Study 9766-CL-0107 is a Phase 2, open-label, non-comparative, multicenter study to evaluate the safety and tolerability, efficacy, and PK of isavuconazole for the treatment of invasive aspergillosis or mucormycosis in paediatric patients aged 1 to < 18 years.
As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2, and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 9.1 of the RMP has also been submitted.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Cresemba was designated as an orphan medicinal product EU/3/14/1284 on 2014-07-04 in the following condition: treatment of invasive aspergillosis.

Cresemba was designated as an orphan medicinal product EU/3/14/1276 on 2014-06-04 in the following condition: treatment of mucormycosis.

The new indication, which is the subject of this application, falls within the above-mentioned orphan designations.

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0479/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0479/2021 was completed.

The PDCO issued an opinion on compliance for the PIP P/0479/2021.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Protocol assistance

The MAH did not seek Protocol assistance at the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Patrick Vrijlandt

The application was received by the EMA on	31 August 2023
The procedure started on	28 September 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 December 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 December 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 January 2024
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	25 January 2024
The MAH submitted the responses to the CHMP consolidated List of Questions on	22 February 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	26 March 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 April 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	25 April 2024
The MAH submitted the responses to the CHMP List of Outstanding Issues	28 May 2024

on	
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	13 June 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for Cresemba on	27 June 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Invasive aspergillosis

Invasive aspergillosis is a life threatening infection that is seen predominantly in immunocompromised patients. Patients at greatest risk are those with prolonged neutropenia related to antineoplastic chemotherapy and/or hematopoietic stem cell transplantation (HSCT), those receiving immunosuppressants following solid organ transplants, advanced HIV infection and those given high doses of corticosteroids.

Management
Invasive aspergillosis is treated with systemic antifungal agents, such as polyenes (Amphotericin B), mould active triazoles (isavuconazole, voriconazole, itraconazole, posaconazole) and echinocandins (caspofungin, micafungin, and anidulafungin). Certain conditions of invasive aspergillosis warrant consideration for surgical resection of the infected focus.

Prognosis
Despite the current available antifungal therapies (AFTs) for invasive aspergillosis IFD is still associated with high mortality rates (30-40% in treated patients and 95% in untreated patients).

Mucormycosis
Mucormycosis is extremely rare and refers to several different diseases caused by infection with fungi in the order of Mucorales. *Rhizopus* species are the most common causative organisms. Mucoraceae are ubiquitous fungi that are commonly found in soil and in decaying matter. *Rhizopus* can be found in mouldy bread. Most humans are exposed to these organisms on a daily or weekly basis. The major route of infection is via inhalation of conidia; other routes include ingestion and traumatic inoculation. They rarely cause disease because of the low virulence of the organisms; instead, they mainly affect immunocompromised patients. Patients with uncontrolled diabetes mellitus, especially with ketoacidosis, are at high risk. Patients with cancer—especially those who are neutropenic and receiving broad-spectrum antibiotics—as well as individuals receiving immunosuppressive agents—including oral or intravenous steroids and tumour necrosis factor (TNF)–alpha blockers—are at risk. In addition, hematologic cancer patients with opportunistic herpetic infections (e.g., cytomegalovirus) and graft versus host disease are at increased risk.

Most mucormycosis infections are life-threatening. Severe infection of the facial sinuses, which may extend into the brain, is the most common presentation. Pulmonary, cutaneous, and gastrointestinal (GI) infections

are also recognised. Rhinocerebral disease causes significant morbidity in patients who survive, because treatment usually requires extensive, and often disfiguring, facial surgery.

Management
Surviving mucormycosis requires rapid diagnosis and aggressive coordinated medical and surgical therapy. Successful mucormycosis treatment requires correction of the underlying risk factor(s), antifungal therapy with liposomal amphotericin B or isavuconazole (also posaconazole has some anti- *Mucorales* activity), and aggressive surgery.

Prognosis
Still mucormycosis carries a mortality rate of 50-85%. The mortality rate associated with rhinocerebral disease is 50-70%. Pulmonary and gastrointestinal (GI) diseases carry an even higher mortality rate, because these forms are typically diagnosed late in the disease course. Disseminated disease carries a mortality rate that approaches 100%. Cutaneous disease carries the lowest mortality rate (15%).

2.2. About the product

Cresemba contains isavuconazonium sulfate as the active ingredient. Isavuconazonium sulfate is triazole antifungal agent and the prodrug of the active moiety isavuconazole. Isavuconazonium sulfate is currently indicated in *adults* for the treatment of

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

The currently approved posology *in adults* is:

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.

Cresemba is currently available as powder for concentrate for solution for infusion (each vial contains 200 mg isavuconazole (as 372.6 mg isavuconazonium sulfate) and as hard capsules for oral use (each capsule contains 100 mg isavuconazole (as 186.3 mg isavuconazonium sulfate).

Mode of action

Isavuconazonium sulfate is a water-soluble triazole antifungal agent and the prodrug of the active moiety isavuconazole. Isavuconazole is the active moiety formed after oral or intravenous administration of isavuconazonium sulfate. 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.

Clinical efficacy has been demonstrated for the following *Aspergillus* species: *Aspergillus fumigatus*, *A. flavus*, *A. niger*, and *A. terreus.*

PK-PD relationship

In animal models of disseminated and pulmonary aspergillosis, the pharmacodynamic (PD) index important in efficacy is exposure divided by minimum inhibitory concentration: AUC/MIC.

No clear correlation between *in vitro* MIC and clinical response for the different species (*Aspergillus* and *Mucorales*) could be established.

Paediatric development

The MAH is seeking extension of both indications (IA and IM) to the paediatric population aged from 1 up to 18 years. For this purpose, the MAH also developed a dedicated new pharmaceutical form: a hard capsule containing 40 mg of isavuconazole (as 74.5 mg isavuconazonium sulfate).

2.3. Type of Application and aspects on development

Paediatric development

The MAH has submitted two paediatric clinical trials, 9766-CL-0046 and 9766-CL-0107. Both studies have been submitted in accordance with Article 46 in January 2020 and May 2023, respectively and assessed (EMA/H/C/002734/P46/006, EMA/H/C/002734/P46/007).

No scientific advice with regards to the paediatric development was requested; the studies have been discussed as part of the Paediatric Investigation Plan (PIP) by the PDCO.

Both paediatric studies (study 9766-CL-0046 and study 9766-CL-0107) were conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP).

2.4. Quality aspects

2.4.1. Introduction

This extension application introduces an additional strength to the approved oral formulation (capsule, hard; approved: 100 mg; new: 40 mg) grouped with a type II variation (C.I.6) to extend the approved indications to paediatric patients aged 1 year and older. The extension of indication to paediatric patients covers all approved presentations including the powder for concentrate for solution for infusion (200 mg).

The finished product is presented as hard capsule containing isavuconazonium sulfate equivalent to 40 mg of isavuconazole as active substance.

Other ingredients are:

Capsule contents: magnesium citrate (anhydrous), microcrystalline cellulose (E460), talc (E553b), silica, colloidal anhydrous and stearic acid;

Capsule shell: hypromellose, red iron oxide (E172) and titanium dioxide (E171);

Printing ink are: shellac (E904), propylene glycol (E1520), potassium hydroxide, black iron oxide (E172).

The product is available in aluminium blisters with each capsule pocket connected to a pocket with desiccant as described in section 6.5 of the SmPC.

2.4.2. Active Substance

No new information on the active substance has been provided with this line extension application. The new hard capsule presentation contains active substance of the same quality as used in the approved hard capsule presentation and the active substance is manufactured by the approved manufacturing sites. The approved specification of the active substance is suitable for the new presentation and no additional tests are required.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product Cresemba capsules, hard (40 mg) is presented as size three capsules with a capsule length of 15.9 mm. The colour of the capsule body and cap is Swedish Orange (reddish-brown). The capsule is imprented on the capsule cap with "CR40" in black ink. The finished product contains 74.5 mg isavuconazonium sulfate which corresponds to 40 mg isavuconazole.

The aim of formulation development was to develop a smaller hard capsule presentation in a lower strength which is suitable as an oral formulation for use in the paediatric population.

Cresemba has been previously developed as a powder for concentrate for solution for infusion for intravenous use (200 mg strength) and as a hard capsule for oral use (100 mg strength). The development of the new lower-strength hard capsule presentation in a strength of 40 mg built on knowledge from development of the approved hard capsule presentation.

The capsules contain isavuconazonium sulfate, a pro-drug of the active substance isavuconazole. The pro-drug was chosen due to its high aqueous solubility enabling parenteral delivery by infusion as well as oral bioavailability with low inter-subject variability and well-controlled linear pharmacokinetics. This specific pro-drug moiety was selected based on preclinical data demonstrating fast and complete conversion to the active substance isavuconazole by enzymatic cleavage.

The proposed formulation containing 74.5 mg isavuconazonium sulfate (40 mg strength) is dose proportional to the approved capsules containing 186.3 mg isavuconazonium sulfate (100 mg strength). This approach allowed to fully utilise prior knowledge from pharmaceutical development of Cresemba 100 mg hard capsules and will allow for interchangeability of the two capsule presentations.

There is no difference in the final blend components used for the proposed new capsule presentation and the approved presentation. For the new 40 mg strengths presentation, a size 3 capsule is used instead of the size 0-elongated capsules used for the approved 100 mg presentation. For the new 40 mg hard capsules, both capsule cap and body have the colour Swedish Orange (reddish-brown colour), whereas for the approved 100 mg capsule the body is in the colour Swedish Orange and the cap is white. The imprint design is also different (see above for the new 40 mg capsules; the approved 100 mg capsules are imprinted with "C" on the cap

and "100" on the body in black ink). The differences are sufficient to distinguish the two strengths. The use of the proposed capsule size 3 was justified with reference to experience gained in clinical studies where these were used in the target age group.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, with the exception of the colourants which comply with food standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. The excipients are considered safe for use in the paediatric population.

The quality target product profile (QTPP) was previously defined for the Cresemba 100 mg hard capsules and is equally applicable to the new 40 mg strength presentation. Information on the identified critical quality attributes was provided.

As regards the manufacturing process, the same process and process control are used as already approved for Cresemba 100 mg hard capsules.

Due to the instability of isavuconazonium sulfate at pH > 3, it is not possible to facilitate administration of the product by opening the capsule and/or mix it with food. This is in line with the information in the SmPC for the approved 100 mg strength and is also reflected in the proposed SmPC for the 40 mg strength.

Bioequivalence of the new 40 mg hard capsules with the approved 100 mg hard capsules was investigated in a bioequivalence study and the two strengths were found to be bioequivalent. The *in vitro* dissolution profile of the two strengths was also investigated and comparative dissolution data complementary to the bioequivalence study was provided. However, due to the variability of the capsule disintegration, the data are not amenable to comparative statistical analysis. At the same time, it has been demonstrated that the capsule content dissolves easily at all three investigated pH levels. Considering that the bioequivalence of the two capsule strengths was confirmed in a in vivo bioequivalence study, the presented information is sufficient. The multidisciplinary major objection initially raised by the CHMP on the dissolution profile comparisons in support of the proposed biowaiver of strength was resolved following the submission of the bioequivalence study results and additional *in vitro* dissolution data.

The primary packaging is aluminium blisters with each capsule pocket connected to a pocket with desiccant. The container closure system is similar to the container closure system used for the approved 100 mg hard capsules and only the cavity size was adapted. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site, with further sites involved for primary and secondary packaging as well as batch release. The manufacturing sites are the same as already approved for the 100 mg hard capsules.

The manufacturing process consists of 7 main steps: pre-blending I, pre-blending II, blending of pre-blend I and II, roller compacting, final blending, encapsulation and packaging. The process is considered to be a standard manufacturing process.

The manufacturing process uses conventional and well-established pharmaceutical production equipment and conventional unit operations.

No critical steps were identified in the finished product manufacturing process, however, in process controls are implemented to ensure uniformity of the dosage form and tightness of the blister.

The manufacturing process has been validated on three full-scale batches using the proposed process settings. Blend uniformity was tested, and the encapsulation process was validated by taking samples at beginning, middle and end of the process. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

The proposed bulk holding time of 3 months is acceptable and is supported by data.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (HPLC, HPLC-PDA), related substances (HPLC), BAL481 (HPLC), 2-Butenal (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), disintegration (Ph. Eur.), water (Ph. Eur.), microbial limits (Ph. Eur.) and assay (HPLC).

The release and shelf-life specifications of the finished product are acceptable. The specification parameters and acceptance criteria for Cresemba 40 mg hard capsules are identical to the approved Cresemba 100 mg hard capsules with the exception of the description of the product and the absence of a disintegration test for the 100 mg hard capsules (see next paragraph).

The finished product specification for the 40 mg hard capsule includes a test and limit for dissolution as well as for disintegration, considering that the variable disintegration of the hypromellose capsule shell is the rate limiting step for the dissolution profile which leads to highly variable dissolution data. The initially raised major objection related to the specification limit for dissolution was resolved as the applicant included the disintegration test in the specification of the finished product. Based on the discussions on dissolution and disintegration in the context of this application, and the fact that the 40 mg and 100 mg hard capsules are dose proportional, the applicant committed that the specification in the dossier of the approved 100 mg hard capsules will also be updated to include a disintegration test (*via* submission of a variation).

Stability trends (see also below for further details) confirm that the shelf-life specification limits do not need to be widened, while tightening was not considered necessary as the existing limits are toxicologically qualified and in line with batch analysis results.

The analytical methods used are the same as for the approved 100 mg strength capsules, however the sample preparation is adapted for the proposed 40 mg capsules to achieve the same concentration in the analytical samples. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for of two commercial-scale and six pilot-scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from two commercial-scale batches of finished product stored for up to 36 months, one commercial-scale batch stored for up to 24 months and one commercial-scale batch stored for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product were identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, identification, related substances, BAL481, 2-butenal, dissolution, disintegration, water, microbial limits and assay. The analytical procedures used are stability indicating. While no significant change was detected, a change in colour of the capsule content was noted under accelerated conditions (from white powder to yellowish or yellow powder). The change in colour corresponded with an increase of related substances levels. The observed physical and chemical changes were small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC. Results remained within specification.

Result of stress tests were also provided to evaluate the impact of environmental stress on the product quality. Samples were exposed to elevated temperature (50 °C) and higher humidity (25 °C / 75% RH) and results showed that the finished product is stable when exposed to elevated temperature but is sensitive to higher humidity (see also storage conditions below).

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The study demonstrated the product was not sensitive to light.

Based on available stability data, the proposed shelf life of 30 months with the storage conditions 'Do not store above 30°C' and 'Store in the original packaging in order to protect from moisture' as stated in the SmPC (section 6.3 and 6.4) is acceptable.

Stability studies supporting the extension of indication of the approved powder for concentrate for solution for infusion:

During the procedure, and in view of the inclusion of paediatric patients in the target population, the SmPC instructions for reconstitution and dilution for paediatric use were also updated and reviewed. In this context, these instructions were not considered sufficiently clear, and a major objection was raised by CHMP requesting the applicant to perform additional in-use stability studies to demonstrate the stability of the powder for concentrate for solution for infusion in concentrations relevant for use in paediatric patients.

The applicant performed additional in-use stability studies and demonstrated stability of the product at a concentration of 0.4 mg/mL and 0.8 mg/mL which is a range that is considered relevant in clinical (paediatric) practice. The related information in the SmPC has been updated as requested, including reference to the possible use of an infusion pump and confirmation of the duration of infusion as studied in the clinical trials.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During the procedure, one multidisciplinary major objection relating to dissolution comparative data in support of the initially strength biowaiver request and bioequivalence was raised as discussed above. Responses were satisfactory to resolve the major objection. In addition, two major objections were raised on quality aspects relating to the specification limit for dissolution testing and the need to update the SmPC instructions for the reconstitution and dilution for the approved powder for concentrate for solution for

infusion presentation supporting the extension of indication to paediatric patients. Both major objections were addressed in a satisfactory manner as further discussed above and the major objections are resolved.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, a minor quality issue was identified applicable to the authorised 100 mg strength having no impact on the benefit-risk ratio of the product, which pertain to aligning the specification of the authorised 100 mg strength with that of the new 40 mg strength. This point is put forward and agreed as recommendations for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation for future quality development

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The MAH is recommended to update (via the appropriate regulatory procedure) the specification of the approved 100 mg hard capsule formulation, to include a disintegration test in line with the agreed specification for the new 40 mg hard capsule formulation.

2.5. Non-clinical aspects

2.5.1. Pharmacology

Not applicable

2.5.2. Pharmacokinetics

Not applicable

2.5.3. Toxicology

2.5.3.1. Single dose toxicity

Not applicable

2.5.3.2. Repeat dose toxicity

Not applicable

2.5.3.3. Genotoxicity

Not applicable

2.5.3.4. Carcinogenicity

Not applicable

2.5.3.5. Reproductive and developmental toxicity

A three-month repeat-dose JAS initiated in PND4 rats was performed to investigate possible juvenile toxicity of isavuconazonium (BAL8557, prodrug) and its active metabolite Isavuconazole (BAL4815). The study design was considered sufficient to study a human equivalent of dosing from neonate through adolescence and into adulthood. Main adverse findings in the rat JAS were similar to adverse findings observed earlier in adult rat 3- and 6-month repeat-dose toxicity studies and consisted of increased liver, adrenal and thyroid gland weights, thyroid follicular cell hypertrophy in both sexes, and evidence of anaemia at the highest dose tested in females only. The NOAEL of 10 mg/kg/day was lower than the NOAEL in the adult rat 3 month study (30 mg/kg/day), but similar to the NOAEL in the adult rat 26 week study (10 mg/kg/day).

2.5.3.6. Toxicokinetic data

Not applicable

2.5.3.7. Local tolerance

Not applicable

2.5.4. Ecotoxicity/environmental risk assessment

In the updated ERA, Fpen refinement was based on prevalence values as presented in the Arlington Medical Resources (AMR 2011) database. Further, the ERA was adapted based on more realistic duration of treatment than the worst case scenarios used in the original ERA. Isavuconazole is considered not to be PBT, nor vPvB.

Based on the prescribed use of Cresemba, a potential risk to the surface water compartment is identified.

2.5.5. Discussion on non-clinical aspects

The toxicological profile and safety margins in the juvenile toxicity study performed with isavuconazole is similar to what is observed in adult animal studies.

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of isavuconazole to the STP, groundwater, and sediment compartment. This is already reflected in the current SmPC section 5.3, which states that Cresemba may pose a risk for the aquatic environment.

2.5.6. Conclusion on the non-clinical aspects

The CHMP considers the non-clinical aspects of the application to be supportive of approval.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Isavuconazonium sulfate (a prodrug of the active moiety isavuconazole) has been registered in the EU since 2015 for the treatment of invasive aspergillosis and mucormycosis in adults and is available as hard capsules (186 mg isavuconazonium sulfate - equivalent to 100 mg isavuconazole) and as powder for concentrate for solution for infusion (372 mg isavuconazonium sulfate - equivalent to 200 mg isavuconazole). The posology in adults is a loading dose of 200 mg of isavuconazole every 8 hours for the first 48 hours followed by a maintenance dose of 200 mg of isavuconazole once daily, starting 12 to 24 hours after the last loading dose.

In this application, the MAH requests a line extension for an additional strength of the currently approved oral formulation and an extension of indication for paediatric patients aged 1-18 years. Two clinical studies (studies 9766-CL-0046 and 9766-CL-0107) were conducted in paediatric patients for the paediatric line extension and a biowaiver of strength is applied for the new 40 mg strength. The paediatric studies were already assessed in procedures EMA/H/C/002734/P46/006 and EMA/H/C/002734/P46/007, respectively. The proposed posology in paediatric patients is:

- 1 to <18 years weighing <37 kg 5.4 mg/kg IV.
- 6 to 18 years weighing 16–17 kg 80 mg orally.
- 6 to 18 years weighing 18–24 kg 120 mg orally.
- 6 to 18 years weighing 25–31 kg 160 mg orally.
- 6 to 18 years weighing ≥32 kg 180 mg orally.

Biowaiver of strength for the 40 mg strength

A human bioequivalence study in Japan in healthy male subjects (study AK1820-102) was conducted. In this study, bioequivalence between 40 mg and 100 mg capsules was investigated at a dose of 200 mg isavuconazole. The 40 mg and 100 mg strengths were bioequivalent.

Analytical methods

A validated analytical method has been used for the analysis of isavuconazole in human plasma. This analytical method was also submitted at the time of the initial marketing authorisation application and therefore suitable to measure isavuconazole in plasma from paediatric studies 9766-CL-0046 and 9766-CL-0107.

Population pharmacokinetic (PopPK) modelling

A PopPK model was developed for study 9766-CL-0046. The PK data from study 9766-CL-0107 were added to the existing data to update the PopPK model developed in study 9766-CL-0046 (report A9766-PK-0010). A total of 73 paediatric patients were included in the model of which 15 patients were 1-5 years (157 samples), 29 patients were 6-11 years (300 samples) and 29 patients were 12-17 years (258 samples). The population pharmacokinetic analyses is adequately conducted and described. However, the number of patients aged <3 years of age is limited (n=5). Seven patients aged 6 to <18 years received IV to oral switch. Ten patients received IV only, five received oral only, and three had several switches from IV to oral and back. The route of administration and the actual dose administered to the patients treated within the clinical studies were added to the PopPK model. 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, but the PopPK model is suitable for purpose.

Pharmacokinetics in adults

After IV and oral administration, isavuconazonium is rapidly converted into isavuconazole. Very low isavuconazonium plasma levels are observed, which rapidly decline. Following oral administration, maximum isavuconazole plasma concentrations are observed after about 2-3 h. The absolute oral bioavailability of the oral formulation is 98%. The inter-individual variability in C_{max} and AUC was generally about 20–30%, for IV as well as for oral administration. After a single IV administration, a more than dose proportional increase in C_{max} and AUC_{inf} is observed over the 40–160 mg dose range. After multiple doses, a more or less proportional increase is observed over a 50–600 mg once daily. After a single oral administration, C_{max} and AUC_{inf} increased more than dose proportional over a 100–400 mg dose range. After multiple doses, proportional increases were observed over the 50-600 mg once daily dose range. Isavuconazole did not show time-dependent pharmacokinetics and no unexpected accumulation was observed. Steady state is achieved at day 3 with the posology of applying a loading dose three times a day at day 1 and 2, followed by a maintenance dose once daily.

Isavuconazole is highly bound to plasma proteins (about 99.3%) and is not actively taken up into red blood cells. Isavuconazole has a high volume of distribution of 450 L in adults.

Isavuconazonium is converted to isavuconazole by butyrylcholinesterase (hBChe). Isavuconazole is further metabolised by oxidation, hydrolysis of cyano group and oxidation of the carbamoyl form. In addition, after cleavage of the thiazole ring, additional metabolites were formed by oxidation and subsequent glucuronide and acetylcysteine conjugation, or hydrolysis of cyano group, and oxidation of the carbamoyl form and glucuronide or acetylcysteine conjugation. Except for the active moiety isavuconazole, no individual metabolite was observed with an AUC >10% of the parent. Isavuconazole is mainly metabolised by CYP3A4 and to a more limited extent by CYP3A5.

After oral administration, the mean recovery of total radioactivity was 45.5% in urine and 46.1% in faeces (total recovery 91.6% over a 600 h sampling period). The radioactivity excreted is mainly as metabolite.

Pharmacokinetics in paediatric patients

The PK was investigated in paediatric patients in clinical studies 9766-CL-0046 and 9766-CL-0107.

Study 9766-CL-0046 is a Phase 1, open-label, multi-centre, non-comparative pharmacokinetics and safety study of intravenous and oral isavuconazonium sulfate in paediatric patients. In Part 1, the currently approved intravenous formulation (Cresemba for injection) was administered to Cohorts 1 (1 to <6 years; n= 11), Cohort 2 (6 to <12 years; n = 8), and Cohort 3 (12 to <18 years; n= 10). Subjects received an intravenous loading regimen which consisted of a dose every 8 hours on days 1 and 2 (a total of 6 doses), followed by once daily maintenance dosing for up to 26 additional days (for a maximum of 28 days of dosing). In Part 2, an oral capsule formulation (40 mg isavuconazole) administered orally to Cohorts 4 (6 to <12 years; n = 10) and Cohort 5 (12 to <18 years; n = 10). Subjects received a loading regimen of isavuconazonium sulfate by oral administration, comprising one dose every 8 hours (± 2 hours) on day 1 and day 2 (a total of 6 doses), followed by once-daily oral maintenance dosing for up to 26 additional days (a maximum of 28 days of dosing). The administered dose of isavuconazole is shown in the table below.

	Loading + Maintenance dose
Part 1 ≤40 kg	5.4 mg/kg
Part 1 >40 kg	200 mg
Part 2 16-17 kg	80 mg (4.7-5.0 mg/kg)
Part 2 18-24 kg	120 mg (5.0-6.7 mg/kg)
Part 2 25-31 kg	160 mg (5.2-6.4 mg/kg)
Part 2 ≥32 kg	200 mg

Study 9766-CL-0107 is a Phase 2, open-label, non-comparative, multi-centre 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. The route of administration could change at the investigator's discretion as needed. Subjects received an IV loading dose every 8 hours for 6 doses followed by an IV or oral once daily maintenance dose starting 12 to 24 hours after the last loading dose. The oral formulation is only given to participants aged 6 to <18 years and with a body weight of at least 12 kg. The administered dose of isavuconazole is shown in the table below.

	Loading + Maintenance dose
IV <37 kg	5.4 mg/kg
IV ≥37 kg	200 mg
PO 12-17 kg	80 mg (4.7-6.7 mg/kg)
PO 18-24 kg	120 mg (5.0-6.7 mg/kg)
PO 25-31 kg	160 mg (5.2-6.4 mg/kg)
PO ≥32 kg	200 mg

No subjects with a body weight of <9 kg were included in the clinical studies. The C_{trough} values at Day 7 for studies 9766-CL-0046 and are summarised in the table below.

Age	**C_{trough} at Day 7**	
	study 9766-CL-0046	**study 9766-CL-0107**
1-5 years	3320 ± 1710 (1140-5950)	2965 ± 1770 (1350-6280)
6-11 years	2970 ± 1680 (770-5230)	3732 ± 1885 (837-6320)
12-17 years	2730 ± 1120 (1710-4960)	3862 ± 1427 (1510-6280)

In study 9766-CL-0046, mean AUC_{tau}, C_{trough} and C_{max} were approximately 30% to 35% higher in children aged <12 years as compared to children aged 12-17 years. The exposure in paediatric patients 12-17 years appears to be comparable to adults in study 9766-CL-0046. In study 9766-CL0107, C_{trough} values were relatively lower in the 1-5 years age group compared to the 6-11 years and 12-17 years age groups on days 7 and 14. Thus, data of study 9766-CL-0107 indicate the opposite in exposure compared to study 9766-CL-0046. The PopPK model was used to estimate the exposure at steady state. In the Tables below the exposure following IV and oral administration with the proposed posologies are shown in paediatric patients and adults.

Exposure following IV administration

Age (dose)	**C_{max} (mg/L)**	**C_{min} (mg/L)**	**AUC (mg × h/L)**
1 to <3 years (8.1 mg/kg)	12.0 (5.5-28.6)	5.4 (0.8-23.9)	163 (42-506)
3 to <18 years weighing <37 kg (5.4 mg/kg)	9.5 (3.9-22.7)	4.7 (0.6-18.5)	138 (31-602)
6 to <18 years weighing ≥37 kg (200 mg)	6.5 (1.9-21.9)	3.8 (0.5-17.6)	113 (27-488)
adults (200 mg)	7.5* (2.9-11.1)	3.6 (0.17-11.0)	101.2 (10-343)

* Healthy adult study (9766-CL-0017), since no $C_{max,ss}$ was determined in study 9766-CL-0104.

Exposure following oral administration

Age (dose)	C_{max} (mg/L)	C_{min} (mg/L)	AUC (mg × h/L)
6 to <18 years weighing 16-17 kg (80 mg)	4.4 (1.5-18.5)	3.4 (0.5-17.6)	116 (31-539)
6 to <18 years weighing 18-24 kg (120 mg)	4.6 (1.3-15.8)	4.1 (0.8-15.2)	129 (33-474)
6 to <18 years weighing 25-31 kg (160 mg)	5.0 (1.4-14.4)	4.4 (0.4-13.9)	140 (36-442)
6 to <18 years weighing 32-36 kg (180 mg)	5.4 (1.3-24.6)	4.4 (0.5-26.6)	137 (27-677)
6 to <18 years weighing ≥37 kg (200 mg)	6.5 (1.9-21.9)	3.8 (0.5-17.6)	113 (27-488)
adults (200 mg)	7.5* (2.9-11.1)	3.6 (0.17-11.0)	101.2 (10-343)

* Healthy adult study (9766-CL-0017), since no $C_{max,ss}$ was determined in study 9766-CL-0104.

The posology leads to similar exposure in paediatric patients and adults.

Special populations

In adult patients with mild, moderate and severe renal impairment, C_{max} and AUC were not statistical significant affected. The AUC_{0-72h} was about 30% higher post-dialysis in ESRD subjects. No dose adjustment based on renal function is required for isavuconazole.

In adult patients with mild and moderate hepatic impairment, total plasma CL decreased by 27-30% and 42-51% in patients with mild and moderate hepatic impairment, respectively. No PK data is available in patients with severe hepatic impairment.

No clinical significant effect of gender, age or body weight was observed in adult patients.

DDIs as perpetrator

The risk of interactions with isavuconazole as perpetrator is expected to be similar in paediatric patients and adult patients if the exposure is comparable.

DDIs as victim

The risk of interactions with isavuconazole as victim is expected to be similar in paediatric patients and adult patients if the exposure is comparable.

2.6.3. Discussion on clinical pharmacology

The application concerns a grouped variation to extend the indication for paediatric patients aged 1-18 years and a line extension for an additional strength of the currently approved oral formulation. Two clinical studies (studies 9766-CL-0046 and 9766-CL-0107) were conducted in paediatric patients for the paediatric line extension and a bioequivalence study was conducted for the new 40 mg strength. The paediatric studies were already assessed in procedures EMA/H/C/002734/P46/006 and EMA/H/C/002734/P46/007, respectively.

2.6.4. Conclusions on clinical pharmacology

The two clinical studies (studies 9766-CL-0046 and 9766-CL-0107) for the paediatric line extension were already assessed in procedures EMA/H/C/002734/P46/006 and EMA/H/C/002734/P46/007.

2.6.5. Clinical efficacy

Tabular overview of clinical studies (9766-CL-0046 and 9766-CL-0107):

Table 1 Synopses of paediatric studies

Type of study	Study identifier / link	Study objectives	Study design	Test products / Dosage regimen / Route of administration	Number of participants	Participant population	Duration of treatment	Study status / Type of report
PK	9766-CL-0046: Part 1 Part 2	PK, safety, and tolerability of multiple doses of isavuconazole in paediatric patients	Phase 1, open-label, non-comparative pharmacokinetics and safety study in paediatric patients	**Part 1: iv administration** Isavuconazole: Patients with bw 40 ≤ kg: 5.4 mg/kg (q8h) on Days 1–2 and 5.4 mg/kg (qd) on Day 3 to EOT Patients with bw > 40 kg: 200 mg (q8h) on Days 1–2 and 200 mg (qd) on Day 3 to EOT. **Part 2: oral administration** Isavuconazole: Patients with bw 16–17 kg: 80 mg (q8h) on Days 1–2 and 80 mg (qd) on Day 3 to EOT. Patients with bw 18–24 kg: 120 mg (q8h) on Days 1–2 and 120 mg (qd) on Day 3 to EOT. Patients with bw 25–31 kg: 160 mg (q8h) on Days 1–2 and 160 mg (qd) on Day 3 to EOT. Patients with bw ≥ 32 kg: 200 mg (q8h) on Days 1–2 and 200 mg (qd) on Day 3 to EOT.	46 **Part 1**: 27 **Part 2**: 19	Paediatric patients aged from 1 year to less than 18 years with haematologic malignancy	Up to 28 days	Completed Full

S/PK/E 9766-CL-0107	Safety, tolerability, efficacy, and PK of isavuconazole in paediatric patients with invasive aspergillosis or mucormycosis	Phase 2, open-label, non-comparative, multicenter study	Isavuconazole (iv): Patients with bw ≤ 37 kg: 5.4 mg/kg (q8h) on Days 1–2 and 5.4 mg/kg (qd) on Day 3 to EOT Patients with bw > 37 kg: 200 mg (q8h) on Days 1–2 and 200 mg (qd) on Day 3 to EOT. Isavuconazole (oral): Patients with bw 12 to < 18 kg: 80 mg (q8h) on Days 1–2 and 80 mg (qd) on Day 3 to EOT. Patients with bw 18 to < 25 kg: 120 mg (q8h) on Days 1–2 and 120 mg (qd) on Day 3 to EOT. Patients with bw 25 to < 32 kg: 160 mg (q8h) on Days 1–2 and 160 mg (qd) on Day 3 to EOT. Patients with bw ≥ 32 kg: 200 mg (q8h) on Days 1–2 and 200 mg (qd) on Day 3 to EOT.	31	Paediatric patients aged 1 to < 18 years with possible, probable or proven invasive aspergillosis or mucormycosis	Up to 84 days (invasive aspergillosis); Up to 180 days (mucormycosis)	Completed Full

bw = bodyweight; E = efficacy and tolerability; EOT = end of treatment; iv = intravenous; PK = pharmacokinetics; q8h = every 8 hours; qd = once daily.

2.6.5.1. Dose response studies

No dedicated dose response studies were conducted in the paediatric population.

Proof of efficacy in both indications will be mainly based on adult clinical 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 paediatric population.

2.6.5.2. Main studies

Phase 1 **study 9766-CL-0046** evaluated the pharmacokinetics, safety and tolerability of multiple doses of intravenous and oral isavuconazonium sulfate administered daily in paediatric subjects in a *prophylactic* setting. This study does not provide support for efficacy in the therapeutic setting but the safety data from this study are considered relevant.

Phase 2 **study 9766-CL-0107** is a single armed study which evaluated 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. This study does provide some supportive, descriptive, data on clinical efficacy however the main evidence for the efficacy in the paediatric indication is still to be extrapolated from the adult patient population.

The MAH submitted an integrated summary of safety, including data from both trials, which is considered justifiable since the enrolled patient populations regarding age and underlying disease/condition were rather comparable and the treatment schemes similar.

Title

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.

Methods

Study design

This was an open-label, non-comparative, multicenter study.

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

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

Study Participants

Paediatric patients aged 1 to <18 years could be enrolled if they met the following key criteria:

Key inclusion criteria were:

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

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 mould 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 (corresponding to 5.4 mg/kg isavuconazole) 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) (corresponding to 200 mg isavuconazole) 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

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 1):

Table 1 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

Maximum daily loading and maintenance dose were 372 mg per individual dose. All capsules per dose must be taken at the same time.

Switch from IV to oral therapy (or back)

Following protocol ISN/Protocol 9766-CL-0107 Version 4.0, the investigator may determine the appropriate route of administration for each subject and can switch between the 2 routes of administration (intravenous D oral) throughout the treatment period if considered necessary. On request the MAH provided an tabulated overview for all individual patients showing all switches (intravenous D oral) made. The majority of the patients stayed on IV treatment (15/31, 48.4%). Five patients (16.1%) received only oral treatment from the start. Eight patients (25.8%) were successfully switched from IV to oral treatment. Only three patient (9.7%) were switched back from oral to IV treatment, but for comprehensible clinical reasons. Two patients were switched several times during their long-term therapy (181 days).

Prohibited therapies:

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

Objective

The objective was of the study was 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.

Outcomes/endpoints

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

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 2.

Table 2 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)

Sample size

No formal sample size calculation was performed. Approximately 30 participants were planned, at least 5 evaluable participants per age cohort: 1 to <12 years of age and 12 to <18 years of age.

Randomisation and blinding (masking)

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

Statistical methods

Analysis sets

- The full analysis set (FAS) consists of all subjects who are enrolled and receive at least one dose of study drug. This is 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 summarised for FAS and mFAS analysis sets.

Results

Participant flow

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 and were included in the safety analysis and in the full analysis set (SAF=FAS), 13/31 (41.9%) participants were included in the in the modified FAS (mFAS) and 28/31 (90.3%) in the pharmacokinetic analysis set (PKAS).

Conduct of the study

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

Date of First Enrolment: 22 Aug 2019

Date of Last Evaluation: 14 Dec 2022

Nineteen (61.3%) of participants completed treatment by either achieving the maximum treatment duration (12/31; 38.7%) or achieving a successful outcome before maximum treatment duration was reached (7/31; 22.6%). The proportion of participants who prematurely discontinued treatment was 12/31 (38.7%). The 3 most common reasons for discontinuation of treatment 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 (28/31; 90.3%) participants completed both the 30-day and 60-day follow-up visits (SAF). Three (3/31; 9.7%) participants prematurely discontinued the study due to death (all unrelated to study treatment) and thus did not complete the EOT+30-day or EOT+60-day follow-up visits.

Baseline data

In the FAS population, the mean age of participants was 9.7 years, and the majority 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

Malignancy was reported in the majority of participants (19/31; 61.3%). Most common were acute lymphocytic leukaemia (9/31) and acute myelogenous leukaemia/relapse acute myelogenous leukaemia (5/31). Nearly two-thirds of participants (64.5%) had recently resolved or ongoing neutropenia, approximately half (45.2%) were on other recognised T-cell immunosuppressants and approximately one-third (32.3%) were on prolonged use of corticosteroids. Medical history included anaemia (58.1%), pyrexia (58.1%), hypoalbuminemia (41.9%), hypertension (32.3%) and sepsis (29.0%).

Prior used antifungal agents: In the FAS population amphotericin B was used in 11/31 (35.5%) and voriconazole in 5/31 (16.1%) of subjects, which are known to be active against IA and/or IM.

Concomitant used antifungal agents: The medication used in FAS population included posaconazole [2/31 (6.5%)], voriconazole [11/31 (35.5%)] and amphotericin B [11/35 (35.5%)].

Numbers analysed

Nineteen (61.3%) of participants completed treatment by either achieving the maximum treatment duration (12/31; 38.7%) or achieving a successful outcome before maximum treatment duration was reached (7/31; 22.6%). The proportion of participants who prematurely discontinued treatment was 12/31 (38.7%). The 3 most common reasons for discontinuation of treatment 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 (28/31; 90.3%) participants completed both the 30-day and 60-day follow-up visits (SAF). Three (3/31; 9.7%) participants prematurely discontinued the study due to death (all unrelated to study treatment) and thus did not complete the EOT+30-day or EOT+60-day follow-up visits.

Outcomes and estimation

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 4).

Table 4 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, 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 *5*).

Table 5 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 13 participants with proven or probable Invasive Aspergillosis (n=12) or Invasive Mucormycosis (n=1), eight participants were assessed by the Adjudication Committee (AC) as having a successful *overall response* at the EOT (8/13: 61.5%).

The only patient diagnosed with proven or probable invasive mucormycosis (caused by *Rhizopus arrhizus*) failed on isavuconazole therapy and showed progression of the disease. Mucormycosis is a difficult to diagnose rare disease and the diagnosis is often made with delay, which also seems to have been the case here. High-dose liposomal amphotericin B is still considered first-line treatment for mucormycosis. In this particular case liposomal amphotericin B was initiated relatively late and therefore the treatment regimen may not have been optimal.

Relation between clinical efficacy parameters

On request, the MAH provided a tabular overview of how the primary clinical endpoint 'overall response' relates to the other secondary co-endpoints (clinical, mycological and radiological responses).

Radiological response

The outcome of primary efficacy parameter 'Overall response at EOT' appears to have been largely determined by the outcome of 'radiological response at EOT'. This could be expected because even in the case of a 'complete clinical response', radiological abnormalities may persist for a longer period of time and may not resolve completely within the time frame of the study of even become permanent.

Clinical response

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.

Mycological response

In a considerable number of the paediatric patients [16/31 (51.6%)] no mycological evidence of infection was found. However, this finding is consistent with mycological data from Study 9766-CL-0104 (adults with invasive Aspergillosis), where no pathogen was identified in approximately half of the overall population [72/143 (50.3%)].

2.6.6. Discussion on clinical efficacy

The MAH submitted two paediatric clinical trials, 9766-CL-0046 and 9766-CL-0107. Both studies have been submitted in accordance with Article 46 in January 2020 and May 2023, respectively (EMA/H/C/002734/P46/006, EMA/H/C/002734/P46/007).

Phase 1 study 9766-CL-0046 does not provide any support for efficacy in the therapeutic setting however contributes to the paediatric safety database.

Phase 2 study 9766-CL-0107, a single armed study, evaluated the pharmacokinetics, efficacy and safety/tolerability in paediatric participants aged 1 to <18 years in the treatment of Invasive Aspergillosis or Invasive mucormycosis. No formal prospectively defined efficacy assessments were planned in study 9766-CL-0107. Efficacy data were collected during the study only for descriptive purposes. The main evidence for the efficacy in the paediatric indication is therefore to be extrapolated from the adult patient population.

Methods: Study objectives, outcomes and endpoints, inclusion and exclusion criteria (except for age) and analyses sets (FAS, mFAS, SAF) were generally consistent with those defined for adults.

Treatments:
IV: Subjects weighing > 37 kg received loading doses of 200 mg (three times daily on Day 1 and 2) followed by maintenance doses of 200 mg (once daily on Day 3 and further on) ("adult posology"). Subjects weighing ≤ 37 kg were administered a loading regimen of 5.4 mg/kg isavuconazole (three times daily on Day 1 and 2, followed by maintenance doses of 5.4 mg/kg isavuconazole (once daily).

Oral: Administration of the newly developed capsules containing 40 mg of isavuconazole was only an option 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 5.4 mg/kg. The oral and intravenous formulations are equivalent on a mg:mg basis.

Switch from IV to oral therapy (or back)
The investigator determined the appropriate route of administration for each subject and could switch between intravenous ⇆ oral throughout the treatment period if needed. Eight patients (25.8%) were successfully switched from IV to oral treatment. Only three patient (9.7%) were switched back from oral to IV treatment, but for comprehensible clinical reasons. Two patients were switched several times during their long-term therapy (181 days).

Results:
Female patients were overrepresented (M:F= 19.4% vs 80.6%) while in most IFD studies males are slightly in the majority. Primary underlying disease/condition was malignancy, with acute lymphocytic leukaemia most commonly diagnosed.

Prior use of mould active antifungal therapy, was allowed for a maximum of 4 days during the 7 days preceding the first dose of study drug (as for adults in study 9766-CL-104). In the FAS population amphotericin B was used in 11/31 (35.5%) and voriconazole in 5/31 (16.1%) of subjects.

According to study protocol the *concomitant* use of other systemic mould active antifungal agents (posaconazole, amphotericin B and voriconazole) was to be avoided. Nevertheless, these agents were used in a significant number of patients with *proven or probable* IA or IM [8 of 13, (61.5%)].
Also in adults (study 9766-CL-104) concomitant mould active antifungal agents were extensively used [92/258 (35.7%)]. It reflects all the problems that exist in diagnosing IFD. Treatment policy often requires adjustment. At the same time makes it more difficult to determine the exact contribution of isavuconazole to the clinical success of treatment.

Mycology: The category classification (ratio between proven, probable, possible or no IFD) and the pathogens causing IFD as identified by the AC in the paediatric population of study 9766-CL-107 corresponded well with those in study 9766-CL-104 (adult patients).

Efficacy

Primary Efficacy Endpoint in study 9766-CL-0107 was *All-cause Mortality Through Day 42 (FAS)*. Two of 31 total (6.5%) paediatric patients died during the first 42 days, which is a relatively low number when compared to that reported in adults [48/258 (18.6%)]. In the important subset of patients diagnosed with *proven or probable* Invasive Aspergillosis (IA) (n=12) or Invasive Mucormycosis (IM) (n=1) (*mFAS*), one participant died [1/13 (7.7%)]. The cause of death was related to IA infection. No participants died while on study drug treatment (all deaths occurred during the follow-up period).

The AC-assessed overall response rates (combined endpoint of clinical, mycological and radiological responses) for the FAS set at day 42 and day 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 outcome of primary efficacy parameter 'Overall response at EOT' appears to have been largely determined by the outcome of 'radiological response at EOT'. Radiological abnormalities may persist for a longer period of time and may not resolve completely within the time frame

of the study of even become permanent. In 51.6% [16/31] of the paediatric patients no mycological evidence of infection was found. This is however in line with the adult data [Study 9766-CL-0104: 50.3% (72/143)].

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 clinical 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 paediatric population.

2.6.7. Conclusions on the clinical efficacy

The clinical data on efficacy (and safety) of isavuconazole in the paediatric population is very limited. The proof of efficacy in both indications will be mainly based on adult clinical 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 paediatric population. This has been achieved.

2.6.8. Clinical safety

Paediatric safety data were obtained from two studies (Phase 1 study 9766-CL-0046 and Phase 2 study 9766-CL-0107). Integrated safety data from both studies is presented below.

2.6.8.1. Patient exposure

The dosage regimen for paediatric participants in studies 9766-CL-0046 and 9766-CL-0107 was 5.4 mg/kg isavuconazole) every 8 hours on Days 1 and 2 (total of six doses, 'loading dose'), followed by 5.4 mg/kg once daily (maintenance dose). The maximum dose per administration was 200 mg isavuconazole.

The safety of isavuconazole in paediatric patients includes data from 77 paediatric patients who received at least one dose of isavuconazole. Mean exposure overall was 31.68 days (range 1 to 181) in the All Paediatric population. In the All Paediatric population, a total of 46 of 77 participants (59.7%) received isavuconazole for at least 14 days, and 34 of 77 participants (44.2%) received isavuconazole for at least 21 days. The **demographics and baseline characteristics** are presented in Table 6 below.

Table 6 Demographic and baseline characteristics (Safety analysis set)

Parameter Category	9766-CL-0046 (N = 46)	9766-CL-0107 (N = 31)	All Pediatric (N = 77)	All Adult (N = 403)
Sex, n (%)				
Male	29 (63.0)	6 (19.4)	35 (45.5)	245 (60.8)
Female	17 (37.0)	25 (80.6)	42 (54.5)	158 (39.2)
Race, n (%)				
White	33 (71.7)	19 (61.3)	52 (67.5)	319 (79.2)
Black or African American	5 (10.9)	1 (3.2)	6 (7.8)	11 (2.7)
Asian	3 (6.5)	5 (16.1)	8 (10.4)	68 (16.9)
Other[†]	5 (10.9)	4 (12.9)	9 (11.7)	5 (1.2)
Missing/not calculated	0	2 (6.5)	2 (2.6)	0
Ethnicity, n (%)				
Hispanic or Latino	18 (39.1)	10 (32.3)	28 (36.4)	44 (10.9)
Not Hispanic or Latino	27 (58.7)	19 (61.3)	46 (59.7)	359 (89.1)
Missing/not calculated	1 (2.2)	2 (6.5)	3 (3.9)	0

Age (years)[‡]				
Mean (SD)	10.3 (4.6)	9.7 (5.0)	10.1 (4.7)	50.7 (16.4)
Median	10.5	10.0	10.0	53.0
Range	1 – 17	1 – 17	1 – 17	17 – 92
Age group (years), n (%)				
1 to < 6 years	9 (19.6)	6 (19.6)	15 (19.5)	0
6 to < 12 years	17 (37.0)	13 (41.9)	30 (39.0)	0
12 to ≤ 18 years	20 (43.5)	12 (38.7)	32 (41.6)	1 (0.2)
> 18 years	0	0	0	402 (99.8)
Body mass index (kg/m^2)				
Mean (SD)	19.79 (5.16)	19.17 (4.33)	19.55 (4.83)	24.25 (5.28)
Median	18.67	17.84	18.18	23.44
Range	13.6 – 31.6	13.5 – 28.5	13.5 – 31.6	13.9 – 50.0

[†] This 'Other' category includes all other races besides White, Black or African American, or Asian. It may differ from what was defined in each individual study.
[‡] One participant in the All Adult population from study 9766-CL-0104 was aged 17 years at the time of enrolment.
Source: **ISS Table 2.1**

2.6.8.2. Adverse events

Common adverse events

The most common TEAEs (occurring in ≥ 15% of participants) are summarised in Table 7. Approximately 75.3% of participants experienced at least one TEAE, with the most common being pyrexia (39.0%), diarrhoea (26.0%), and vomiting (20.8%).

Table 7 Frequently reported (≥ 15% in any group) adverse events in ISA-treated participants

System Organ Class Preferred Term	9766-CL-0046 (N = 46) n (%)	9766-CL-0107 (N = 31) n (%)	All Pediatric (N = 77) n (%)	All Adult (N = 403) n (%)
Overall	**34 (73.9)**	**24 (77.4)**	**58 (75.3)**	**273 (67.7)**
Blood and lymphatic system disorders				
Anaemia	8 (17.4)	3 (9.7)	11 (14.3)	16 (4.0)
Total	**8 (17.4)**	**3 (9.7)**	**11 (14.3)**	**16 (4.0)**
Cardiac disorders				
Tachycardia	7 (15.2)	3 (9.7)	10 (13.0)	20 (5.0)
Total	**7 (15.2)**	**3 (9.7)**	**10 (13.0)**	**20 (5.0)**
Gastrointestinal disorders				
Abdominal pain	11 (23.9)	3 (9.7)	14 (18.2)	38 (9.4)
Diarrhoea	12 (26.1)	8 (25.8)	20 (26.0)	88 (21.8)
Nausea	6 (13.0)	4 (12.9)	10 (13.0)	105 (26.1)
Stomatitis	1 (2.2)	5 (16.1)	6 (7.8)	14 (3.5)
Vomiting	9 (19.6)	7 (22.6)	16 (20.8)	100 (24.8)
Total	**21 (45.7)**	**16 (51.6)**	**37 (48.1)**	**205 (50.9)**
General disorders and administration site conditions				
Mucosal inflammation	13 (28.3)	0	13 (16.9)	28 (6.9)
Non-cardiac chest pain	0	5 (16.1)	5 (6.5)	4 (1.0)
Pyrexia	21 (45.7)	9 (29.0)	30 (39.0)	81 (20.1)
Total	**24 (52.2)**	**13 (41.9)**	**37 (48.1)**	**102 (25.3)**
Musculoskeletal and connective tissue disorders				
Pain in extremity	8 (17.4)	2 (6.5)	10 (13.0)	18 (4.5)
Total	**8 (17.4)**	**2 (6.5)**	**10 (13.0)**	**18 (4.5)**
Nervous system disorders				
Headache	6 (13.0)	3 (9.7)	9 (11.7)	67 (16.6)
Total	**6 (13.0)**	**3 (9.7)**	**9 (11.7)**	**67 (16.6)**
Respiratory, thoracic and mediastinal disorders				
Epistaxis	7 (15.2)	3 (9.7)	10 (13.0)	28 (6.9)
Total	**7 (15.2)**	**3 (9.7)**	**10 (13.0)**	**28 (6.9)**

Sorting order: ascending order alphabetically by System Organ Class; in case of ties, ascending order by Preferred Term was applied.
Source: **ISS Table 3.2.10**

2.6.8.3. Serious adverse events, deaths and other significant events

Deaths

Three out of 71 participants in the All Paediatric population (3.9%) experienced a TEAE leading to death, while in the adult population 104/403 (25.8%) participants did.

All three deaths in the paediatric population in study 9766-CL-0107 occurred during the follow-up period. These patients had relevant medical history. There were no TEAEs leading to death that were considered by the investigators to be related to study drug.

Overall treatment-emergent serious adverse events

The overall pattern of serious TEAEs and proportion of participants with serious TEAEs was similar between the All Paediatric and All Adult populations (Table 8).

Table 8 Serious adverse events in ≥ 2% of ISA-treated paediatric participants and adults

System Organ Class Preferred Term	9766-CL-0046 (N = 46) n (%)	9766-CL-0107 (N = 31) n (%)	All Pediatric (N = 77) n (%)	All Adult (N = 403) n (%)
Overall	**20 (43.5)**	**18 (58.1)**	**38 (49.4)**	**223 (55.3)**
Septic shock	0	3 (9.7%)	3 (3.9%)	20 (5.0%)
Respiratory failure	0	1 (3.2%)	1 (1.3%)	19 (4.7%)
Febrile neutropenia	2 (4.3%)	2 (6.5%)	4 (5.2%)	16 (4.0%)
Acute kidney injury	1 (2.2%)	0	1 (1.3%)	14 (3.5%)
Pneumonia	1 (2.2%)	1 (3.2%)	2 (2.6%)	14 (3.5%)
Pyrexia	5 (10.9%)	0	5 (6.5%)	10 (2.5%)
Sepsis	0	1 (3.2%)	1 (1.3%)	10 (2.5%)
Acute respiratory failure	1 (2.2%)	0	1 (1.3%)	8 (2.0%)
Abdominal pain	2 (4.3%)	0	2 (2.6%)	6 (1.5%)
Neutropenia	2 (4.3%)	0	2 (2.6%)	4 (1.0%)
Cardio-respiratory arrest	0	1 (3.2%)	1 (1.3%)	4 (1.0%)
Diarrhoea	3 (6.5%)	0	3 (3.9%)	4 (1.0%)
Vomiting	2 (4.3%)	0	2 (2.6%)	4 (1.0%)
Cytomegalovirus infection	2 (4.3%)	0	2 (2.6%)	3 (0.7%)
Hypoxia	1 (2.2%)	0	1 (1.3%)	3 (0.7%)
Nausea	1 (2.2%)	0	1 (1.3%)	3 (0.7%)
Pneumonia bacterial	1 (2.2%)	0	1 (1.3%)	3 (0.7%)
Hypotension	1 (2.2%)	0	1 (1.3%)	3 (0.7%)
Bacteraemia	1 (2.2%)	1 (3.2%)	2 (2.6%)	3 (0.7%)
Graft versus host disease	1 (2.2%)	1 (3.2%)	2 (2.6%)	2 (0.5%)
Pulmonary haemorrhage	1 (2.2%)	0	1 (1.3%)	2 (0.5%)
Escherichia sepsis	0	1 (3.2%)	1 (1.3%)	2 (0.5%)
Pleural effusion	0	1 (3.2%)	1 (1.3%)	2 (0.5%)
Bacterial sepsis	0	1 (3.2%)	1 (1.3%)	1 (0.2%)
Brain abscess	0	1 (3.2%)	1 (1.3%)	1 (0.2%)
Appendicitis	1 (2.2%)	0	1 (1.3%)	1 (0.2%)

System Organ Class Preferred Term	9766-CL-0046 (N = 46) n (%)	9766-CL-0107 (N = 31) n (%)	All Pediatric (N = 77) n (%)	All Adult (N = 403) n (%)
Pneumonia pseudomonal	0	1 (3.2%)	1 (1.3%)	1 (0.2%)
Staphylococcal bacteraemia	1 (2.2%)	0	1 (1.3%)	1 (0.2%)
Hypovolaemic shock	0	0	0	1 (0.2%)
Haematuria	1 (2.2%)	0	1 (1.3%)	1 (0.2%)
Mucosal inflammation	2 (4.3%)	0	2 (2.6%)	0
Pericardial effusion	0	1 (3.2%)	1 (1.3%)	0
Tachycardia	1 (2.2%)	0	1 (1.3%)	0
Ear pain	0	1 (3.2%)	1 (1.3%)	0
Diplopia	1 (2.2%)	0	1 (1.3%)	0
Abdominal distension	0	1 (3.2%)	1 (1.3%)	0
Anal incontinence	1 (2.2%)	0	1 (1.3%)	0
Stomatitis	0	2 (6.5%)	2 (2.6%)	0
Injection site reaction	0	1 (3.2%)	1 (1.3%)	0
Infusion site pain	0	1 (3.2%)	1 (1.3%)	0
Infusion site pruritus	0	1 (3.2%)	1 (1.3%)	0
Venoocclusive liver disease	0	1 (3.2%)	1 (1.3%)	0
Engraftment syndrome	1 (2.2%)	0	1 (1.3%)	0
Graft versus host disease in lung	1 (2.2%)	0	1 (1.3%)	0
Clostridium difficile infection	1 (2.2%)	0	1 (1.3%)	0
Rhinovirus infection	1 (2.2%)	0	1 (1.3%)	0
Streptococcal sepsis	0	1 (3.2%)	1 (1.3%)	0
Pneumococcal sepsis	0	1 (3.2%)	1 (1.3%)	0
Viral infection	1 (2.2%)	0	1 (1.3%)	0
Enterovirus infection	1 (2.2%)	0	1 (1.3%)	0
Activated partial thromboplastin time prolonged	1 (2.2%)	0	1 (1.3%)	0
Prothrombin time prolonged	1 (2.2%)	0	1 (1.3%)	0
Electrocardiogram QT prolonged	1 (2.2%)	0	1 (1.3%)	0
Hyperglycaemia	1 (2.2%)	0	1 (1.3%)	0
Synovitis	0	1 (3.2%)	1 (1.3%)	0
Arthralgia	0	1 (3.2%)	1 (1.3%)	0
Rhabdomyolysis	0	1 (3.2%)	1 (1.3%)	0
Cytarabine syndrome	1 (2.2%)	0	1 (1.3%)	0
Tumour pain	1 (2.2%)	0	1 (1.3%)	0
Dysuria	1 (2.2%)	0	1 (1.3%)	0
Cystitis haemorrhagic	1 (2.2%)	0	1 (1.3%)	0
Penile pain	1 (2.2%)	0	1 (1.3%)	0
Oedema genital	1 (2.2%)	0	1 (1.3%)	0
Epistaxis	1 (2.2%)	0	1 (1.3%)	0
Pulmonary mass	1 (2.2%)	0	1 (1.3%)	0
Pruritus	1 (2.2%)	0	1 (1.3%)	0
Social problem	0	1 (3.2%)	1 (1.3%)	0
Circulatory collapse	0	1 (3.2%)	1 (1.3%)	0
Embolism	1 (2.2%)	0	1 (1.3%)	0
Hypertension	0	1 (3.2%)	1 (1.3%)	0
Infusion related reaction	0	1 (3.2%)	1 (1.3%)	0

Sorting order: descending percentage in All Adult population for all adverse events.
Source: **ISS Table 3.2.3**

The frequency and types of serious TEAEs that occurred in the All Paediatric population were reflective of the participants' complex medical histories, which often included immunosuppression, infection, severe genetic conditions, and malignancy. Pyrexia (6.5%) and febrile neutropenia (5.2%) were the most common serious TEAEs in the All Paediatric population.

Drug-related treatment-emergent serious adverse events

Three paediatric participants in the All Paediatric population (3.9%) experienced at least one drug-related serious TEAE, two participants in study 9766-CL-0046 and one in study 9766-CL-0107. This compares to 41 drug-related serious TEAEs reported in the 403 adult participants in the All Adult population (10.2%). Drug-related serious TEAEs in the All Paediatric population included vomiting (1.3%), pyrexia (1.3%), nausea (1.3%), infusion-related reaction (1.3%), tachycardia (1.3%), infusion-site pain (1.3%), infusion-site pruritus (1.3%), and electrocardiogram QT prolonged (1.3%).

Anaphylactic reactions

Adverse events in the SMQ (broad and narrow) of anaphylactic reactions were reported at a similar frequency across the All Paediatric and All Adult populations (46.8% vs 50.1%, respectively). In the All Paediatric population, the most common adverse events were pruritus (11.7%), hypotension (9.1%), rash (9.1%), and cough (6.5%). In the All Adult population, cough (11.9%), dyspnoea (11.9%), hypotension (7.9%), and pruritus (7.4%) were the most common adverse events.

No Severe cutaneous adverse reactions were reported in the All Paediatric population.

Infusion related reactions

Infusion-related reactions were reported at a similar frequency across the All Paediatric and All Adult populations (58.5% vs 63.3%, resp.). For one participant did the infusion-related reaction (non-serious hypotension) result in permanent discontinuation of study drug.

2.6.8.4. Laboratory findings

There were no specific trends in haematology parameter changes in the All Paediatric population.

In study 9766-CL-0046, liver enzymes and total bilirubin (TBL) values for the majority of participants tended to be within the normal laboratory ranges during the study. ALT was elevated beyond 5 × ULN in one participant. No participants had a value of AST or ALT > 3 × ULN coupled with TBL > 2 × ULN in the same sample. Two participants met the criteria for potentially clinically significant increases in values in liver enzymes.

In study 9766-CL-0107, clinically relevant changes from baseline in chemistry parameters were observed in some participants. Four participants had elevations of ALT or AST > 5 × ULN, including one participant who also had AST or ALT > 10 × ULN, and one participant who had AST or ALT > 20 × ULN. These last two participants had multiple serious comorbidities assessed by the investigator as unrelated to study drug treatment. No participants were discontinued from study drug as a result of hepatic abnormalities.

The hepatic abnormalities in both studies were more likely to be related to the participants' complex medical conditions, underlying comorbidities, and multiple concomitant medications than to be related to isavuconazole.

2.6.8.5. Safety in special populations

Age: No clear age-related trends were seen, although TEAEs in the SOC Musculoskeletal and connective tissue disorders occurred with highest frequency in the 12 to < 18 years age group [8/32 (25.0%)], than in 12 to < 18 years age group [5/30 (16.7%)] and lowest frequency in the 1 to < 6 years age group [1/15 (6.7%)].

Sex: The percentage of participants with TEAEs of special interest was similar between males and females. Elevated liver transaminases and hepatitis occurred slightly more frequently in females [14/42 (33.3%)] than in males [8/35 (22.9%)], while Arrhythmia due to QT shortening was more common in males [6/35 (17.1%) than in females 5/42 (11.9%).

2.6.8.6. Discontinuation due to adverse events

Overall, the frequency of study drug-related TEAEs leading to withdrawal was comparable between the All Paediatric and All Adult populations (7/77, 9.1% vs 28/403, 6.9%, respectively). The types of study drug-related TEAEs leading to withdrawal were also similar in the All Paediatric and All Adult populations.

2.6.8.7. Post-marketing experience

Post-marketing safety data in paediatric patients has been reviewed on an ongoing basis during routine pharmacovigilance signal surveillance activities. No noteworthy differences in adverse drug reactions between paediatric patients and adults have been reported in the available post-marketing data. No new trends or other types of new safety information have been identified in the paediatric patient population.

2.6.9. Discussion on clinical safety

The MAH submitted two paediatric clinical trials, 9766-CL-0046 and 9766-CL-0107. Both studies have been submitted in accordance with Article 46 in January 2020 and May 2023. Patient populations and treatment schemes were very similar which makes a pooled analysis justifiable. For proof of efficacy and safety it is crucial that adult clinical data can be extrapolated to the paediatric population. For that purpose, the MAH compared the paediatric data with the safety data from adults.

The demographics and underlying diseases of the paediatric participants enrolled in the two studies are considered to be representative of the target indication (IA and IM).

Patient exposure

The dosage regimen for paediatric participants in studies 9766-CL-0046 and 9766-CL-0107 was 5.4 mg/kg isavuconazole every 8 hours on Days 1 and 2 (loading dose), followed by 5.4 mg/kg once daily (maintenance dose). The safety of isavuconazole in paediatric patients includes data from 77 paediatric patients who received at least one dose of isavuconazole. Mean exposure overall was 31.68 days (range 1 to 181) in the All Paediatric population.

Adverse events

Adverse events occurred very frequently. Study 9766-CL-0046: in IV treated participants 25/27 (92.6%) and in orally treated 18/19 (94.7%). Study 9766-CL-0107: 29/31 (93.5%) of participants experienced TEAEs. In the pooled analysis, frequently reported TEAEs (occurring in ≥ 15% of participants) were pyrexia (39.0%), diarrhoea (26.0%), and vomiting (20.8%). Nausea, vomiting, and diarrhoea occurred at similar frequencies as those in the phase 3, controlled study in adult patients with IFD (Study 9766-CL-0104). Pyrexia occurred at a higher frequency in the All Paediatric population than in the All Adult population (39.0% vs 20.1%), which is probably related to the use of isavuconazole by febrile neutropenic children undergoing induction chemotherapy and receiving isavuconazole for antifungal prophylaxis.

Non-cardiac chest pain, stomatitis and aphthous ulcer were not common in the adult study population. In Study 9766-CL-0046 mucosal inflammation occurred in 13/46 (28.3%) compared to 28/403 (6.9%) of the All Adult population. In study 9766-CL-0107 non-cardiac chest pain occurred in 5/31 (16.1%) of paediatric participants [adults: 4/403 (1.0%)] and stomatitis in 5/31 (16.1%) [adults: 14/403 (3.5%)]. On request the MAH provided more details on TEAEs chest pain, stomatitis and aphthous ulcer. From the submitted data it did not appear that these TEAEs were drug related or age related but rather due to induction chemotherapy that these children underwent.

Deaths

Three out of 71 participants in the All Paediatric population (3.9%) experienced a TEAE leading to death, while in the adult population 104/403 (25.8%) participants did. All three deaths in the paediatric population occurred during the follow-up period. Deaths are not unexpected to occur in this severely-ill study population (due to the underlying medical disease/condition). There were no TEAEs leading to death that were considered by the investigators to be related to study drug in either of the paediatric studies.

Rates of serious TEAEs were similar in the All Paediatric and All Adult populations (49.4% vs 55.3%). The most common serious TEAEs for the All Paediatric population included pyrexia (6.5%) and febrile neutropenia (5.2%). The most common serious TEAEs for the All Adult population included septic shock (5.0%) and respiratory failure (4.7%).

Three paediatric participants in the All Paediatric population (3.9%) experienced at least one drug-related serious TEAE, two participants in study 9766-CL-0046 and one in study 9766-CL-0107. This compares to 41 drug-related serious TEAEs reported in the 403 adult participants in the All Adult population (10.2%). Drug-related serious TEAEs in the All Paediatric population included vomiting (1.3%), pyrexia (1.3%), nausea (1.3%), infusion-related reaction (1.3%), tachycardia (1.3%), infusion-site pain (1.3%), infusion-site pruritus (1.3%), and electrocardiogram QT prolonged (1.3%)

Infusion related reactions occurred in the majority of paediatric 31/53 (58.5%) and adult 226/357 (63.3%) populations. Some of these occurred more often in adults (respiratory tract related reactions, but not for respiratory distress and tachypnoea), while other reactions appeared to be more common in children (hypersensitivity related reactions). No clear pattern emerges from these data, which may be due to the relative low number of children enrolled in two separate studies.

Age

No clear age-related trends were seen, although TEAEs in the SOC Musculoskeletal and connective tissue disorders occurred with highest frequency in the 12 to < 18 years age group [8/32 (25.0%)], than in 12 to < 18 years age group [5/30 (16.7%)] and lowest frequency in the 1 to < 6 years age group [1/15 (6.7%)]. The reason for this is unknown. No obvious difference in overall and individual-type AEs was observed between the age cohorts, although numbers of patients per cohort were very low and definitive conclusions cannot be drawn.

Laboratory findings

Elevated liver transaminases and hepatitis were observed in 22/77 (28.6%) of the All Paediatric population compared to 90/403 (22.3%) in the All Adult population. TEAEs in the All Paediatric population were mainly driven by hypoalbuminaemia (9.1% vs 3.0% in the All Adult population). It is noted that 28.8% of the paediatric participants had hypoalbuminaemia reported in their medical histories, compared to 13.4% of the adult participants. This finding is considered consistent with the participants' underlying medical conditions. 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 paediatric 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 (AUC dependent) but from the MAH's response it does not appear that such an association exists.

2.6.10. Conclusions on the clinical 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 was very high. Reported TEAEs were generally consistent with those expected in a paediatric oncology population undergoing treatment for malignancy or with the known safety profile of isavuconazole in adults.

Mortality rate in the investigated paediatric population was relatively low.

Non-cardiac chest pain, stomatitis and aphthous ulcer were more common in the paediatric population than in the adult study population. From additional data submitted it however does not appear that these TEAEs were drug related or age related but rather due to induction chemotherapy that these children underwent.

Frequently reported TEAEs (occurring in ≥ 15% of participants) were pyrexia (39.0%), diarrhoea (26.0%), and vomiting (20.8%). No new TEAEs emerged in the paediatric population.

The safety profile of isavuconazole, used in the posology as recommended in the SmPC, is generally considered acceptable and in line with that in adults.

2.7. Risk Management Plan

The MAH submitted an updated RMP v. 9.1, dated 30 August 2023, in support of this procedure. The (main) proposed changes were the following:

- PART I – PRODUCT OVERVIEW

The proposed indication was updated to include patients from 1 year up to 18 years for the treatment of invasive aspergillosis and mucormycosis in patients for whom amphotericin B is inappropriate. Moreover, a new strength of the oral hard capsule formulation was added. Consequential update of the dosage to reflect the treatment of paediatric patients was also made.

- PART II – SAFETY SPECIFICATIONS

o Module SIII: Clinical trial exposure

The exposure data was updated.

o Module SV: Post-authorisation experience

The update was made to reflect the latest exposure.

o Module SVII: Identified and potential risks

No major changes were made in this module. The information about mucormycosis registry study was removed, since agreed with procedure EMEA/H/C/002734/II/0035/G having positive opinion on 8 July 2021.

A statement regarding the paediatric population was added in module SVII.3. that the safety profile of isavuconazole in paediatric population was found to be similar to that in the adult population, and no new safety signals were detected. The proposed updates are acceptable.

2.7.1. Safety concerns

2.7.1.1. Summary of safety concerns

No changes were proposed to the summary of safety concerns.

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Infusion related reactions
Important potential risks	Teratogenicity
Missing information	None

2.7.1.2. Discussion on safety specification

No changes were proposed, which is acceptable.

2.7.1.3. Conclusions on the safety specification

Having considered the data in the safety specification, it is agreed that the safety concerns listed by the MAH are appropriate.

2.7.1.4. Protected Personal Data (PPD) and Commercially Confidential Information (CCI) considerations for the RMP Safety Specification

The Safety Specification of the RMP does not contain PPD/CCI.

The MAH is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Protected Personal Data (PPD) and identification of Commercially Confidential Information (CCI) in the updated RMP submitted with the responses.

2.7.2. Pharmacovigilance plan

No changes are proposed to the pharmacovigilance plan, which is endorsed. Only routine pharmacovigilance activity supplemented with two FU questionnaires regarding infusion-related reactions and teratogenicity (pregnancy data collection form) are in place.

2.7.3. Risk minimisation measures

Editorial change to routine risk minimisation measures activities for infusion-related reactions to reflect latest current SmPC and PL wording according to procedure EMEA/H/C/PSUSA/00010426/202109 with EC Decision dated 21 June 2022. The proposed editorial change is accepted. The routine RMMs are sufficient to minimise and mitigate the risk associated with Cresemba use. No additional RMMs are necessary.

2.7.4. Conclusion

The MAH submitted a further revised RMP version 10 in response to the PRAC assessment. The CHMP considered that the risk management plan version 10, dated 9 February 2024 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet for 40mg hard capsules meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Invasive fungal infection (IFI) is a leading cause of infectious disease morbidity and mortality in immunocompromised patients, especially in those considered at high risk for severe and prolonged neutropenia or those who have received HSCT. As in adults, the paediatric patients at risk for developing IFI,

primarily due to neutropenia and T-cell dysfunction, include, but are not limited to, allogeneic stem cell transplant recipients, and patients with acute leukaemia, myelodysplasia, severe aplastic anaemia, and advanced-stage non-Hodgkin lymphoma. The most common IFI in these immunocompromised children are aspergillosis, candidiasis and to a lesser extent mucormycosis.

Despite the current available antifungal therapies (AFTs) for invasive aspergillosis IFD is still associated with high mortality rates (30-40% in treated and 95% in untreated patients).

Still mucormycosis carries a mortality rate of 50-85%. The mortality rate associated with rhinocerebral disease is 50-70%. Pulmonary and gastrointestinal (GI) diseases carry an even higher mortality rate, because these forms are typically diagnosed late in the disease course. Disseminated disease carries a mortality rate that approaches 100%. Cutaneous disease carries the lowest mortality rate (15%).

Isavuconazole is currently indicated for the treatment of the following fungal infections in adults:

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

3.1.2. Available therapies and unmet medical need

Invasive aspergillosis is treated with systemic antifungal agents, such as polyenes (Amphotericin B), mould active triazoles (isavuconazole, voriconazole, itraconazole, posaconazole) and echinocandins (caspofungin, micafungin, and anidulafungin). Sometimes surgical resection of the infected focus is warranted. Successful mucormycosis treatment requires correction of the underlying risk factor(s), antifungal therapy with liposomal amphotericin B or isavuconazole (also posaconazole has some anti- *Mucorales* activity), and aggressive surgery.

Despite the current available antifungal therapies for invasive aspergillosis is still associated with high mortality rates (30-40% in treated and 95% in untreated patients). Mucormycosis carries a mortality rate of 50-85%, disseminated disease up to 100%.

The choice of antifungal prophylaxis or treatment for paediatric patients is limited by side effects profiles, and PK characteristics. More treatment options are therefore needed.

3.1.3. Main clinical studies

This paediatric extension is based on a PK bridge to adult data. For this purpose, the MAH has submitted two paediatric clinical trials. Phase 1 study 9766-CL-0046 evaluated the pharmacokinetics, and safety/tolerability in 46 paediatric participants aged 1 to <18 years in the treatment of Invasive Aspergillosis (IA) or Invasive mucormycosis (IM). It does not provide support for efficacy.

Phase 2 study 9766-CL-0107 was a single armed study, evaluated the pharmacokinetics, efficacy and safety/tolerability in 31 paediatric participants aged 1 to <18 years in the treatment of IA or IM. Efficacy data were collected only for descriptive purposes.

3.2. Favourable effects

The use of a 5.4 mg/kg dose of isavuconazole (IV or orally) in paediatric participants aged 1 to 18 years was associated with a relatively low mortality rate when compared to that in adults [48/258 (18.6%)]. Primary

efficacy endpoint *All-cause Mortality Through Day 42 (FAS)* was 2/31 (6.5%). One additional participant died between days 42 and 84. None of the 3 deaths was considered related to study treatment. All deaths occurred during the follow-up period.

The AC-assessed overall response rates (combined endpoint of clinical, mycological and radiological responses) for the FAS set at day 42 and day 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%).

3.3. Uncertainties and limitations about favourable effects

- This was an open-label, non-comparative trial.
- The sample size was very low. A limited number of 31 paediatric patients were enrolled in study 9766-CL-0107. Only 12 patients were diagnosed with *proven or probable* Invasive Aspergillosis and a single patient with *proven or probable* Invasive mucormycosis (subpopulation of major interest).
- According to study protocol the *concomitant* use of other systemic mould active antifungal agents (posaconazole, amphotericin B and voriconazole) was to be avoided. Nevertheless, these agents were used in a significant number of patients with *proven or probable* IA or IM [8 of 13, (61.5%)]. Although there may have been good reasons for adding other concomitant mould active agents to the study drug, the exact contribution of isavuconazole to the clinical success of the overall treatment is therefore difficult to determine.

3.4. Unfavourable effects

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 was very high. Nevertheless, reported TEAEs were generally consistent with those expected in a paediatric oncology population undergoing treatment for malignancy and in line with the known safety profile of isavuconazole in adults, which is important since this paediatric extension is based on a PK bridge to adult data.

Mortality rate in the investigated paediatric population was relatively low (compared to in adults). There were no TEAEs leading to death that were considered to be related to study drug.

In the pooled analysis, frequently reported TEAEs (occurring in ≥ 15% of participants) were pyrexia (39.0%), diarrhoea (26.0%), and vomiting (20.8%). Nausea, vomiting, and diarrhoea occurred at similar frequencies as those in the phase 3, controlled study in adult patients with IA (Study 9766-CL-0104). Pyrexia occurred at a higher frequency in the All Paediatric population than in the All Adult population (39.0% vs 20.1%), which is probably related to the use of isavuconazole by febrile neutropenic children undergoing induction chemotherapy and receiving isavuconazole for antifungal prophylaxis.

Non-cardiac chest pain, stomatitis and aphthous ulcer were more common in the paediatric population than in the adult study population. From additional data submitted by the MAH it however does not appear that these TEAEs were drug related or age related but rather due to induction chemotherapy that these children underwent.

Elevated liver transaminases and hepatitis were observed in 22/77 (28.6%) of the All Paediatric population compared to 90/403 (22.3%) in the All Adult population. TEAEs in the All Paediatric population were mainly driven by hypoalbuminemia (9.1% vs 3.0% in the All Adult population). It is noted that 28.8% of the paediatric participants had hypoalbuminemia reported in their medical histories, compared to 13.4% of the adult participants. This finding is considered consistent with the participants' underlying medical conditions.

No new TEAEs emerged in the paediatric population and clinical laboratory evaluations did not provide new insights.

3.5. Uncertainties and limitations about unfavourable effects

- Data were collected from two open-label, non-comparative trials.
- The sample sizes were low. A limited number of 77 paediatric patients were enrolled in study 9766-CL-0107. Only 12 patients were diagnosed with *proven or probable* Invasive Aspergillosis and a single patient with *proven or probable* Invasive mucormycosis (subpopulation of major interest).
- *Concomitant* use of other systemic mould active antifungal agents was to be avoided, but were still used in a significant number of patients with *proven or probable* IA or IM [8 of 13, (61.5%)]. The exact contribution of isavuconazole to the safety profile of the overall treatment is therefore difficult to determine.

3.6. Effects Table

Not applicable as this is a PK bridging application.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Despite the current available antifungal therapies for invasive aspergillosis and mucormycosis both diseases are still associated with high mortality rates. There are currently only a few treatment options for adults but even fewer in children. More treatment options are therefore needed, especially for children. Treatment with isavuconazole might be such an option for the treatment of both IA and IM. 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 clinical 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 paediatric population. Sufficient exposure data was provided to show that the exposure is similar in most paediatric patients and adults. However, currently the MAH provided too limited data to conclude similar exposure between paediatric patients aged 6 to <18 years weighing 32-36 kg and adult patients.

3.7.2. Balance of benefits and risks

There is a need for effective antifungal therapies for invasive aspergillosis and mucormycosis since there are currently only a few treatment options for adults and children. Treatment with isavuconazole might be such an option for the treatment of both IA and IM. 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 clinical 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 paediatric population.

Bridging is possible for paediatric patients and adults.

Therefore, the balance of benefit and risks of the use of isavuconazole in the paediatric population is positive.

3.8. Conclusions

The overall benefit-risk balance of Cresemba is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Cresemba is favourable in the following indications:

Powder for concentrate for solution for infusion:

Cresemba is indicated in patients from 1 year of age and older for the treatment of

- *invasive aspergillosis*
- *mucormycosis in patients for whom amphotericin B is inappropriate (see sections 4.4 and 5.1)*

Consideration should be given to official guidance on the appropriate use of antifungal agents.

Hard capsules:

Cresemba hard capsules are indicated in adults and in paediatric patients from 6 years of age for the treatment of

- *invasive aspergillosis*
- *mucormycosis in patients for whom amphotericin B is inappropriate (see sections 4.4 and 5.1)*

Consideration should be given to official guidance on the appropriate use of antifungal agents.

Cresemba 40 mg hard capsules are intended to be used for paediatric patients.

The CHMP therefore recommends the extension of the marketing authorisation for Cresemba subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0479/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.