EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2015
EMA/596950/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cresemba

International non-proprietary name: isavuconazole

Procedure No. EMEA/H/C/002734/0000

Note

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

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List of abbreviations

AE	adverse event
AUC	area under the concentration-time curve
AUCinf	area under the concentration-time curve till infinity
AUCt	area under the concentration-time curve till the last sampling time
ΔΔQTcF	time-matched baseline-and placebo-adjusted QT interval corrected for heart rate using Fridericia's formula
AFT	antifungal therapy
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	Aspartate transaminase
AmB	amphotericin B
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate transaminase
AUC	area under the concentration time curve
BAL4815	isavuconazole
BAL8557	isavuconazonium sulfate (prodrug)
BAL8728	Inactive cleavage product of isavuconazonium sulfate
β-HCG	urine or serum pregnancy test
b.i.d.	twice daily
BLQ	below the limit of quantification
BMI	body mass index
BMT	bone marrow transplant
bpm	beats per minute
BRCP	Breast cancer resistance protein
BUN	blood urea nitrogen
BW	body weight
CI	confidence interval
CL	clearance
Clcr	creatinine clearance
Clint	intrinsic clearance
Clr	renal clearance
CLSI	clinical and Laboratory Standards Institute
Cmax	maximal plasma concentration
Cmin	minimum plasma concentration
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CPK	creatinine phosphokinase
CrCl	creatinine clearance
CRF	case record form
CSF	cerebrospinal fluid
CT	computed tomography
C_τ	concentration at the end of the dosing interval
Ctrough	trough plasma concentration

DRC	Data Review Committee
ECG	electrocardiogram
ESCMID/ECMM	European Society of Clinical Microbiology and Infectious Diseases/European Confederation of Medical Mycology
ECV	epidemiological cut off value
eGFR	estimated glomerular filtration rate
eGFR-MDRD	estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula
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
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	US Food and Drug Administration
FLU	fluconazole
FU	follow-up period
GCP	Good Clinical Practice
GGT	gamma glutamyl transpeptidase
GM	galactomannan
GMR	geometric mean ratio
GTI	Genotoxic Impurity
h	hour
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplant
IA	Invasive aspergillosis
IDSA	Infectious Diseases Society of America
IFD	Invasive Fungal Disease
ISA	Isavuconazole
ITT	intent-to-treat population
IV	intravenous
l-AmB	lipid-based formulations of amphotericin B
l	liter
LDH	lactate dehydrogenase
LFU	late follow-up visit
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LRTD	Lower respiratory tract disease
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MIC_{50}	MIC at which 50% of the isolates are inhibited at the specified endpoint
MIC_{90}	MIC at which 90% of the isolates are inhibited at the specified endpoint
mITT	modified ITT
ml	mililiter
MRI	Magnetic Resonance Imaging
myITT	mycological ITT
NA	not available
N/A	not applicable

ND	not detected
NIM	Non-inferiority margin
NOS	not otherwise specified
NRI	non renally impaired patients
OCT1 or OCT2	Organic cation *transporters 1 or 2*
P-gp	P-glycoprotein
PIP	Paediatric Investigation Plan
PKAS	pharmacokinetic analysis set
popPK	population pharmacokinetic analysis
PPS-ITT	Per-protocol set (subset of ITT analysis set)
PPS-mITT	Per-protocol set (subset of mITT analysis set)
PTA	Probability of target attainment
q.d. (QD)	once daily
QIDP	Qualified Infectious Disease Product
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia formula
RI	renally impaired patients
RMP	Risk Management Plan
SAE	serious adverse event
SBECD	sulfobutyl ether beta-cyclodextrin sodium
SCAR	severe cutaneous adverse reactions
s.d. (SD)	standard deviation
SFU	short-term follow-up visit
SOC	System Organ Class
ss	steady state
t1/2	half-life
tmax	time of observed maximal plasma concentration
t > MIC	time-dependent attainment of free drug concentrations above the MIC
TOC	Test-of-cure visit
TEAE	treatment-emergent adverse event
UDP	uridine diphosphate
UGT	uridine diphosphate-glucuronosyltransferases
ULN	upper limit of normal
Vd	Volume of distribution
VRC	Voriconazole
WFI	Water for Injection

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Basilea Medical Ltd submitted on 16 July 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Cresemba, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 April 2012.

Cresemba, was designated as an orphan medicinal product EU/3/14/1276 and EU/3/14/1284 on 04 June 2014 and 04 July 2014, respectively. Cresemba was designated as an orphan medicinal product in the following indication: mucormycosis and invasive aspergillosis.

The applicant applied for the following indication in adults for:

- treatment of invasive aspergillosis
- treatment of mucormycosis.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designations of Cresemba as an orphan medicinal product in its approved indications. The outcome of the COMP review can be found on the Agency's website:

ema.europa.eu/Find medicine/Human medicines/Rare disease designation (invasive aspergillosis)

ema.europa.eu/Find medicine/Human medicines/Rare disease designation (mucormycosis)

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that isavuconazole was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0135/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0135/2013 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the applicant 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.

New active Substance status

The applicant requested the active substance isavuconazole (as isavuconazonium sulfate) contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Protocol Assistance

The applicant did not seek Protocol Assistance at the CHMP.

Licensing status

A new application was filed in the following countries: United States of America

The product was not licensed in any country at the time of submission of the application.

Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Greg Markey

CHMP Peer reviewer(s): Kristina Dunder

- The application was received by the EMA on 16 July 2014.
- The procedure started on 20 August 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 November 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 5 November 2014.
- PRAC assessment overview, adopted by PRAC on 4 December 2014.
- During the meeting on 18 December 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 18 December 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 March 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 27 April 2015.
- PRAC RMP Advice and assessment overview, adopted on 7 May 2015.
- During the CHMP meeting on 21 May 2015, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 June 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of

Questions to all CHMP members on 1 July 2015.

- PRAC RMP Advice and assessment overview, adopted on 9 July 2015.
- During the meeting on 23 July 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Cresemba.

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

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.

The transmission of fungal spores to the human host is via inhalation and *Aspergillus* primarily affects the lungs, causing 4 main syndromes: allergic bronchopulmonary aspergillosis (ABPA), chronic necrotizing *Aspergillus* pneumonia (also termed chronic necrotizing pulmonary aspergillosis [CNPA]), aspergilloma, and invasive aspergillosis. The majority of human illness is caused by *Aspergillus fumigatus* and *Aspergillus niger* and, less frequently, by *Aspergillus flavus* and *Aspergillus clavatus*. *Aspergillus* may hematogenously disseminate beyond the lungs and the CNS, cardiovascular system, and other tissues may be infected as a result.

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

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 moldy 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 tumor 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 recognized. Rhinocerebral disease causes significant morbidity in patients who survive, because treatment usually requires extensive, and often disfiguring, facial surgery.

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, and aggressive surgery.

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%).

2.1.2. About the product

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

The following indications were initially proposed:

- treatment of invasive aspergillosis in adults
- treatment of mucormycosis in adults

The posology proposed with the initial submission is:

Posology

CRESEMBA can be administered orally or via intravenous infusion.

CRESEMBA is available as hard capsules and as powder for concentrate for solution for infusion.

Adults

Loading dose

Therapy must be initiated with the specified loading dose regimen of either intravenous or oral CRESEMBA. The recommended loading dose is two capsules or one vial of CRESEMBA 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 two capsules or 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 treatment

Duration of therapy should be based on the nature and severity of the underlying disease, recovery from immunosuppression, clinical and mycological response.

For long term treatment beyond 6 months, the benefit-risk balance should be carefully considered (see SmPC sections 5.1 and 5.3).

On the basis of the high oral bioavailability (98%, see SmPC section 5.2), switching between intravenous and oral administration is appropriate when clinically indicated.

Paediatric population

The safety and efficacy of CRESEMBA in children aged below 18 years has not yet been established. No data are available.

Older people

No dose adjustment is necessary for older patients.

Renal impairment

No dose adjustment is necessary in patients with renal impairment, including patients with end stage renal disease (see SmPC section 5.2).

Hepatic impairment

No dose adjustment is necessary in patients with mild and moderate hepatic impairment (Child-Pugh A and B) (see SmPC section 5.2). There is no clinical experience in patients with severe hepatic impairment (Child-Pugh C).

Method of administration

Precautions to be taken before handling or administering the medicinal product

CRESEMBA must be reconstituted and then further diluted to a concentration corresponding to approximately 0.8 mg/ml isavuconazole prior to administration by intravenous infusion over a minimum of 1 hour to reduce the risk for infusion related reactions. The infusion must be administered via an infusion set with an in-line filter with a microporous membrane pore size of 0.2 µm to 1.2 µm. CRESEMBA must not be given as a bolus injection.

For detailed instructions on the reconstitution and dilution of CRESEMBA before administration, see SmPC section 6.6.

The final agreed indication and dosage for Cresemba are:

CRESEMBA is indicated in adults for the treatment of

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

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

<u>Posology</u>

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) or alternatively two capsules (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 or alternatively two capsules (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 (see SmPC section 5.1).

For long-term treatment beyond 6 months, the benefit-risk balance should be carefully considered (see SmPC sections 5.1 and 5.3).

Switching between isavuconazole dosage forms

CRESEMBA is available powder for concentrate for solution for infusion containing 200 mg isavuconazole, equivalent to 372 mg isavuconazonium sulfate and as hard capsules containing 100 mg isavuconazole, equivalent to 186 mg isavuconazonium sulfate.

On the basis of the high oral bioavailability (98%, see SmPC section 5.2), switching between intravenous and oral administration is appropriate when clinically indicated.

Elderly

No dose adjustment is necessary for elderly patients; however the clinical experience in elderly patients is limited.

Renal impairment

No dose adjustment is necessary in patients with renal impairment, including patients with end-stage renal disease (see SmPC section 5.2).

Hepatic impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Classes A and B) (see SmPC sections 4.4 and 5.2).

CRESEMBA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Use in these patients is not recommended unless the potential benefit is considered to outweigh the risks. See SmPC sections 4.4, 4.8 and 5.2.

Paediatric population

The safety and efficacy of CRESEMBA in children aged below 18 years has not yet been established. No data are available.

Method of administration

Intravenous use

Precautions to be taken before handling or administering the medicinal product

CRESEMBA must be reconstituted and then further diluted to a concentration corresponding to approximately 0.8 mg/mL isavuconazole prior to administration by intravenous infusion over a minimum of 1 hour to reduce the risk of infusion-related reactions. The infusion must be administered via an infusion set with an in-line filter with a microporous membrane made of polyethersulfone (PES) and with a pore size of 0.2 µm to 1.2 µm. CRESEMBA must only be given as an intravenous infusion.

For detailed instructions on the reconstitution and dilution of CRESEMBA before administration, see SmPC section 6.6.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented in two pharmaceutical forms:

a) powder for concentrate for solution for infusion containing 200 mg isavuconazole as active substance per vial (corresponding to 372.6 mg isavuconazonium sulfate). It is administered by intravenous infusion after reconstitution with 5.0 ml of water for injection and further dilution with 250 ml of 0.9% sodium chloride solution or 5% dextrose solution and
b) hard capsules containing 100 mg isavuconazole as active substance corresponding to 186.3 mg isavuconazonium sulfate.

Other ingredients of the powder for concentrate for solution for infusion are: mannitol and sulfuric acid, as described in section 6.1 of the SmPC.

Other ingredients of the hard capsules are: *capsule contents:* magnesium citrate (anhydrous), microcrystalline cellulose, talc, anhydrous colloidal silica, stearic acid; *Capsule shell:* hypromellose, water, red iron oxide (E172), titanium dioxide (E171), gellan gum, potassium acetate, disodium edetate, sodium laurilsulfate; *Printing ink:* shellac, propylene glycol, potassium hydroxide, black iron oxide (E172), as described in section 6.1 of the SmPC.

Cresemba powder for concentrate for solution for infusion is available in Type I glass vial with a teflon-coated butyl rubber stopper and an aluminium/plastic flip-off seal, as described in section 6.5 of the SmPC.

Cresemba hard capsules is available in Alu/Alu blisters, as described in section 6.5 of the SmPC.

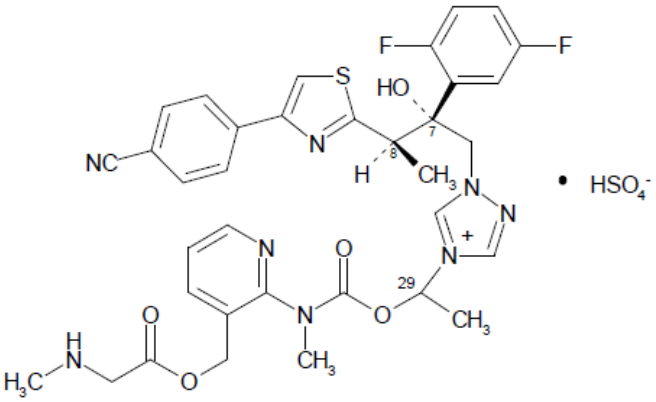
2.2.2. Active Substance

General information

The active substance is isavuconazonium sulfate, a highly water soluble pro-drug of the active triazole isavuconazole.

The chemical name of the active substance isavuconazonium sulfate is 1-{(2*R*,3*R*)-3-[4-(4-cyanophenyl)-1,3-thiazol-2-yl]-2-(2,5-difluoro-phenyl)-2-hydroxybutyl}-4-[(1*RS*)-1-({methyl[3-({[(methylamino)acetyl] oxy}methyl) pyridin-2-yl]carbamoyl}oxy)ethyl]-1*H*-1,2,4-triazol-4-ium monosulfate (IUPAC), corresponding to the molecular formula $C_{35}H_{35}F_2N_8O_5S{\cdot}HSO_4$ and has a relative molecular mass of 814.84 g/mol. The relative molecular mass of isavuconazole is 437.47. The active substance has the following structure:

Figure 1: Structure of isavuconazonium sulfate



The structure of the active substance has been confirmed by elemental analysis, mass spectrometry, UV, IR, ^{1}H-, ^{13}C- and ^{19}F-NMR spectrometry, and single crystal X-ray analysis, all of which support the chemical structure.

It appears as a white, amorphous, hygroscopic powder. It is very soluble in water and over the pH range 1-7. It is also very soluble in methanol and sparingly soluble in ethanol. Two pKa values have been found and calculated to be 2.0 and 7.3. Its log$P_{oct/wat}$ calculated by software is 1.31.

Isavuconazonium sulfate has three chiral centres. The stereochemistry of the active substance is introduced by one of the starting materials which is controlled by appropriate specification. The two centres, C7 and C8 in the isavuconazole moiety and in an intermediate of the active substance, have *R* configuration. The third chiral centre, C29, is not located on isavuconazole moiety and has both the *R* and *S* configurations. The non-defined stereo centre at C29 has been found in all batches produced so far to be racemic. Erosion of stereochemical purity has not been observed in the current process. The active substance is a mixture of two epimers of C29. An enantiomer of drug substance was identified as C7 (S), C8 (S) and C29 (R/S) structure. The control of the stereochemistry of isavuconazonium sulfate is performed by chiral HPLC on the active substance and its two precursors.

Subsequent intermediates are also controlled by relevant specification in the corresponding steps.

Two crystal forms have been observed by recrystallisation studies. However the manufacturing process as described yields amorphous form only.

Manufacture, characterisation and process controls

Isavuconazonium sulfate is manufactured in 10 converging synthetic steps from 5 regulatory starting materials. The different steps are performed by two different manufacturing sites. The currently proposed starting materials are simple molecules, which contribute significant structural fragments to the final active substance, are commercially available and are acceptable in line with ICH Q11 and current European regulatory practice. The synthetic schemes and specification for each one of the five starting materials have also been presented. Several intermediates are produced and isolated in the commercial manufacturing process. These intermediates are sufficiently controlled to assure the quality of active substance. The synthetic route involves some re-processing, which does not introduce any new solvents or reagents. It has been adequately described and is thus acceptable. The process, raw materials, reagents, and equipment used

were adequately described and the manufacturing process parameters, proven acceptable ranges and normal acceptable ranges were justified.

Two different salt forms of isavuconazonuium (chloride and sulfate) were identified during development. The sulfate salt was selected for further development. A polymorph screening study was also performed. None of the investigated salts could be obtained in crystalline form.

The active substance manufacturing process was developed using QbD elements such as Failure Mode and Effects Analysis (FMEA) and Design of Experiments (DoE) Study and Design Space to identify the critical processing steps and parameters that have an impact on critical quality attributes (CQAs) of the substance and to define proven acceptable ranges (PAR) and normal operating ranges (NOR) for the process. Additional risk assessment (FMEA) was also performed following identification of critical process parameters (CPPs), taking into account historical batch data, equipment capabilities and operational control to establish the final CPPs ranges. However no design spaces have been claimed by the applicant in the manufacturing process of the active substance. The in-process controls (IPCs) applied for the 10 steps were presented. The manufacturing process will be validated using three consecutive commercial scale batches prior to commercialisation.

The origin and fate or impurities, including those which are potentially genotoxic was evaluated. Many of the potential compounds discussed are purely theoretical compounds. However all identified and also theoretical compounds were considered. Two potential genotoxic impurities (GTI) have been specified GTI1 and GTI2.The first is a process-related impurity that tested positive in the Ames test and is controlled as an IPC. The second one is a secondary degradantandis controlled in the final active substance specification.

None of the specified related substances in the active substance originate from the starting materials. None of the related substances or other impurities contained in the intermediates defined in the process carries over to the final active substance. Adequate controls for all residual solvents have been included at the appropriate steps of active substance manufacture. No catalysts are used.

The active substance is packed in polyethylene sleeve, or polyethylene powder transfer bags, with desiccant, inside a sealed aluminium laminated water impermeable bags placed inside rigid containers.

Specification

The active substance specification includes appropriate tests and limits for: appearance (visual inspection), appearance of solution (Ph. Eur.), pH (Ph. Eur.), identity (IR, HPLC), enantiomer (HPLC), assay (HPLC), related substances (HPLC), genotoxic impurities (HPLC/MS, HPLC), sulfate anion (ion chromatography), residual solvents (GC), water content (Ph. Eur.), sulphated ash (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and microbiological quality (Ph. Eur.). The sum of maximum observed value in active substance of the (potential) genotoxic impurities is considered acceptable, since this calculated intake is below the acceptable daily intake of 60 µg total impurities based on the maintenance dose of 200 mg/day isavuconazole.

For GTI 1 the proposed limit would lead to a daily intake of 37µg of this impurity. This intake exceeds the allowable intake of 1.5 µg per day for genotoxic impurities (EMA/CHMP/SWP/431994/2007 Rev. 3). However this is not a concern, because this impurity is rapidly degraded in plasma- half-time of < 2 min- and, as such, GTI 1 poses a negligible genotoxic risk. The proposed limit has been toxicologically qualified. For GTI 2 higher limit than the TTC is also justified, since human exposure to this impurity is greater from other natural sources (e.g. atmosphere, food, even produced endogenously). On the same basis as well as on batch results, it has been justified not to include a specification limit for acetaldehyde.

The proposed active substance specification and limits has been satisfactorily justified. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Full details of the reference standards used were provided.

Batch analysis data on three consecutive commercial scale validation batches were provided. Supportive data from laboratory and development smaller scale batches use during the product development program were also provided. The submitted batch analysis data confirm that the manufacture is sufficiently robust and provide reassurance that the process yields active substance of consistent quality, complying with the specification.

Stability

Stability data on three pilot scale batches of active substance stored in the intended commercial packaging for up to 36 months under long term conditions at -20±5°C and for up to 24 months under accelerated conditions at 5±3°C according to the ICH guidelines were provided. The batches were analysed for description, identification, pH, appearance of solution, related substances, GTI 2, enantiomer, C-29 epimer ratio, anion (sulfate), water content, microbial limits, assay and specific optical rotation using the analytical procedures proposed for release testing. All batches were compliant with the specifications at all time points and no significant trends were observed.

In addition supportive stability data for another two pilot and four commercial scale batches under long term conditions at -20±5°C for up to 36 months were presented. One of these batches was packaged in a different material that the one intended for commercial use. The active substance showed no significant change or trend in any of the parameters monitored. Further supportive stability data for another three pilot and four commercial scale batches at 5±3°C for up to 24 months were presented. The container closure system used for these batches is the same as the commercial container. A slight increase in amounts of some impurities has been observed under the storage condition at 5 ± 3 °C for all of the seven batches, however, all results of the quality attributes tested complied with the corresponding acceptance criteria in the specification.

Forced degradation studies were conducted in the solid state and in solution using 3 batches (one laboratory, one pilot and one commercial scale) placed on stability in high temperature (60^{o}C, 7days, commercial packaging), high humidity (51%RH, 7 days) and light (ICH Q1B compliant) stress conditions. Forced degradation studies of the drug substance, prepared as aqueous solutions was conducted in acidic, oxidative and basic stress conditions. The batches were analysed for related substances, degradation, assay, peak purity, and mass balance. Degradation was observed in high heat, high humidity, acidic and basic conditions, and no degradation observed in light or oxidative stress conditions. The analytical methods used for stability studies were consistent with those proposed for release testing with the exception of methods for turbidity and completeness of solution (Ph. Eur. 2.2.1), colour of solution (Ph. Eur. 2.2.2), C29 epimer ratio (HPLC), and assay (HPLC). All methods were well described and were considered acceptable. The results from the forced degradation studies show that the method on related substances is sufficiently stability indicating.

In conclusion, the proposed re-test period of 24 months, when stored in polyethylene bags packed in heat sealed aluminium laminated bags at -20^{o}C is adequately supported by the stability data provided and is acceptable.

2.2.3. Finished Medicinal Product

Cresemba has been developed as a powder for concentrate for solution for infusion for i.v. use and as hard capsules for oral use. The active substance is isavuconazonium sulfate, a highly water soluble pro-drug of the active triazole isavuconazole. The specific prodrug moiety was chosen based on preclinical data on fast and complete conversion rates by enzymatic cleavage to the active moiety. The focus was the increase of the aqueous solubility to enhance and enable the parenteral application by infusion, and also the oral bioavailability with low inter-subject variability and well controlled linear pharmacokinetics.

Powder for concentrate for solution for infusion

Description of the product and pharmaceutical development

The aim of pharmaceutical development was to manufacture a stable freeze dried powder for solution for infusion.

Isavuconazonium sulfate is manufactured as an amorphous material. It has been demonstrated that the amorphous form is consistently maintained throughout finished product manufacture, and that the lyophilisation process does not influence the polymorphic form. The key physicochemical property of the active substance that influences the quality of the product is sensitivity to hydrolytic degradation by moisture and temperature. Therefore the objective of the pharmaceutical development was to protect the prodrug from hydrolysis caused by moisture, temperature and pH. In the initial phases of formulation development the chloride salt of isavuconazonium was used, which was later replaced by the sulfate salt.The choice of the salt of the active substance has been justified.

Different bulking agent systems and buffering systems were tried before mannitol and sulphuric acid were selected as a bulking agent and for pH adjustment, respectively. The choice of excipients has been justified.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur 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 and in paragraph 2.1.1 of this report. Compatibility of these excipients with the drug substance has been demonstrated through stability studies.

Conventional terminal sterilisation by heat in the final container was not possible because isavuconazonium sulfate is sensitive to hydrolysis in solid state and in solution. To produce a sterile product in dry state, lyophilisation which is a common and effective manufacturing method was selected. Sterility of the product is assured by sterile filtration of the bulk solution and aseptic processing. The sterile filtration process utilizes standard procedures and equipment for a lyophilized product manufactured by aseptic process. The manufacturing process has not been changed significantly throughout the development. The stability of the bulk solution was evaluated and the bulk holding time from the addition of isavuconazonium sulfate into the formulation vessel to the start of lyophilisation cycle was established.

The lyophilisation cycle parameters have been optimised over the course of development to reduce the residual moisture in the lyophilized cake as low as practically possible because the residual moisture is the cause of degradation of the isavuconazonium sulfate to isavuconazole. The freeze drying process was optimised by thermal characterisation studies in order to ensure the reliable and reproducible formation of a solid freeze-dried cake.

In addition, to ensure the withdrawal of the labelled amount of drug product from the vials, a 6% overfill is applied during vial filling.Isavuconazonium sulfate powder for concentrate for solution for infusion is reconstituted in 5 ml sterile water for injection. The reconstituted solution is further diluted into 250 ml of 0.9% sodium chloride infusion solution (saline) or 5 % glucose infusion solution (D5W).

The re-constitution time of the finished product was investigated and data from 10 batches were presented The reconstitution time is found to be appropriate for an intravenous product.

The infusion solution is administered through an inline filter placed between the infusion bag and patient access. In the clinical setting, the reconstituted solution may be stored for up to one hour prior to preparation of the infusion solution. The infusion solution must be stored refrigerated at 2°C - 8°C, and the patient infusion must be completed within 24 hours after reconstitution of the lyophilized powder.
The stability of the administration solution in 250 ml saline and D5W was evaluated to confirm compatibility with these infusion solutions. A white precipitate formed during preparation of the administration solution when the reconstituted solution was mixed with saline or D5W. This precipitate was observed throughout the compatibility study and the assay and impurity values were consistent.

Theoretically the formation of the precipitate could pose a risk of systemic arterial embolism from intravenous administration; therefore the issue was raised as a major objection. The precipitate has been identified as the active moiety isavuconazole. A detailed discussion has been provided on the issue of potential formation of the precipitate, the risks of omission of in-line filtration, presentation of precaution measures to limit the formation of this precipitate, and test data on available in-line filters suitable to be used with the product. Concrete data related to the particle formation as well as quantitative aspects of these particle formation were provided together with solubility data for isavuconazole (both as sulfate as well as free base) in various media and conditions. The amount and density of the particles in the infusion solution are too low to be quantifiable. Herewith it can be concluded, that potential loss of this small amount of isavuconazole precipitate on the filter does not have any impact on the assay contents of the infusion solution.

On the other hand it has been shown that isavuconazole particles readily dissolve in human plasma by strongly binding to proteins. This strong plasma-protein binding promotes a rapid dissolution of the precipitate in human plasma.

In addition the dissolution experiments that have been performed represent most likely a 'worst-case scenario' when compared to the actual loose agglomerated particles that are formed *in situ* in the infusion bag. It was estimated that the hydrated agglomerates isavuconazole formed in the infusion solution will not exceed 1 mg and will be dissolved in human plasma within few seconds.

Despite several experiments the precise mechanism of the formation of particles could not be identified, although data suggest that the equilibrium of the system is stable under normal in-use conditions. Also the exact reason of increased formation of particles due to vigorous mixing or shaking could not be definitely explained. It is possibly attributed to the formation of additional seed nuclei, as well as generation of very small air bubbles, thus affecting the equilibrium between dissolved and undissolved isavuconazole.

Based on the information presented it can be concluded that the potential formation of isavuconazole particles in the infusion solution does not have an impact on the safety or efficacy of the product. The warning in the SmPC (section 6.6) against unnecessary vibration or vigorous shaking, and the recommended method of administration (section 4.2), requiring in-line filtration with a microporous membrane prior to administration, are considered justified and appropriate measures to mitigate any risk from the possible formation of isavuconazole particles in the infusion solution with regard to the safety or efficacy of the product.

The primary packaging is 10 ml Type I glass vial with rubber stopper and an aluminum cap with plastic seal. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process includes eight steps: weighing, compounding, sterile filtration, aseptic filling, lyophilisation, capping, inspection, and packaging. The aseptic production of isavuconazonium sulfate powder for concentrate for solution for infusion is described and the commercial batch size has been defined. Weighing and compounding are performed in a Grade C area. Sterile filtration, the aseptic filling and lyophilisation are performed in a Grade A area. Capping is performed under Grade A air supply with Grade C background. All processes are carried out using equipment and facilities that have been appropriately qualified and validated. The critical steps in the final drug product manufacturing process were identified as pH adjustment during compounding, sterile filtration and aseptic filling and sufficient in process controls are in place. In line with the guideline on process validation (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1), the aseptic processing and lyophilisation are considered to be non-standard manufacturing processes. Therefore the process has been validated using 3 consecutive commercial scale batches and one additional commercial scale validation batch manufactured later. The process has been also validated using a media fill study and showed that the sterile integrity of the process was maintained throughout.

Product specification

The finished product release and shelf life specification includes appropriate tests for this kind of dosage form description (visual), identification (HPLC, HPLC-PDA), pH (Ph. Eur.), assay (HPLC), related substances (HPLC), isavuconazole (HPLC), GTI 2 (HPLC), water content (Ph. Eur.), uniformity of dosage units (Ph. Eur.), particulate contamination visible particles (Ph. Eur.), particulate contamination sub-visible particles (Ph. Eur.), reconstitution time, bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.). The proposed limits for related substances were justified on the basis of ICH Q6A and ICH Q3B (R2). The limit for GTI 2has been thoroughly justified and is in accordance with ICH M7 Draft Guidance, in that the 120 µg/day maximum is not exceeded for isavuconazonium iv product because the duration of administration is projected to be less than 30 days. Extractable volume has been accepted to be omitted from the proposed specification on the basis of the 6% overfill. Isavuconazole is the active moiety of the drug substance and is, therefore, considered qualified.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The same reference standards used for the active substance analyses are used for the iv drug product.

Batch analysis results are provided for 3 registration batches / primary stability batches and 5 process validation batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three consecutive commercial scale batches of finished product stored under long term conditions for 24 months at 5 ºC and for 6 months under accelerated conditions at 25 ºC / 60% RH according to the ICH guidelines were provided. The batches of the product are identical to those proposed for marketing

and were packed in the primary packaging proposed for marketing. Supportive stability data were provided for a further two commercial scale batches of the proposed product. The batches were placed on stability in long term (5 ºC) for up to 33 months and accelerated conditions (25 ºC) for 6 months. Samples were tested for: description, reconstitution time, pH, visible particles, sub-visible particles, related substances, isavuconazole, GTI 2, water, assay, bacterial endotoxins and sterility. The analytical procedures used are stability indicating. All batches showed good compliance with the specification limits and meet the specification when stored at 5°C. No significant trends were observed under long term conditions.

In accelerated conditions, a decrease in assay and increase in impurities, including GTI 2 was observed. Whilst the data are within the specification limits proposed, the storage conditions of the finished product should be restricted to 5°C (studied long term conditions).

In-use stability data of reconstituted solution were provided for one commercial scale batch, selected from initial release, and following storage at 5 °C for 12 months, reconstituted with 5 ml WFI then diluted with 250 ml 0.9% NaCl or 5% dextrose solution, and placed on stability for up to 24 hours in long term (5 °C) and 6 hours in ambient conditions. No significant differences were observed in the diluted solutions made with fresh, and 12 month old finished product samples. As such, the changes during the in-use storage period of the reconstituted solution observed are considered acceptable.

In-use stability data of the diluted solution, prepared from initial and 12 months storage sample, were provided for the same batch which was analysed pre- and post- in line filtration immediately following dilution in 0.9% NaCl or 5% dextrose, and following 6 hours storage at ambient conditions, or 24 hours at 5 °C. The data show the filter is effective in reducing the sub-visible particulate counts, and that assay is unaffected.

No significant differences were observed between the diluents however an increase in isavuconazole particulate formation was observed in batches of the lyophilisate diluted following storage (12 months at 5°C) and particulates were higher in samples diluted with saline, than those diluted with dextrose. However based on the information presented regarding the precipitate formation the differences observed are not expected to have any impact on the safety or efficacy of the product when used in accordance with the recommendations of the SmPC.

Forced degradation studies were conducted with one commercial scale batch of the finished product, placed on stability under heat and humidity (40°C, 75%RH, 2 months), and humidity (25°C/75%RH, 2 months) stress conditions. The forced degradation data provided indicate the product is sensitive to high heat, and has some sensitivity to moisture. The storage instructions in the SmPC (section 6.3 and 6.4) specify that the storage temperature should be restricted for this product (2-8 °C).

A photostability study was conducted in accordance with ICH Q1B guideline. All the data met the acceptance criteria indicating that the product is photostable.

Based on available stability data, the shelf-life of 24 months at 2 to 8 °C, as stated in the SmPC is acceptable. The in-use stability shelf life of 24 hours at 2 to 8 °C, or 6 hours at room temperature for the reconstituted and diluted solution as stated in the SmPC are acceptable.

Adventitious agents

No excipients derived from animal or human origin are used in the manufacture of Cresemba powder for concentrate for solution for infusion.

Hard capsules

Description of the product and pharmaceutical development

Cresemba 100 mg hard capsules contain 100 mg isavuconazole as active substance corresponding to 186.3 mg isavuconazonium sulfate. Isavuconazonium sulfate is a pro-drug of the active moiety isavuconazole.

The primary objective of development was to produce a capsule of an acceptable size, accommodating the minimum possible number of capsules per dose, and a manufacturing process that is robust and reliable. A traditional approach, with some enhanced approach tools (e.g. risk assessment, design of experiments) was used for the development of the formulations and manufacturing processes. The quality target product prolfile (QTPP) was defined as an oral immediate release capsule, containing 100 mg of the active moiety. It should meet specification limits for description, dissolution, assay, uniformity of dosage units, related substances and GTI 2, and it should be stable for at least 2 years at 25 ^{o}C. The product should be packaged in a container closure system that will provide adequate protection from moisture, protection throughout distribution and use, as well as convenience of use for the patients. From the defined QTPP, the finished product critical quality attributes (CQAs) were identified as dissolution, description, assay, uniformity of dosage units, and related substances.

The initial formulation development used the chloride salt. The salt form of isavuconazonium was changed from chloride to sulfateduring developmentThe choice of the salt of the active substance has been justified. Isavuconazonium sulfate is an amorphous material. Its solubility is >1.0 g/ml in any of the pH conditions tested (pH 1, 3, 5 and 7) and it is a BCS class I substance. The active moiety (isavuconazole) is poorly water-soluble but is highly permeable; the mean absolute bioavailability of isavuconazole after a single oral dose of isavuconazonium sulfate hard capsules (equivalent to 400 mg isavuconazole) was 98%, demonstrating complete absorption. The capsule manufacturing uses a standard dry granulation process. The particle size distribution (PSD) of isavuconazonium sulfate is not regarded as a critical quality attribute since the drug substance is highly soluble.

The initial formulation was further optimised to improve the physical properties of the blend. As isavuconazonium sulfate is a moisture-sensitive substance, a desiccant, anhydrous magnesium citrate, has been selected as a component to prevent degradation of the isavuconazonium sulfate due to hydrolysis. Magnesium citrate is normally used as drug substance for the treatment of constipation and there is no excipient monograph but a Ph. Eur. drug substance monograph is available. When used as a laxative, a dose of 11-25 g is required for therapeutic effect, whereas when used as magnesium dietary supplement, it is given in a dose of approximately 2 g daily (Martindale: The Complete Drug Reference). These doses are much higher than the anticipated exposure to magnesium from the isavuconazonium sulfate capsule Therefore magnesium citrate is a well-described chemical entity and its use of as an excipient at the levels proposed is considered justified. All of the other excipients selected are widely used for pharmaceutical products and are regarded as being safe for human use. Also with respect to isavuconazonium sulfate sensitivity to moisture, HPMC capsules are used. The choice of HPMC over hard gelatin capsules has been justified.The compatibility of drug substance with excipients was investigated using binary mixtures.

The proposed commercial formulation is the same as the formulation that has been used in Phase III clinical studies except from the capsule shells colour and imprint.

A detailed and satisfactory discussion on selection and optimisation of the dissolution media and test conditions has been provided. Isavuconazonium sulfate is a highly water soluble drug. The development of the dissolution method has been described and the choice of dissolution conditions has been justified. Considering the presented data and given that the capsule shell dissolution is the main rate limiting step, the method used for dissolution is considered to be discriminatory enough to identify differences in rate of dissolution.

The dissolution profiles of 16 clinical batches including and 3 registration batches were compared.

The batch which showed the slowest dissolution profile among the historical batches tested, demonstrated the high oral bioavailability in the absolute bioavailability study against the i.v. formulation. It should also be noted that no substantial differences in t_{max}, C_{max} and AUC of isavuconazole were observed across the different capsule variants including formulation, manufacturing process, type of capsule shell (gelatin/hypromellose), and salt of isavuconazonium (chloride/sulfate). In addition, similar pharmacokinetic parameters including t_{max}, C_{max} and AUC were observed with isavuconazonium sulfate oral solution (^{14}C-labeled isavuconazonium sulfate used in a mass balance study) and the isavuconazonium sulfate hard capsules (used in single dose pharmacokinetic studies). These observations suggest the dissolution behaviour of isavuconazonium sulfate hard capsules tested is unlikely to affect the pharmacokinetic parameters. Based on the above, the interchangeability between isavuconazonium capsules and i.v. drug product is proposed.

The criticality of each step of the manufacturing process was evaluated. A risk analysis based on manufacturing experience was performed to systematically identify the processing parameters and their interrelations impacting quality attributes of the finished product. Based on the outcome of the analysis, the influence of blending time and the compaction process parameters were further optimised. All potentially impacting attributes or parameters were evaluated and no critical steps were identified.

The same manufacturing process has been used throughout clinical development with only minor modifications.

The bulk capsules are packaged in polyethylene bags, placed with a desiccant inside an aluminium pouch and packaged in an outer carton. The specifications and acceptance criteria for the packaging materials have been provided as well as representative certificates of analysis.

The primary packaging of the finished product is Alu/Alu blisters with each capsule pocket connected to a pocket with desiccant. The material complies with Ph. Eur. and EC requirements. The container closure system is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product manufacturing process comprises 7 steps: Pre-blending I and II, blending of pre-blend I and II, roller compacting, final blending, encapsulation and packaging using conventional and well-established pharmaceutical production equipment and conventional unit operations. No critical steps were identified in the drug product manufacturing process however in process controls are proposed to ensure uniformity of the dosage form and tightness of the blister.

The manufacturing process has been validated at the proposed manufacturing site prior to commercialisation with three consecutive commercial batches. A satisfactory validation report was provided.

Product specification

The finished product release and shelf life specification includes tests and limits for: appearance (visual), identification (HPLC, HPLC-PDA), assay (HPLC), isavuconazole (HPLC), related substances (HPLC), GTI 2 (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), water content (Ph. Eur.) and microbial limits (Ph. Eur). The proposed finished product specifications have been justified on the basis of batch analysis and stability data, capability of the manufacturing process, Ph. Eur. monograph and ICH guidelines.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The same reference standards used for the active substance analyses are used for the hard capsules product.

Batch analysis data for three commercial scale batches were presented and all batches meet the specification. Supportive batch analysis data were provided for 7 pilot scale batches of the finished product used in Phase I and II clinical trials. In addition batch analysis data for 16 pilot scale batches used in Phase III clinical trials were provided. Some of the supportive batches were manufactured at the development facility but the majority was manufactured at the commercial site. Testing was conducted according to the methods in place at the time of release. All the batches met the specification in place at that time or the occurred deviations were assessed and accepted. The presented information confirms the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three commercial scale batches of the finished product stored under long term conditions for up to 18 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The stability batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. The batches were analysed according to the proposed shelf life specifications for description, assay, related substances, isavuconazole, GTI 2, dissolution, water content and microbial limit. The stability results of the primary stability batches met the set specifications, both at long-term and accelerated conditions. The analytical procedures used are stability indicating.

A photostability study was conducted on one commercial scale batch in accordance with ICH Q1B guideline. No significant difference was observed except the water content and the attributes sensitive to moisture but all the results met the acceptance criteria after the light exposure.

Forced degradation studies were conducted with one commercial scale batch of the finished product, placed on stability under heat (50 ^{o}C, 1 month) and high humidity (open blister, 25 ^{o}C / 75% RH, 7 days). The samples were evaluated for description, assay, related substances, isavuconazole, GTI 2, dissolution and water. Degradation was observed under all conditions. An instruction to store in the original packaging in order to protect from moisture has been included in the SmPC.

Based on available stability data, the shelf-life of 30 months if stored in aluminium blister without specific storage temperature, as stated in the SmP (section 6.3) are acceptable. The product should be stored in the original packaging in order to protect from moisture (SmPC section 6.4).

Adventitious agents

No excipients derived from animal or human origin are used in the manufacture of Cresemba hard capsules.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance is isavuconazonium sulfate, a highly water soluble pro-drug of the active triazole isavuconazole. The prodrug of isavuconazole was selected because of its increased solubility, and PK characteristics. Information on development, manufacture and control of the active substance has been presented in a satisfactory manner.

The finished product is presented in two pharmaceutical forms: powder for concentrate for solution for infusion and hard capsules. The formulation and manufacturing process development for both pharmaceutical forms has been described in sufficient detail. The proposed specifications and the overall control strategy are considered acceptable. It has been demonstrated by appropriate in vitro and in vivo data that capsules and powder for concentrate for solution for infusion may be used interchangeably. 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.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Cresemba powder for concentrate for solution for infusion and Cresemba hard capsules 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.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

In the nonclinical program, the pharmacodynamics, pharmacokinetics and toxicology of isavuconazonium sulfate have been extensively characterized. The safety of isavuconazonium sulfate in animals has been evaluated by the oral or by the intravenous route. All pivotal toxicity studies were performed in compliance with the principles of Good Laboratory Practice (GLP). Most of the early dose-range finding or pilot studies were performed as non-GLP studies, but in GLP-accredited laboratories and according to their standards.

2.3.2. Pharmacology

Isavuconazonium sulfate is a water soluble prodrug of the antifungal triazole, isavuconazole. Following oral or intravenous administration of isavuconazonium sulfate, the prodrug is rapidly cleaved by plasma esterases into the active moiety, isavuconazole, and an inactive cleavage product (BAL8728).

Isavuconazole exhibits broad-spectrum *in vitro* antifungal activity, including that against *Aspergillus spp*., several species of Mucorales, and *Candida spp*, as well as against a broad range of rare, but important pathogenic fungi. This *in vitro* activity is not markedly affected by the existing triazole resistance mechanisms, which translates into a comparable or superior efficacy in animal models of infection. Isavuconazole also shows activity against voriconazole-resistant Mucorales and fluconazole-resistant *Candida spp.*, however it is generally not active against voriconazole-resistant *Aspergillus* spp. Isavuconazole does appear to retain activity against some itraconazole-resistant and posaconazole-resistant *Aspergillus* spp. both *in vitro* and *in vivo*.

Primary pharmacodynamics

A substantial amount of *in vitro* data has been submitted by the applicant. Most of the MIC data were determined using the CLSI methodology.

An *in vitro* selection experiment was performed with *Aspergillus fumigatus*, in which isavuconazole-resistant mutants were found, which were cross-resistant to other azoles. The mechanism of resistance is unknown, but it seems plausible that mechanisms of resistance for isavuconazole are similar to other azoles.

Mechanisms of resistance of Mucorales are largely unknown, but data published in the literature suggest that the presence of multiple copies of genes involved in the ergosterol biosynthesis pathway may play a role, thus providing a genetic flexibility to adapt to hostile environments.

Overall the MIC90 of isavuconazole against *Aspergillus* spp. was 2 mg/L. The activity of isavuconazole was also shown against a wide range of uncommon *Aspergillus* species. *In vitro* data determined by using the CLSI methodology showed that activity of isavuconazole against *Aspergillus* spp. was comparable to that of itraconazole, voriconazole and caspofungin. Isavuconazole was less active than posaconazole, micafungin and anidulafungin and more active than amphotericin B and flucytosine. *In vitro* data generated by using the EUCAST method also indicated that the activity of isavuconazole against *Aspergillus* species was comparable to voriconazole and that isavuconazole is less active against *Aspergillus* species than posaconazole and more active than amphotericin B. However, in this dataset, isavuconazole was less active than itraconazole. The i*n vitro* activity of isavuconazole and of comparators was investigated against CYP51A mutants with elevated MIC to at least one triazole. Increased MIC values were found for isavuconazole against mutants with mutations at L98, M220, G138, Y431, G434 and G448, but not for G54 mutations. In most cases, the activity of isavuconazole against these mutants was roughly comparable to that of voriconazole. The mutation L98 had a larger impact on isavuconazole MIC than on voriconazole MIC.

The MIC values against Mucorales genera were considerably higher than those against *Aspergillus* spp (MIC90 for *Lichtheimia* spp. 8 mg/L, *Cunninghamella* spp. 32 mg/L, *Mucor* spp. 16 mg/L, *Rhizomucor* spp 4 mg/L and *Rhizopus* 8 mg/L). Isavuconazole was less active than itraconazole (except for *Rhizopus* spp. against which activity was comparable), posaconazole and amphotericin B against Mucorales.

The MIC90 of isavuconazole against Candida spp. was 0.5 mg/L, with the highest activity against *C. albicans* (MIC90 0.03 mg/L), *C. parapsilosis* (MIC90 0.06 mg/L) and *C. tropicalis* (MIC90 0.06 mg/L) and slightly lower activity against *C. krusei* (MIC90 0.5 mg/L), *C. glabrata* (MIC90 2 mg/L), and *C. guilliermondii* (MIC90 1 mg/L). Overall, the *in vitro* activity of isavuconazole against *Candida* was approximately comparable to that of other azoles. Against fluconazole-resistant Candida isolates, the MICs of isavuconazole were increased compared to those of voriconazole and posaconazole. MICs of isavuconazole were increased by the expression of CDR multidrug efflux transporter genes and by mutations in ERG11, as were MICs of other

azoles. MICs of isavuconazole were not affected by MDR1 or FLU1 transporters. Overall, the activity of isavuconazole against fluconazole-resistant *Candida* isolates was comparable to that of other azoles.

For *Cryptococcus* spp, no MIC data determined by the EUCAST methodology were available. Based on data obtained using the CLSI methodology, the MIC90 of isavuconazole against *Cryptococcus* spp was 0.06 – 0.12 mg/L (comparable to that of itraconazole, posaconazole and voriconazole).

Isavuconazole was active against various other moulds and yeasts *in vitro* (data obtained using the CLSI methodology). *Fusarium* spp and *Scedosporium* spp were not susceptible (MIC90 was 32 mg/L).

Oral isavuconazole was effective against *A. fumigatus* and *A. flavus* in several systemic and pulmonary aspergillosis *in vivo* mouse models. Isavuconazole was not active in one pulmonary mouse model in which isavuconazonium was administered subcutaneously, most likely because isavuconazonium is not tolerated when administered subcutaneously. Isavuconazole was not effective in guinea pigs, which could be explained either by a too low systemic exposure or by the occurrence of acute toxicity.

In neutropenic mice infected intravenously with *A. flavus*, the tissue burden after 3 days of treatment starting 24 h post-infection was comparable following treatment with 15 or 30 mg/kg/day oral isavuconazole or 25 mg/kg/day oral voriconazole (with grapefruit to increase exposure). Also survival and clearance of organs after 10 days of treatment starting 4 or 24 h post-infection was comparable for 15 or 30 mg/kg/day oral isavuconazole or 25 mg/kg/day oral voriconazole.

In a neutropenic rabbit pulmonary infection model (inoculated endotracheally with *A. fumigatus*), oral treatment for 12 days started post-infection with 40 and 60 mg/kg/day isavuconazole equivalents was superior to oral voriconazole at 30 mg/kg/day with respect to reduction in pulmonary fungal burden and pulmonary injury.

In an immunocompetent murine model of disseminated aspergillosis, after infection with one wild-type isolate or one of 3 mutants of *A. fumigatus*, G54W, M220I and TR34/L98H followed by 14 days oral isavuconazonium, 100% survival was achieved with 30.7 and 61.4 mg/kg/day and 122.9 mg/kg BID isavuconazole equivalents in mice infected with the wild-type isolate, with G54W mutants and with M220I mutants; 100% survival was not achieved in mice infected with TR34/L98H mutants.

In a neutropenic mice pulmonary infection model, mice were inoculated with *A. fumigatus* (4 wild-type isolates and 6 mutants with MIC 0.125 – 8 mg/L). The reduction in log10 conidial equivalents per ml lung homogenate following treatment with oral isavuconazonium correlated with AUC/MIC (R^2 = 0.75). Stasis was achieved in all isolates with MIC ≤ 1 mg/L and 1log10 kill was achieved in all isolates with MIC ≤ 0.5 mg/L. AUCtotaldrug/MIC associated with stasis was 361 – 1111 and associated with 1log10 kill 657 – 1242.

Isavuconazole was active against *Rhizopus oryzae* in a pulmonary infection model in neutropenic mice but not in diabetic ketoacidotic mice. Oral treatment with 116 mg/kg TID isavuconazole equivalents for 4-5 days was comparable to liposomal amphotericin B at 15 mg/kg/day i.v. with respect to survival and reduction of fungal load in lungs and brain.

Isavuconazole at 1.5 – 36 mg/kg (subcutaneous, single dose) significantly reduced the kidney burden of *C. albicans* in neutropenic mice. Isavuconazole at 15 – 120 mg/kg/day (oral) was effective against *C. tropicalis* in a neutropenic mice kidney burden model. Isavuconazole at 30 – 120 mg/kg/day (oral) reduced the kidney and brain burden of *C. krusei* in neutropenic mice.

In a neutropenic mouse model of disseminated candidiasis involving isolates of *C. albicans*, *C. glabrata* and *C. tropicalis*, AUC/MIC correlated best with kidney burden reduction. AUC/MIC for treatment of *C. tropicalis* and *C. glabrata* was approximately 10 times lower than for *C. albicans*.

Pharmacodynamic drug interactions

In an *in vitro* interaction study, isavuconazole in combination with amphotericin B was antagonistic against the investigated *Aspergillus* isolates in one of two applied methods and therefore this does not seem to be a suitable combination against *Aspergillus*, based on this *in vitro* study. Isavuconazole in combination with micafungin was synergistic against the investigated *Aspergillus* isolates. Micafungin alone was not active against *Aspergillus*. The combination of isavuconazole and amphotericin B was antagonistic against *R. microsporus*.

Conclusion on pharmacodynamics

Most *in vitro* data were determined using the CLSI methodology. For Mucorales, almost no *in vitro* data determined by EUCAST methodology were provided in the initial submission, MIC values against Mucorales were considerably higher than against *Aspergillus spp*, which could pose a problem for the treatment of patients. Some additional data were provided by the applicant, which were obtained by comparing EUCAST and CLSI methodology. These data showed distribution towards higher MICs especially for *Lichtheimia* and *Rhizopus* compared to the data obtained by CLSI methodology. Based on the *in vitro* data and on the clinical trough level of approximately 4 mg/l, it could be derived that the isavuconazole levels in mucormycosis patients will not always be sufficient for an adequate treatment. *In vitro* data for Mucorales are however very limited and the acceptability of isavuconazole for Mucorales infections largely depends on the clinical data.

Comparisons of susceptibility data for *Aspergillus* spp obtained by CLSI and EUCAST methods showed that the MIC data determined by the EUCAST method may be up to maximally 2 dilutions higher than the MIC data determined by the CLSI method. However, based on the data that were provided and the data in the original submission, the *in vitro* data still indicate that *Aspergillus* spp are susceptible to isavuconazole, also when these methodological differences are taken into account.

In a neutropenic mice pulmonary infection model of *Aspergillus fumigatus* infection, efficacy correlated well with AUC/MIC. Although no direct comparison was made between the three PK/PD indices, available data indicate that AUC/MIC is the most likely parameter that correlates best with efficacy.

In a pulmonary mouse model in which isavuconazonium was administered subcutaneously, isavuconazole was not effective. Isavuconazonium is not tolerated when administered subcutaneously.

2.3.3. Pharmacokinetics

Analytical methods: Plasma concentrations of isavuconazonium, isavuconazole, and BAL8728 in mice, rats, rabbits and monkeys were simultaneously analysed by LC-MS/MS. The same method was validated for isavuconazole concentrations in rat milk.

Single dose absorption and plasma pharmacokinetic characteristics: In rats and monkeys, the *in vivo* conversion of isavuconazonium by plasma esterases to isavuconazole and BAL8728 is very fast. In addition, isavuconazonium is hydrolyzed due to instability at physiological pH. In monkeys, bioavailability at very high single oral doses was < 10%, indicating saturation of absorption. The distribution volume was high in rats, monkeys and humans. Due to systemic conversion, plasma clearance of isavuconazonium is very high. Oral

absorption and bioavailability are high. After a single oral dose of isavuconazonium, plasma isavuconazole levels after reaching C_{max} are similar to those after the same dose administered intravenously. Distribution volume is high. Elimination half-life values differ between species: rat (5 h) < monkey (9.8 h) << human (110-115 h). Systemic exposure to the unchanged prodrug was very low to below quantifiable levels after the first few hours after i.v. administration or from the first sampled time point (30 min) on after an oral dose. Systemic exposure to BAL8728 was very low. This part of the molecule had much shorter elimination half-life than isavuconazole and a smaller distribution volume.

Toxicokinetics in the species used for toxicity studies: Toxicokinetic data during oral and intravenous administration in mice and rats have shown higher exposure in females as compared to males after single and repeated dosing. In monkeys, after single or repeated oral or intravenous dosing there was no evidence of a gender effect. Overall exposure to isavuconazole increased approximately dose-proportionally in all three species. Exposure to isavuconazonium was generally either below detection levels or very low. In mice, a decrease in the exposure to isavuconazole was observed during a 13 weeks oral treatment period. In rats, repeated oral treatment administered for 13 weeks resulted in an increased exposure at a low and mid dose, and in a decreasing exposure at the highest dose. Between 13 and 26 weeks, no clear change in exposure was seen. During a 2-week intravenous rat study, little change in exposure was observed. In monkeys, no change in the isavuconazole exposure was seen during the repeated oral or intravenous dosing studies. In all studies, exposure to BAL8728 was low compared to that to isavuconazonium. In the repeated dose toxicity studies, up to the highest tested doses, exposure in general was lower than or similar to that in humans at the recommended human dose, see also toxicology section.

Plasma protein binding: Plasma protein binding of isavuconazole over the concentration range of 0.2-20 µg/mL was high with small interspecies differences: 98.7%-99.1% in ICR mice, 97.3%-97.9% in Wistar rats, 97.3%-97.8% in SD rats, 96.4%-97.2% in Hartley guinea pigs, 97.3%-98.0% in Himalayan rabbits, 99.0% in Cynomolgus monkeys, and 99.2%-99.4% in humans (Caucasians). In the tested rodents, guinea pigs and rabbits, binding was slightly concentration dependent, whereas in monkeys and humans no concentration dependence was observed.

Distribution to red blood cells: Blood to plasma concentration ratios observed in rats and monkeys indicate a low red blood cell penetration of the main circulating components, in particular of isavuconazole, during the first 24 hours after administration, with blood to plasma concentration ratios predominantly in the range 0.53 to 0.75.

Tissue distribution studies: Single dose (oral and intravenous) studies were conducted in male Sprague Dawley (SD) and Long Evans rats, single dose intravenous studies in pregnant and lactating female SD rats, and repeated oral dose studies were conducted in male SD rats. The radiolabel on both of the two different labelling sites (the isavuconazole part and the BAL8728 part of the molecule) was quickly absorbed and distributed. The radiolabel in the isavuconazole part showed a wide distribution, with highest concentrations in the liver (T/P 15.2) and in the adrenal cortex (T/P 13.5). Other tissues with T/P ≥ 5(in descending order) were: small intestinal mucosa, brown fat, Harderian gland, pancreas, intra-orbital lacrimal gland, kidney cortex, adrenal medulla, stomach mucosa, and the thyroid. It was also high in bile and urine (bile >> urine). The radiolabel in the BAL8728 part showed lower concentrations than the isavuconazole part. A wide distribution was shown, with the highest concentrations noted in the parodontium (T/P>10), kidney (T/P 2.5) and liver (T/P 1.5). It was also high in urine. Disappearance from tissues was fast. Both radiolabels cross the brain blood barrier. In an oral single dose rat study with unlabelled prodrug, isavuconazole exposure of brain was slightly less than twice that in plasma. There was no evidence of a specific affinity for melanin containing tissues. After repeated oral dose in rats of prodrug labelled in the isavuconazole part, maximum plasma and

tissue concentrations increased from day 1 to 21 (with about a factor of 2), while AUC values for liver and adrenal cortex increased with a factor 3.6 and 8.

Passage of the placenta was shown: after a low single intravenous dose or radiolabelled isavuconazonium in pregnant rats (GD14 and GD19) fetal isavuconazole-related radioactivity was similar to maternal plasma and BAL8728-related radioactivity in foetuses was lower than maternal plasma. Transfer to the rat milk was shown on LD14 after a single intravenous dose (5 mg/kg) and isavuconazole related radioactivity showed concentrations in milk higher than in the maternal plasma. Looking at the BAL8728-related radioactivity, the concentration in milk was this time lower than that in the maternal plasma. Both labels were present at very low concentrations (up to non-detectable) in blood and tissues of pups of the treated dams on LD14. In a pre- and post-natal rat development study with non-labelled oral doses, milk to plasma ratios of mean concentrations 4 h post-dose (lactation day 16) increased from 3 at the lowest dose to 7 at the high dose (plasma concentration high dose: 4060 ng/mL). The highest individual milk to plasma ratio was 17.

Conversion to active drug and inactive moiety: Isavuconazonium was quantitatively converted to the active moiety, isavuconazole, with a $t_{1/2}$ < 2 min *in vitro,* in rat, rabbit, Cynomolgus monkey, and in the human plasma. This rate of conversion was found for both diastereomers in rat, Cynomolgus monkey, and human plasma. In contrast, isavuconazonium was minimally (less than 20% in 5 min) converted in dog plasma. The use of an esterase inhibitor led to the inhibition of the conversion in rat, Cynomolgus monkey, and human plasma, suggesting the involvement of plasma esterases. *In vivo*, t_{max} of isavuconazole and BAL8728 after intravenous administration to rats and monkeys was 5 min. At physiological pH, isavuconazonium is also hydrolysed due to instability at this pH. It is plausible that after oral administration enzymatic as well non-enzymatic conversion (due to high intestinal pH) in the intestine, intestinal wall, and liver play a role in the conversion process.

In vitro biotransformation of isavuconazole and isavuconazonium by liver microsomes/hepatocytes: Liver microsomes formed mono-oxidised (rat, monkey, human, rabbit: two isomers: epoxides and/or -OH metabolites) and di-oxidised (rabbit: di-OH) metabolites. Rat hepatocytes formed glutathion-, cystein- and N-acetylcystein- conjugates of defluorinated mono-oxidised isavuconazole. All metabolites observed in incubations with human microsomes and hepatocytes were also observed with rat and monkey microsomes and hepatocytes. The rate and extensiveness of biotransformation in rats was higher than in monkeys and humans. Rabbit microsomes formed higher amounts of oxidation products than the other species. Little metabolism was found with dog microsomes. In all these test systems the amounts of metabolites were only minor compared to isavuconazole. Microsomal incubations of the pro-drug isavuconazonium resulted in the same metabolites but at lower quantities.

In vivo biotransformation: Plasma, urine, bile or faeces samples from rats, Cynomolgus monkeys, and humans following intravenous or oral administration of [cyano-^{14}C] isavuconazonium or [pyridinylmethyl-^{14}C] isavuconazonium were used to identify metabolites. Chemical structures of a total of 77 metabolites were estimated based on various analytical methods, most of these metabolites occurred only in small quantities. In rats, after single intravenous or oral administration of radiolabelled isavuconazonium sulfate, M7 (carboxylic acid form of destriazole isavuconazole) and M4 (oxidative carbamate cleavage metabolite of BAL8728) were the most abundant components in plasma in addition to the primary cleavage products and lower concentrations of a number of other identified and unidentified components.

In Cynomolgus monkeys, after single intravenous or oral administration of radiolabelled isavuconazonium sulfate, isavuconazole and M4 were the main detected components. Lower amounts of M61 (O-glucuronide of isavuconazole) and M1 (hydroxylated isavuconazole carbamoyl form) and BAL8728 (only after intravenous

administration) were found, and lower concentrations of a number of other identified and unidentified components.

*Metabolic pathway of isavuconazonium in rats and Cynomolgus monkeys: The m*ajor metabolic pathways of isavuconazonium in rats and in Cynomolgus monkeys were the cleavage of isavuconazonium, followed by generation of isavuconazole and BAL8728 (M5). After the thiazole ring of isavuconazole was cleaved, metabolites were formed by oxidation and subsequent glucuronidation, acetylcysteine conjugation, hydrolysis of cyano group, oxidation of the carbamoyl form in rats and Cynomolgus monkeys. Isavuconazole was also metabolized by oxidation and subsequent glucuronidation or glutathione conjugation, and then cysteinylglycine conjugation through hydrolysis in rats, and by glucuronidation, oxidation and subsequent glucuronidation, hydrolysis of cyano group, oxidation of the carbamoyl form or cysteinylglycine conjugation, and then cysteine conjugation through hydrolysis in Cynomolgus monkeys. The carbamate group of BAL8728 was cleaved and metabolized by oxidation or glucuronide conjugation in rats and Cynomolgus monkeys. BAL8728 was also metabolized by glutathione conjugation, and then cysteine conjugation through hydrolysis in rats, and by cysteine and acetylcysteine conjugations in Cynomolgus monkeys.

Comparison to humans: Overall, the biotransformation pathways in rats, monkeys and humans are similar, with limited contribution of metabolites to overall drug-related exposure. There were no human metabolites occurring at ≥ 10% of the overall radioactivity. Therefore, with regard to biotransformation and exposure to metabolites, rat and monkey can be considered sufficiently similar to humans.

Liver enzyme induction: Liver enzyme induction was studied in SD rats and in Cynomolgus monkeys which received a 2-h continuous infusion of isavuconazonium chloride (0, 10, 30, 60 mg/kg/day) for 2 weeks. Induction of testosterone 2β- and 6β-hydroxylase activities (CYP3A markers) and testosterone 16β-hydroxylase activity (CYP2B marker) was observed in female (but not in male) rats. In monkeys, induction of total P450 concentration, p-nitroanisole O-demethylase activity and testosterone 16β-hydroxylase activity (CYP2B marker) was observed without a clear gender difference. These changes almost recovered to control levels after a 4-week recovery period.

Excretion: In both rats and monkeys, the excretion route of isavuconazole-related and BAL8728-related radioactivity was hardly or not affected by the administration route (oral vs intravenous). In the rat excretion of isavuconazole (active moiety)-related radioactivity was predominantly faecal (81% vs in 16-20 % in urine), whereas in the monkey the difference between faecal (55-58%) and urinary (38-43%) excretion was much smaller. Excretion of BAL8728-related radioactivity did not differ between rats and monkeys, and was predominantly urinary (84-90%), with smaller amounts in faeces (7-11%). Studies in bile duct-cannulated rats and monkeys showed that biliary excretion of isavuconazole-related radioactivity after intravenous administration was similar (rats 81-88 %, monkeys 56%) to faecal excretion in intact animals, however biliary excretion of BAL8728-related radioactivity was higher (rats 19 - 35 %, monkeys 18 %) than faecal excretion in intact animals, concomitant with lower urinary excretion (rat 64%, monkey 81%) than in intact animals. These data suggest that in intact animals, part of the excreted BAL8728-related biliary radioactivity is reabsorbed and subsequently excreted in urine. Enterohepatic circulation of constituents derived from both parts of the isavuconazonium sulfate molecule was confirmed in enterohepatic circulation studies in rats. The main excretion route of the reabsorbed material was the same as for the initially absorbed radioactivity: predominantly biliary for isavuconazole related radioactivity and predominantly urinary for reabsorbed BAL8728-related radioactivity.

2.3.4. Toxicology

Single dose toxicity

Single dose oral and intravenous administration studies with isavuconazonium were conducted in rats and Cynomolgus monkeys.

In both species, adverse effects included neurological effects (decrease of spontaneous activity, prone position, staggering gait, jumping) and effects on the respiratory system (laboured respiration, cyanosis) at approximately 15 minutes after dosing. These effects are consistent with toxicities expected for triazole antifungal agents.

Maximal non-lethal doses were 500 mg/kg in rats and 1000 mg/kg in monkeys after oral administration. After intravenous administration in rats, these values were 5 mg/kg at an infusion rate of 1 ml/min and 20 mg/kg at an infusion rate of 0.1 ml/min. In monkeys, maximum non-toxic doses were 32 mg/kg after a single, intravenous bolus injection and 90 mg/kg after 2-h intravenous infusion. The slightly higher toxicity at a faster intravenous administration suggests that this compound should not be too rapidly infused clinically.

Toxicokinetics after single dose administration have only been performed in monkeys. These data showed that Cmax values for isavuconazole at the maximal oral non-lethal dose of 1000 mg/kg (≈ 18600 ng/ml) were in the same range as the measured Cmax value in human at the starting dose of 600 mg (≈ 20028 ng/ml). After i.v. bolus and i.v. infusion, these Cmax values were in the same range.

Higher dose levels induced death preceded by liver dysfunction and/or hepatic injury (such as increased plasma levels of ALT, AST, creatinine, and decreased levels of protein, albumin and cholesterol) and disturbance of serum electrolytes (sodium, potassium, inorganic phosphorus, calcium). Animals that escaped death smoothly recovered to the normal condition.

All these suggest a steep dose-response curve for the lethal and toxic effects of isavuconazole. The relevance of this finding for humans is not clear.

Repeat dose toxicity

Oral studies

Repeated dose toxicity after oral administration was studied in mice (up to 13 weeks), rats (up to 26 weeks), and Cynomolgus monkeys (up to 39 weeks) at exposures of isavuconazole up to 1.2-fold, 0.5-fold and 0.8-fold, respectively, when compared to human exposure at the maintenance dose of 200 mg per day. Adverse effects included dose-related effects on the liver (mice, rats, monkeys), adrenals (monkeys), thyroid (rats) and adverse effects on the CNS and respiratory system (mice). These effects were consistent with toxicities expected for triazole antifungal agents and showed evidence of reversibility following a recovery period.

In mice, there was induction of centrilobular hepatocellular hypertrophy, a higher incidence of hepatocellular vacuolation and increased liver weight. These effects are common histological changes associated with the induction of drug metabolizing enzymes in animals. Elevated alanine aminotransferase levels were observed in high dose females. The lower cholesterol levels in high dose males and females were attributed to adverse effects on the liver and reduced general condition, respectively. In the high dose group, there were transient signs of respiratory distress and/or impaired general condition. Sustained effects on the CNS or respiratory system were not seen at non-lethal doses.

In rats, mortality, adverse effects on the nervous and respiratory system were not observed in the tested dose range (up to 0.5-fold of the human exposure). The increased liver weight and centrilobular hypertrophy

were not accompanied by increases of liver enzymes in plasma, suggesting that liver injury did not occur at these low exposures. A new finding in rats was that the thyroid was enlarged with minimal to slight follicular thyroid cell hypertrophy/hyperplasia. This effect may be caused by an accelerated thyroxine catabolism in the liver, secondary to liver enzyme induction. Rats are particularly sensitive to changes in thyroxine and T4 in plasma, as their blood contains no thyroxin-binding globulin, in contrast to most other mammals, including humans. The thyroid findings in rats are unlikely to be relevant for human.

There were minimal increases in adrenal weights, but, in the tested dose range, there were no associated morphological changes at microscopic examination. Effects on the adrenals are well-known for triazole antifungal agents. Compounds of this class inhibit the activity of several enzymes necessary for the conversion of cholesterol to steroid hormones and glucocorticoids.

In the 26-week study in rats, changes in the pancreas, consisting of minimal to slight islet fibrosis, minimal to slight yellowish pigment-loaded macrophages and minimal islet cell inflammation, were observed in males. The applicant commented that these changes were not related to the test item, but that this was rather a chance finding. The provided argumentation was considered reasonable by the CHMP. Although these changes were not found in the study controls, they were present in the controls at the end of the treatment-free period with a similar incidence as in the high dose group at the end of the treatment period (50% vs. 56%). Acute pancreatitis is discussed in the Risk Management Plan as a class effect of this type of antifungal agents.

In the 26-week oral rat study with the sulfate salt of BAL8557 (study 9766-TX-0016) thyroid findings were seen at 90 mg/kg/day in both males and females that consisted of minimal to slight follicular cell hypertrophy/hyperplasia. These findings were considered to be adaptive. In the final study report it is stated that these findings were no longer present after an additional 4-week treatment-free period, except for persistence of pre-neoplastic lesions (focal hyperplasia) in the thyroids of 2/6 recovery animals at 90 mg/kg, suggesting a potentially increased incidence of proliferative lesions (focal hyperplasia) in the thyroid after prolonged duration of treatment of rats at 90 mg/kg/day. This effect is considered to be the result of prolonged hyperstimulation of the thyroid gland as a consequence of drug-related liver enzyme induction. These effects are commonly reversible; however, as the recovery period was short, recovery was not seen. As already mentioned, the rat is sensitive to the stimulation of TSH due to the absence of circulating thyroxin-binding globulin.

In monkeys, adverse effects in the tested dose range were focused on increased liver and adrenal weight and slightly increased heart weight (up to 0.5-fold of the human exposure).

In the four weeks study, mortality and severe toxicity occurred at exposures which were in the same range as that in human at the starting dose of 600 mg. This was also found in the single dose toxicity study in monkeys.

The increased liver weight was slight and was identified as hepatocellular hypertrophy related to enzyme induction.

The increased adrenal weights correlated with enlarged adrenals and slight vacuolation/hypertrophy of the adrenocortical cells. Atrophic or necrotic lesions were not observed. These adrenal changes are well-known effects of triazole antifungal agents (including voriconazole and fluconazole) and are thought to result from inhibition of CYP enzymes and steroidogenesis. There were no effects in other organs or effects or changes in cholesterol levels in plasma that could point to an effect on steroid biosynthesis or cholesterol metabolism.

There was a slight increase in the heart weight and this was only observed in males of the 39-week study. There were no histopathological findings. The uncorrected mean QT-interval was minimally but significantly prolonged in week 26, but remained within the physiological range after correction for the slightly lower heart rates when compared with controls. However, isavuconazole inhibited the L-type calcium channel (hCav1.2) with an IC50 of 6.57 µM (38-fold the human non-protein bound Cmax at the clinical maintenance dose of 200 mg/day) (see section safety pharmacology, study 9766-PT-0003). This ion channel finding is consistent with the QTcF interval shortening reported in the clinical thorough QT study (clinical assessment report on safety pharmacology). Triazole antifungal agents, such as voriconazole and fluconazole, have been associated with QT-interval prolongation.

Intravenous studies

The intravenous repeat-dose toxicity studies were conducted up to 6 weeks in rats and in Cynomolgus monkeys. In the 6-week study in rats, the maximal exposures of isavuconazole were 0.02-fold when compared to human exposure at the maintenance dose of 200 mg. In the 6-weeks study in monkeys, this exposure multiple is 0.73-fold. With these exposure multiples, only the exposure to isavuconazole in the 6 week study in monkeys is in the same range as compared to that in the oral repeated-dose toxicity studies in this species.

In the 6-weeks studies, the NOAEL in rats and monkeys was 10 mg/kg/day based on irritation and intolerance at the infusion site, which in part could in part be reduced by reducing the rate of infusion. At higher doses, the toxicity profile and the target organs of toxicity were basically similar to that observed after oral administration. The low exposure in rats, could explain that effects were limited to the slight effects on the liver.

In rats, the infusion site reaction consisted of local swelling and irritation. In monkeys, it consisted of a moderate/marked inflammation, accompanied by an increase of white blood cells, neutrophils and platelets in blood and a decrease of bone marrow cellularity. In addition, in monkeys, there was a reduction in thymus weight, but there were no remarkable pathology changes. An immunotoxic effect seems not likely there were no alterations in immune system organ weights and/or histology in the oral and intravenous repeated dose toxicity studies.

In monkeys, new findings in the 2-weeks i.v. study included dose-related increased weights of testes, epididymides and seminal vesicles at 0.9-fold and a reduction in uterus weight at 1.9-fold of the human exposures at the maintenance dose of 200 mg/day. These effects could be related to the inhibitory potential of isavuconazole on the synthesis of steroids. These effects were not observed in the 6-weeks i.v. study in in the tested dose range, i.e. up to 0.73-fold of the human exposures at the maintenance dose of 200 mg/day. In addition, there was an increase in thyroid weight, but this effect seems to be incidental finding since it the increase was slight and only observed the high dose males in the 2-week study.

Intravenous administration of the inactive cleavage product BAL8728 for 2 weeks to rats showed no remarkable findings. This suggests that that the toxic effects observed with isavuconazonium were due to isavuconazole and not to the inactive cleavage product BAL8728.

Genotoxicity

Isavuconazonium showed no genotoxic potential. It was non-mutagenic in *in vitro* mutation tests in bacteria (Ames test). In the mouse lymphoma cell thymidine kinase assay for chromosomal aberrations, isavuconazonium showed marginal increases in mutant colonies. The findings were considered as cytotoxicity-related variability and did not indicate a biologically relevant genotoxic activity.

The *in vivo* data indirectly support the view that the inactive cleavage product BAL8728 also had no detectable genotoxic potential. This conclusion was further supported by the fact that the structure of the inactive cleavage product BAL8728 had no genotoxic alerts by DEREK analysis.

Since the active moiety, isavuconazole, contains an azole ring that has been associated with genotoxic potential, an additional bacterial reverse mutation test and an *in vitro* micronucleus test were performed only on the active moiety. The results showed no concerns.

Carcinogenicity

Carcinogenicity studies have not been conducted. Nevertheless, it was acknowledged that in some patients, treatment could be continued beyond 6 months. Since for medicinal products aimed for long-term treatment, carcinogenicity studies are required, CHMP requested the applicant to perform the carcinogenicity testing of isavuconazonium in mice and rats, according to ICH guidelines and to submit the results of these studies by the end of July 2019.

Reproduction Toxicity

In pregnant rats, [cyano-^{14}C]-isavuconazonium-derived material passed the placental barrier and was transferred to the foetus (see also section on pharmacokinetics).

The reproduction toxicity studies showed that isavuconazonium, as a member of the triazole class of antifungal agents, has the potential to adversely affect the embryo-foetal development. For this reason, Cresemba must not be used during pregnancy, except in patients with severe or potentially life-threatening fungal infections, in whom isavuconazole may be used if the anticipated benefits outweigh the possible risks to the foetus. Cresemba is not recommended in women of childbearing potential not using contraception.

The segment I study in rats showed no effect on male and female fertility. However, although not observed in rats, there was a dose-related increased weights of testes, epididymides and seminal vesicles and a reduction in uterus weight in a 2-weeks, i.v. repeated dose toxicity study in monkeys at exposures obtained in human at the therapeutic range of 200 mg per day (study nr 9766-TX-0011 [study nr 9777-ME-007 for toxicokinetics]). The relevance of this finding for human male and female fertility is unknown. Nevertheless, CHMP noted that there were relevant data (non-human primate and rat) that superseded the 2 week non-human primate data, in which these effects were not seen.

The segment II studies in rats showed skeletal abnormalities at maternal systemic exposures of 30 mg/kg/day (0.2-fold the human systemic exposure at the maintenance dose of 200 mg/day). These abnormalities consisted of fusions of the zygomatic arch, unilateral and bilateral rudimentary cervical ribs, and additional ossification of the fourth lumbar vertebral arch. The results of a segment II study in rats did not point to adverse effects of the inactive cleavage product BAL8728 on embryo-foetal development.

The segment II study in rabbits showed a visceral variation, including an additional artery arising from the aortic arch and skeletal abnormalities, including rudimentary cervical ribs were reported at exposures of 0.1-fold the human systemic exposure at the maintenance dose of 200 mg/day. The findings were not associated with maternal toxicity.

The segment III study in rats showed post-natal loss in the high dose group was increased (0.5-fold the human systemic exposure at the maintenance dose of 200 mg/day). Many of the dead pups had no milk in their stomachs. In the surviving pups from the high dose group as well as pups in the mid and low dose groups, the physical development, behavioural tests, and reproductive capacity was not affected by *in utero* and peri-/postnatal exposure to isavuconazole.

Toxicokinetics showed that the concentrations of isavuconazole in rat milk exceeded the plasma concentrations by up to 17-fold. There are no human data. For this reason, breast-feeding should be discontinued during treatment with isavuconazonium.

Local Tolerance

Studies in rabbits on local tolerance did not raise any concern. Minimal eye irritation and clear vascular permeability were observed at 5 mg/ml and slight skin irritation at 10 mg/ml. These concentrations are sufficient above the proposed clinical concentration of 1.5 mg/ml isavuconazonium as concentrate for solution for infusion (corresponding to approximately 0.8 mg/ml isavuconazole).

A haemolytic potential was identified at concentrations of 1 mg/ml and higher. This means that at the estimated Cmax values in humans (20 µg/ml at the starting dose of 600 mg/day and 7.5 µg/ml at the maintenance dose of 200 mg/day), there is clinically little or no haemolytic potential.

Other toxicity studies

Juvenile toxicity

A dose-range-finding study and a pivotal study in juvenile rats are currently ongoing.

Phototoxicity

It is considered unlikely that the exposure to isavuconazonium and isavuconazole could lead to a phototoxic effect. Both compounds have a similar absorption spectrum and a similar molar extinction coefficient in the UV wavelength range of 250 to 320 nm. Thus, it seems that the UV absorption spectrum of isavuconazonium is largely determined by the isavuconazole structure of isavuconazonium. The results of the phototoxicity test in 3T3 fibroblasts showed that that this compound had no phototoxic potential. In aqueous solution, isavuconazonium was hydrolysed to isavuconazole. This hydrolysis occured very quickly in plasma and was caused by plasma esterases.

Immunotoxicity

Immunotoxicity studies have not been conducted. This is considered acceptable by CHMP, since the results of the repeat-dose toxicity studies did not indicate significant effects on organs of the immune system.

Antigenicity

Isavuconazonium showed no discernible antigenic potential in the guinea pig active systemic anaphylaxis assay and the passive cutaneous anaphylaxis assay. However, isavuconazonium showed skin sensitization potential in the more sensitive mouse local lymph node assay (LLNA). For this reason, hypersensitivity is included in the RMP.

Metabolites

The provided data did not point to a toxic effect of the pharmacologically inactive cleavage product BAL8728. The toxicity of other metabolites has not been studied. This was considered acceptable by CHMP. The

nonclinical characterization of a human metabolite is only warranted when that metabolite is observed at exposures greater than 10% of total drug-related exposure and at significantly greater levels in humans than the maximum exposure seen in the toxicity studies (EMA/CPMP/ICH/286/1995).

Impurities

Twelve identified impurities may occur in the drug substance at NMT ≥0.15%. The safety of these impurities has been evaluated by their presence in the batches used in the repeated-dose and reproduction toxicity studies. These impurities have also been evaluated for genotoxic potential. BAL19714 showed an alert for genotoxicity by DEREK analysis. It was positive in a bacterial reverse mutation assay (Ames II test) with the positive response being more prominent in the absence than in presence of metabolic activation. The proposed limit of 100 ppm of this impurity in the drug substance is agreed by CHMP, following the approach of the ICH guideline M7 on mutagenic impurities (EMA/CHMP/ICH/83812/2013), At the proposed maintenance dose of 372.6 mg isavuconazonium sulfate per day (≈ 200 mg isavocunazole), the limit of 100 ppm would lead to a daily intake of 37 µg of this impurity. This intake is lower than the calculated acceptable intakes of 200 µg of a genotoxic impurity if the treatment is administered no longer than 6 months and 100 µg if administered no longer than 12 months.

A mutagenic potential was also identified for BAL17699 and BAL17478. These compound are limit controlled to <1 ppm and, as such would result in administration of less than the threshold for concern (TTC) level of 1.5 µg/day.

The impurities BAL20019, BAL30655, BAL19875 and BAL20027 showed no structural alert for mutagenicity in DEREK analyses. Based on this information, it is concluded that these impurities can be considered to be non-mutagenic (class 5).

The impurity BAL8728 is identical to metabolite M5, which generated by the cleavage of isavuconazonium by plasma esterases to isavuconazole. This impurity had no genotoxic alerts in the DEREK analysis.

The impurities BAL30145, BAL31265 and BAL4815 are qualified by the toxicity studies impurity profile of toxicological batches used in the repeated-dose and reproduction toxicity studies.

Other impurities in the drug substance include BAL16173 and BAL17702, which are starting materials, and the drug substance impurities BAL19715 (chloromethyl-pyridine impurity of BAL8557), BAL31264, BAL31265, diisopropylurea and 2-butenal. The proposed limits of these impurities in the drug substance have been adequately justified and were agreed by CHMP.

2.3.5. Ecotoxicity/environmental risk assessment

It could not be concluded whether isavuconazole is a PBT and/or vPvB substance.

Considering the available data on the environmental risk assessment, CHMP agreed that isavuconazole is not expected to pose a risk to the groundwater compartment and the sewage treatment plant.

Nevertheless, a risk to the surface water compartment and sediment could not be excluded.

The applicant proposed to conduct an algal toxicity test (OECD 201) and a sediment toxicity study (OECD 218) post-approval, and to update the ERA with the results of these studies. However, CHMP requested the applicant to use the total residue approach (resulting in a DOSEai of 384.8 mg/inh/day) when the ERA is when the ERA is updated. In addition, submitted peer review data on incidence in France and Austria were

considered by CHMP as not acceptable as a replacement of the AMR database, since these data cover only two member states and do not invalidate the data from the AMR database. CHMP agreed to request the applicant to use the data from the AMR database when updating the ERA.

The revised environmental risk assessment and the above mentioned study results should be submitted for assessment no later than end of August 2016.

Table 1 Environmental endpoints

Substance (INN/Invented Name): isavuconazole (BAL4815/Cresemba)			
CAS-number (if available): 946075-13-4 (Isavuconazonium sulfate)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log K_{ow} 3.84 (pH 7.2) log K_{ow} 3.89 (pH 7.6-7.7) log K_{ow} 3.86 (pH 6.8-6.9)	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.9	not B
Persistence	ready biodegradability	not readily biodegradable	
	DegT50	$DT_{50, water}$ = 3.3 and 4.4 d $DT_{50, sediment}$ = 222 and 32.8 d $DT_{50, whole\ system}$ = 204 and 32.8 d	DT50 values at 20°C Conclusion: vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	PM	PM
	CMR	not investigated	potentially T
PBT-statement :	It cannot be concluded if isavuconazole is a PBT and/or vPvB substance		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, refined	0.0394	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 2180 L/kg (sludge) K_{oc} = 2660 L/kg (sludge) K_{oc} = 5600 L/kg (soil) K_{oc} = 4700 L/kg (soil) K_{oc} = 3400 L/kg (soil)	List all values
Ready Biodegradability Test	OECD 301 B	not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 3.3 and 4.4 d $DT_{50, sediment}$ = 222 and 32.8 d $DT_{50, whole\ system}$ = 204 and 32.8 d % shifting to sediment = 70% within 7 days and then stabilised until 60 days after which it slightly decreased to 57% after 100 days; 47% after 7 days and then	DT50 values at 20°C; Significant shifting to sediment observed.

		decreased to 9% at the end.			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD 201	NOEC	PM	µg/L	PM
Daphnia sp. Reproduction Test	OECD 211	NOEC	100	µg/L	growth
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	110	µg/L	Growth, survival, hatching
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	>100	µg/L	Loading rate

2.3.6. Discussion on non-clinical aspects

The applicant was requested by CHMP and has agreed to perform after registration the carcinogenicity testing of isavuconazonium in mice and rats, according to the ICH guidelines.

Considering the Environmental Risk Assessment, isavuconazole is not expected to pose a risk to the groundwater compartment and the sewage treatment plant. Nevertheless, CHMP agreed that the ERA part of the dossier was not complete. The applicant proposed to conduct an algal toxicity test (OECD 201) and a sediment toxicity study (OECD 218) post-approval, and to update the ERA with the results of these studies.

However, CHMP required that when the ERA is updated, the total residue approach (resulting in a DOSEai of 384.8 mg/inh/day) should be used by the Applicant. Besides, the peer review data on incidence in France and Austria are not acceptable as a replacement of the AMR database, since these data cover only two member states and do not invalidate the data from the AMR database. Thus, CHMP agreed to request the applicant to use the data from the AMR database when updating their ERA.

The revised risk assessment and study results should be submitted no later than end of August 2016.

2.3.7. Conclusion on the non-clinical aspects

From a nonclinical point of view, CHMP agreed that a marketing authorization can be granted.

The CHMP considers the following measures necessary to address the remaining non-clinical missing data, which can be solved post-approval:

- The remaining concern on the environmental risk assessment (ERA): the algal toxicity test (OECD 201) and a sediment toxicity study (OECD 218) will be conducted the ERA will be updated with the results of these studies. For this update the applicant should use the total residue approach (resulting in a DOSEai of 384.8 mg/inh/day) and the data from the AMR database should. The revised ERA and the results of the above mentioned studies should be submitted for no later than end of August 2016.
- The remaining concern on carcinogenicity: the applicant is requested to perform the carcinogenicity testing of isavuconazonium in mice and rats according to ICH guidelines and to submit the results of these studies no later than the end of July 2019.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant 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.

- **Tabular overview of clinical studies**

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Mass Balance Studies								
PK	9766-CL-0016	Evaluate the PK of [cyano-^{14}C]BAL8557 including routes of excretion and extent of metabolism, identify metabolic profile of BAL4815 in plasma, urine and/or feces, and evaluate safety/tolerability	Phase 1, open-label, one-period, single-dose, mass balance study	radiolabeled BAL8557: 200 mg administered po	7	Healthy male volunteers	Single dose, study release on days 22-29	Completed ; Full
PK	9766-CL-0050	Evaluate the PK of [^{14}C]BAL8728 and BAL4815 including routes of excretion and extent of metabolism, identify metabolic profile of BAL8728 in plasma, urine and/or feces, and evaluate safety/tolerability	Phase 1, open-label, one-period, single-dose, mass balance study	radiolabeled BAL8557: 200 mg administered iv, 1 hour infusion	6	Healthy male volunteers	Single dose, study release on days 4-9	Completed ; Full
Biopharmaceutic Studies								
BA	WSA-CP-010 (9766-CL-0010)/ Germany	BA, safety/tolerability	Phase 1, randomized, open-label, 2-treatment crossover study	IZs, equivalent to ISA: 400 mg oral capsule; fasted IZs, equivalent to ISA: 400 mg iv over 2 hr; fasted	14	Healthy male volunteers	Single dose each treatment followed by a 42-day washout period between crossover	Completed ; Full

Table continued on next page

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Biopharmaceutic Studies continued								
BA, FE	9766-CL-0013 (BAP00582) / Switzerland	PK, FE, BA (Isavuconazole hydrochloride capsules or liquid concentrate) and safety/tolerability	Phase 1, randomized, open-label, parallel-group study	ISA HCL: 400 mg; fasted; oral capsule ISA HCL: 400 mg; fed; oral capsule ISA HCL: 400 mg; fasted; liquid concentrate (oral) ISA HCL: 400 mg fed; liquid concentrate (oral)	Capsule fasted: 6 Capsule fed: 6 Liquid concentrate fasted: 7 Liquid concentrate fed: 5	Healthy male volunteers	Single dose	Completed ; Full
FE	WSA-CP-019 (9766-CL-0015)/ Germany	FE, PK, safety/tolerability	Phase 1, randomized, open-label, 2-treatment crossover study	IZs, equivalent to ISA: 400 mg oral capsule; fed - fasted or fasted - fed	26	Healthy male volunteers	Single dose each crossover period, 42-day washout between treatments	Completed ; Full
Human Pharmacokinetic Studies (SAD and MAD)								
PK	WSA-CP-001 (9766-CL-0001)/ Switzerland	PK, safety/tolerability, SAD	Phase 1, randomized, double-blind, placebo-controlled, single ascending dose study	IZc, equivalent to ISA, or Placebo: 100, 200 or 400 mg; oral capsule; fasted	IZc: 15 Placebo: 8	Healthy male volunteers	Single dose	Completed ; Full
PK	WSA-CP-002 (9766-CL-0002)/ Germany	PK, safety/tolerability, SAD	Phase 1, randomized, double-blind, placebo-controlled, single ascending dose study	IZc, equivalent to ISA, or Placebo: 40, 80 or 160 mg; iv (1-h infusion); fed	IZc: 18 Placebo: 6	Healthy male volunteers	Single dose	Completed ; Full

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Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Human Pharmacokinetic Studies (SAD and MAD) continued								
PK	WSA-CP-003 (9766-CL-0003)/ Germany	PK, 24-hr urinary ratio of 6-beta-hydroxycortisol/cortisol over time and safety/tolerability, MAD	Phase 1, randomized, double-blind, placebo-controlled, multiple ascending dose study	IZc, equivalent to ISA, or Placebo: 200 mg loading dose plus 100 mg maintenance dose (qd) or 100 mg loading dose plus 50 mg maintenance dose (qd) oral capsule; fasted IZc, equivalent to ISA, or Placebo: 200 mg loading dose plus 100 mg maintenance dose (qd) or 100 mg loading dose plus 50 mg maintenance dose (qd); iv (1-h infusion); fasted	IZc (po): 12 IZc (iv): 12 Placebo (po): 4 Placebo (iv): 4	Healthy male volunteers	IZc capsule (qd) for 21 days (days 1 to 21) or iv for 14 days (days 1 to 14)	Completed; Full
Human Pharmacokinetic Studies (Special Populations - Intrinsic Factors)								
PK	9766-CL-0041/ US	PK, safety/tolerability by age and sex	Phase 1, open-label, single-dose, parallel group study	IZs, equivalent to ISA: 200 mg oral capsule	48 Non-elderly: 24 (M 12, F 12) Elderly: 24 (M 12, F 12)	Healthy non-elderly and elderly male and female volunteers	Single dose	Completed; Full
PK	WSA-CP-008 (9766-CL-0008)/ Hungary	PK and safety/tolerability in hepatic impairment (oral vs iv), and metabolism of lidocaine to MEGX	Phase 1, open-label, single-dose, parallel group study	IZs, equivalent to ISA: 100 mg oral capsule IZs, equivalent to ISA: 100 mg iv over 2 h Lidocaine hydrochloride : 1 mg/kg (iv) (3-min infusion)	48 (16 healthy, 16 mild and 16 moderate hepatic impairment)	Healthy male and female volunteers and subjects with mild to moderate hepatic impairment due to liver cirrhosis caused by alcohol abuse	Single dose	Completed; Full

Table continued on next page

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Human Pharmacokinetic Studies (Special Populations - Intrinsic Factors) continued								
PK	WSA-CP-018 (9766-CL-0014)/Ukraine	PK and safety/tolerability in hepatic impairment (oral vs iv) and metabolism of lidocaine to MEGX	Phase 1, open-label, single-dose, parallel group study	IZs, equivalent to ISA: 100 mg oral capsule IZs, equivalent to ISA: 100 mg iv (2-h infusion Lidocaine hydrochloride 1 mg/kg iv (3-min infusion)	48 Healthy: 16 Subjects with mild liver cirrhosis: 16 Subjects with moderate liver cirrhosis: 16	Healthy volunteers and subjects with mild to moderate hepatic impairment due to liver cirrhosis caused by chronic hepatitis B and/or C	Single dose	Completed; Full
PK	9766-CL-0018	**Part 1**: Evaluate effect of ESRD on PK of BAL4815 and BAL8728 relative to subjects with normal renal function, establish if BAL4815 and BAL8728 are dialyzable and safety/tolerability **Part 2**: Evaluate effect of mild, moderate and severe renal impairment on PK of BAL4815 and BAL8728, and evaluated safety/tolerability relative to healthy subjects with normal renal function	Phase 1, open-label, 2-part, parallel group study comparing effect of renal impairment on PK and safety/tolerability of ISA	IZs, equivalent to ISA: 200 mg iv, infused over 1 hour	49 Part 1: 20 Healthy: 9 Subjects with ESRD: 11 Part 2: 29 Healthy: 8 Subjects with Renal Impairment: 21	Healthy volunteers with normal renal function, ESRD, and mild, moderate and severe renal impairment	**Part 1**: Single dose on day 1 of Part 1, and on day 15 for ESRD subjects. Study period of 18 days **Part 2**: Single dose on day 1 of 13-day study period	Completed; Full

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Human Pharmacokinetic Studies (Special Populations - Intrinsic Factors) continued								
PK	9766-CL-0038	Evaluate PK and safety/tolerability of BAL4815 and BAL8728 after single dose and steady-state administration of IZs in healthy Chinese subjects	Phase 1, open-label, single dose (crossover) and multiple dose study of safety and PK of IZs in healthy Chinese volunteers	**Part 1**: IZs, equivalent to ISA: 200 mg po or iv on day 1 of each treatment period (crossover design) **Part 2**: IZs, equivalent to ISA: 200 mg tid for 2 days followed by qd for 10 days administered po or iv	36 **Part 1**: 12 iv to po: 6 po to iv: 6 **Part 2**: 24 iv: 12 po: 12	Healthy Chinese volunteers	**Part 1**: Single dose on day 1 of each 15-day study period (crossover design) followed by a 2-week washout. **Part 2**: IZs administration for first 12 days of 26-day study period	Completed; Full
Human Pharmacokinetic Studies (Drug-drug Interactions)								
PK/DDI	WSA-CP-005 (9766-CL-0005)/The Netherlands	DDI and safety/tolerability of IZs and ketoconazole or rifampicin	Phase 1, open-label, multiple-dose sequential dosing study	Ketoconazole: 200 mg (qd) on days 36-71; oral tablet Rifampin: 600 mg (qd) on days 36-71; oral tablet IZs, equivalent to ISA: 400 mg on day 1 and 100 mg on days 2-14; 400 mg on day 44 and 100 mg on days 45-57; oral capsule	52 (IZs + ketoconazole 26; IZs + rifampin 26)	Healthy male volunteers	IZs (qd) for 2 weeks followed by a 3-week washout period, then a 36-day treatment period (days 36-71) including co-administration of ketoconazole or rifampin with IZs (days 44-57)	Completed; Full

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Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Human Pharmacokinetic Studies (Drug-drug Interactions) continued								
PK/DDI	WSA-CP-006 (9766-CL-0006)/US	DDI, PD (PT and PT AUC) and safety/tolerability of IZs and warfarin	Phase 1, open-label multiple-dose, sequential dosing study	Warfarin: 10 mg (qd) on days 1 and 29; oral tablet IZs, equivalent to ISA: 400 mg on day 9 and 100 mg qd on days 10-36; oral capsule	12	Healthy male volunteers	Single dose of warfarin followed by a 1-week washout period, then a 28-day treatment period (days 9 to 36)	Completed; Full
PK/DDI	WSA-CP-007 (9766-CL-0007)/ Germany	DDI and safety/tolerability of IZs and tacrolimus or cyclosporine	Phase 1, open-label multiple-dose sequential dosing study	Tacrolimus: 5 mg on days 1 and 22; oral capsule Cyclosporine: 300 mg on days 1 and 22; oral capsule IZs, equivalent to ISA: 400 mg on day 8 and 100 mg (qd) on days 9-27; oral capsule	52 (IZs + cyclosporine 26; IZs + tacrolimus 26)	Healthy male volunteers	Single dose cyclosporine or tacrolimus followed by a 1-week washout period, and a 20-day treatment period (days 8 to 27)	Completed; Full
PK/DDI	WSA-CP-009 (9766-CL-0009)/ Germany	DDI and safety/tolerability of IZc and ketoconazole, indinavir or cyclosporine	Phase 1, open-label, single-dose, sequential dosing crossover study	Group A: IZc, equivalent to ISA: 400 mg on days 1 and 36; oral capsule Ketoconazole: 200 mg on day 36; oral tablet Group B: Indinavir: 800 mg on days 1 and 15; oral capsule IZc, equivalent to ISA: 400 mg on day 15; oral capsule Group C: Cyclosporine: 300 mg on days 1 and 15; oral capsule IZc, equivalent to ISA: 400 mg on day 15; oral	36 (IZc + ketoconazole 12; IZc + indinavir 12; IZc + cyclosporine 12)	Healthy male volunteers	Single dose each treatment (day 1) followed by 5-week washout, co-administration of IZc and ketoconazole for one day (day 36) or 2-week washout, co-administration of IZc with indinavir or cyclosporine	Completed; Full

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
				capsule			for 1 day (day 15)	
Human Pharmacokinetic Studies (Drug-drug Interactions) continued								
PK/DDI	WSA-CP-011 (9766-CL-0011)/ France	DDI and safety/tolerability of IZs and omeprazole, and detectable presence of IZs and cleavage product (BAL8728) in urine at steady state	Phase 1, open-label, multiple-dose, single sequence study	Omeprazole: 40 mg on days 1 and 23; oral capsule IZs, equivalent to ISA: 200 mg tid on days 9-10, 200 mg qd on days 11-23; oral capsule	27	Healthy male volunteers	Single dose of omeprazole on day 1 followed by 1-week washout, 15-day treatment period (days 9 to 23) including co-administration of omeprazole and IZs on day 23	Completed; Full
PK/DDI	WSA-CP-012 (9766-CL-0012)/ Germany	DDI and safety/tolerability of IZs and sirolimus	Phase 1, open-label multiple-dose, sequential dosing study	Sirolimus: 1 mg on days 1 and 35; oral tablet IZs, equivalent to ISA: 200 mg tid on days 22-23; 200 mg qd on days 24-44; oral capsule	26	Healthy male volunteers	Single dose of sirolimus followed by 3-week washout, 23-day treatment period (days 22 to 44)	Completed; Full
PK/DDI	9766-CL-0020/US	DDI and safety/tolerability of IZs and sirolimus	Phase 1, open-label, sequential dosing study	Sirolimus: 2 mg on days 1 and 26; oral tablet IZs, equivalent to ISA: 200 mg tid on days 22-23, and 200 mg qd on days 24-34; oral capsule	22	Healthy volunteers	Single dose on day 1 followed by a 21-day washout period, then a 13-day treatment period (days 22-34) including co-administration of sirolimus and IZs on	Completed; Full

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
							day 26	
Human Pharmacokinetic Studies (Drug-drug Interactions) continued								
PK/DDI	9766-CL-0021/US	DDI and safety/tolerability of IZs and tacrolimus	Phase 1, open-label, sequential dosing study	Tacrolimus: 5 mg on days 1 and 20; oral capsule IZs, equivalent to ISA: 200 mg tid on days 16-17, and 200 mg qd on days 18-28; oral capsule	24	Healthy volunteers	Single dose on day 1, followed by a 15-day washout, then a 13-day treatment period (days 16-28) including co-administration of tacrolimus and IZs on day 20	Completed; Full
PK/DDI	9766-CL-0022/US	DDI and safety/tolerability of IZs and cyclosporine	Phase 1, open-label, sequential dosing study	Cyclosporine: 300 mg on days 1 and 15; oral capsule IZs, equivalent to ISA: 200 mg tid on days 11-12, and 200 mg qd on days 13-18; oral capsule	24	Healthy volunteers	Single dose on day 1, followed by a 10-day washout, then an 8-day treatment period (days 11-18) including co-administration of cyclosporine and IZs on day 15	Completed; Full
PK/DDI	9766-CL-023/ US	DDI and safety/tolerability of IZs and midazolam	Phase 1, open-label, sequential dosing study	Midazolam: 3 mg on days 1 and 12; syrup (oral) IZs, equivalent to ISA: 200 mg tid on days 3-4 and 200 mg qd on days 5-13; oral capsule	23	Healthy volunteers	Single dose of midazolam syrup on day 1, followed by a 1-day washout period, then a 10-day treatment	Completed; Full

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
							period (days 3 to 13) including co-administration of midazolam and IZs on day 12	
Human Pharmacokinetic Studies (Drug-drug Interactions) continued								
PK/DDI	9766-CL-0024/ US	DDI and safety/tolerability of IZs and prednisone	Phase 1, open-label, sequential dosing study	Prednisone: 20 mg on days 1 and 9; oral tablet IZs, equivalent to ISA: 200 mg tid on days 5-6, and 200 mg qd on days 7-10; oral capsule	21	Healthy volunteers	Single dose on day 1, followed by a 4-day washout, then a 6-day treatment period (days 5-10) including co-administration of prednisone and IZs on day 9	Completed; Full
PK/DDI	9766-CL-0025/ US	DDI and safety/tolerability of IZs and digoxin	Phase 1, open-label, sequential dosing study	Digoxin: 0.5 mg on days 1 and 19; oral tablet IZs, equivalent to ISA: 200 mg tid on days 15-16, and 200 mg qd on days 17-26; oral capsule	24	Healthy volunteers	Single dose on day 1, followed by a 14-day washout, then a 12-day treatment period (days 15-26) including co-administration of digoxin and IZs on day 19	Completed; Full
PK/DDI	9766-CL-0027/US	DDI and safety/tolerability of IZs and methadone	Phase 1, open-label, sequential dosing study	Methadone: 10 mg on days 1 and 20; oral tablet IZs, equivalent to ISA: 200 mg tid on days 16-17,	23	Healthy volunteers	Single dose on day 1, followed by a 15-day washout, then	Completed; Full

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
				and 200 mg qd on days 18-28; oral capsule			a 13-day treatment period (days 16-28) including co-administration of methadone and IZs on day 20	
Human Pharmacokinetic Studies (Drug-drug Interactions) continued								
PK/DDI	9766-Cl-0030/US	DDI and safety/tolerability of IZs and MMF	Phase 1, open-label, sequential dosing study	MMF: 1 g on days 1 and 13; oral tablet IZs, equivalent to ISA: 200 mg tid on days 9-10, and 200 mg qd on days 11-16; oral capsule	24	Healthy volunteers	Single dose on day 1, followed by a 7-day washout, then an 8-day treatment period (days 9-16) including co-administration of MMF and IZs on day 13	Completed; Full
PK/DDI	9766-CL-0031/US	DDI and safety/tolerability of IZs and EE and NE	Phase 1, open-label, sequential dosing study	Oral Contraceptive: 35 mcg EE and 1 mg NE on days 1 and 13; oral tablet IZs, equivalent to ISA: 200 mg tid on days 9-10, and 200 mg qd on days 11-16; oral capsule	24	Healthy postmenopausal female volunteers	Single dose on day 1, followed by an 8-day washout, then an 8-day treatment period (days 9-16) including co-administration of oral contraceptive and IZs on day 13	Completed; Full
PK/DDI	9766-CL-0033/US	DDI, PD and safety/tolerability	Phase 1, open-label,	Warfarin: 20 mg on days 1 and 20; oral tablet	21	Healthy volunteers	Single dose on day 1,	Completed; Full

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
		of IZs and warfarin	sequential dosing study	IZs, equivalent to ISA: 200 mg tid on days 16-17, and 200 mg qd on days 18-28; oral capsule			followed by an 15-day washout, then an 13-day treatment period (days 16-28) including co-administration of warfarin and IZs on day 20	
Human Pharmacokinetic Studies (Drug-drug Interactions) continued								
PK/DDI	9766-CL-0035/US	DDI and safety/tolerability of IZs and LPV and RTV	Phase 1, randomized, open-label, two-part, 3-arm parallel group study	**Part 1, Arm 1**: IZs, equivalent to ISA: 100 mg tid on days 1-2 and 100 mg qd on days 3-13; oral capsule **Arm 3**: IZs, equivalent to ISA: 100 mg tid on days 1-2 and 100 mg qd on days 3-13; oral capsule LPV/RTV: 400/100 mg bid on days 1-13; oral tablet **Part 2, Arm 1**: IZs, equivalent to ISA: 200 mg tid on days 1-2 and 200 mg qd on days 3-13 oral capsule **Arm 2**: LPV/RTV: 400/100 mg bid on days 1-12 and 400/100 mg qd on day 13; oral tablet **Arm 3**: IZs, equivalent to ISA: 200 mg tid on days 1-2 and 200 mg qd on days 3-13; oral capsule LPV/RTV: 400/100 mg bid on days 1-13; oral tablet	**Part 1:** **Arm 1**: IZs 6 **Arm 3**: IZs + LPV/RTV: 7 **Part 2:** **Arm 1**: IZs 18 **Arm 2**: LPV/RTV: 19 **Arm 3**: IZs + LPV/RTV: 18	Healthy volunteers	Treatment period days 1-13	Completed; Full
PK/DD	9766-CL-	DDI and	Phase 1,	**Arm 1**: IZs, equivalent to	**Arm 1:**	Healthy	**Arm 1:**	Completed

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
I	0040/US	safety/tolerability of IZs and ketoconazole	randomized, open-label, two-arm, parallel group study	ISA: 200 mg on day 1; oral capsule **Arm 2**: IZs, equivalent to ISA: 200 mg on day 4; oral capsule Ketoconazole: 200 mg bid on days 1-24; oral tablet	IZs: 12 **Arm 2:** IZs + ketoconazole: 12	volunteers	Single dose day 1 **Arm 2:** Treatment for 24 days (days 1-24) including co-administration of IZs and ketoconazole on day 4	; Full
Human Pharmacokinetic Studies (Drug-drug Interactions) continued								
PK/DDI	9766-CL-0042/US	DDI and safety/tolerability of IZs and DXM	Phase 1, randomized, open-label, sequential dosing study	DXM: 30 mg on days 1 and 10; oral capsule IZs, equivalent to ISA: 200 mg tid on days 6-7, and 200 mg qd on days 8-12; oral capsule	24	Healthy volunteers	Single dose on day 1, followed by 5-day washout, then a 7-day treatment period (days 6-12) including co-administration of DXM and IZs on day 10	Completed ; Full
PK/DDI	9766-CL-0043/US	DDI and safety/tolerability of IZs and atorvastatin	Phase 1, randomized, open-label, sequential dosing study	Atorvastatin: 20 mg on days 1 and 12; oral tablet IZs, equivalent to ISA: 200 mg tid on days 8-9, and 200 mg qd on days 10-15; oral capsule	24	Healthy volunteers	Single dose on day 1, followed by a 7-day washout, then an 8-day treatment period (days 8-15), including co-administration of atorvastatin and IZs on day 12	Completed ; Full
PK/DDI	9766-CL-0044/US	DDI and safety/tolerability	Phase 1, randomized,	Bupropion: 100 mg on days 1 and 15; oral tablet	24	Healthy volunteers	Single dose on day 1,	Completed ; Full

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
		of IZs and bupropion	open-label, sequential dosing study	IZs, equivalent to ISA: 200 mg tid on days 8-9, and 200 mg qd on days 10-20; oral capsule			followed by a 7-day washout, then a 13-day treatment period (days 8-20), including co-administration of bupropion and IZs on day 15	
Human Pharmacokinetic Studies (Drug-drug Interactions) continued								
PK/DDI	9766-CL-0051	DDI and safety/tolerability of IZs and metformin	Phase 1, open-label, sequential dosing study	Metformin: 850 mg po on days 1 and 8 IZs, equivalent to ISA: 200 mg tid po on days 4-5, and 200 mg qd po on days 6-9	24	Healthy volunteers	Single dose on day 1, followed by a 3-day washout, then a 6-day treatment period (days 4-9), including co-administration of Metformin and IZs on day 8	Completed; Full
PK/DDI	9766-CL-0052	DDI and safety/tolerability of IZs and MTX	Phase 1, open-label, sequential dosing study	MTX: 7.5 mg po on days 1 and 8 IZs, equivalent to ISA: 200 mg tid po on days 4-5, and 200 mg qd po on days 6-9	24	Healthy male volunteers	Single dose on day 1, followed by a 3-day washout, then a 6-day treatment period (days 4-9), including co-administration of MTX and IZs on	Completed; Full

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
							day 8	
Human Pharmacokinetic Studies (Drug-drug Interactions) continued								
PK/DDI	9766-CL-0053	DDI and safety/tolerability of ISA and repaglinide and caffeine	Phase 1, open-label, sequential dosing study	Repaglinide: 0.5 mg on day 1, and 0.5 mg on day 14; oral tablet Caffeine: 200 mg on day 3, and 200 mg on day 16; oral tablet IZs, equivalent to ISA: 200 mg tid on days 5 and 6, and 200 mg qd on days 7-17; oral capsule	24	Healthy volunteers	Single dose of repaglinide on day 1, followed by a single dose of caffeine on day 3, followed by IZs administration (tid on days 5 and 6 and qd on days 7-17) including co-administration of repaglinide with IZs on day 14 and of caffeine with IZs on day 16	Completed; Full
PK/DDI	9766-CL-0054	DDI and safety/tolerability of ISA and esomeprazole	Phase 1, randomized, open-label, 2-arm parallel group study	**Arm 1**:IZs, equivalent to ISA: 200 mg tid on days 1 and 2, and 200 mg qd on days 3, 4 and 5; oral capsule **Arm 2**: Esomeprazole 40 mg qd days 1-10; oral capsule IZs, equivalent to ISA: 200 mg tid on days 6 and 7, and 200 mg qd on days 8, 9 and 10; oral capsule	24 **Arm 1**: IZs: 12 **Arm 2**: esomeprazole + IZs: 12	Healthy volunteers	**Arm 1**: IZs on days 1 to 5 (tid on days 1 and 2, qd on days 3-5) **Arm 2**: Single dose of esomeprazole on days 1 to 10 including co-administration with IZs on days 6 and 7 (tid) and on days 8, 9 and 10 (qd)	Completed; Full

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Human Pharmacodynamic Studies								
PD/PK	WSA-CP-004 (9766-CL-0004)/ The Netherlands	PK, safety/tolerability, and cardiac repolarization using QTcI	Phase 1, randomized, double-blind, placebo- and active-controlled, parallel group, multiple-dose study	**IZs, equivalent to ISA, or Placebo:** 400, 300 and 200 mg (qd) on days 4, 5 and 6, respectively; 100 mg qd on days 7-10; 300, 250 and 200 mg (qd) on days 12, 13 and 14, respectively; and 150 mg (qd) on days 15-18; oral capsule **IZs, equivalent to ISA, or Placebo:** 100 and 150 mg (qd) on days 11 and 19, respectively; iv (1 h) **Moxifloxacin:** 400 mg (qd) on day 1; oral capsule	82 IZs + Moxifloxacin : 41 Placebo + Moxifloxacin : 41	Healthy volunteers	Single dose moxifloxacin followed by 2-day washout period, 2 consecutive treatments 8 days each (days 4 to 19)	Completed ; Full
PD/PK	9766-CL-0017/ US	PK, safety/tolerability and QTcF	Phase 1, randomized, double-blind, placebo- and active-controlled, parallel group study	**Group 1**: IZs, equivalent to ISA: 200 mg tid on days 1-2, and 200 mg qd on days 3-13, oral capsule **Group 2**: IZs, equivalent to ISA: 200 mg tid on day 1-2, and 600 mg qd on day 3-13; oral capsule **Group 3**: Placebo: tid on days 1-2, and qd on days 3-13; oral capsule **Group 4**: Placebo: tid on days 1-2, and qd on days 3-12; oral capsule Moxifloxacin: 400 mg on day 13, oral tablet	161 **Group 1**: IZs 41 **Group 2**: IZs 40 **Group 3**: Placebo 40 **Group 4**: Placebo + Moxifloxacin 40	Healthy volunteers	13 days	Completed ; Full

Table continued on next page

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Human (Patient) PK and Efficacy and Safety Studies								
E/S	WSA-CS-001 (9766-CL-0101)/ South Africa	DDI and safety/tolerability and relapse rate of IZc and fluconazole in EC	Phase 2, randomized, multicenter, double-blind, parallel group study	**Group A:** IZc, equivalent to ISA: 200 mg on day 1, 50 mg qd on day 2 to EOT; oral capsule **Group B:** IZc, equivalent to ISA: 400 mg on day 1, 400 mg on days 7, 14, 21; oral capsule **Group C:** IZc, equivalent to ISA: 400 mg on day 1, 100 mg (qd) on day 2 to EOT; oral capsule **Group D:** fluconazole: 200 mg on day 1, 100 mg (qd) on day 2 to EOT; oral capsule	IZc: 122 (Group A 40; Group B 40, Group C 42) Fluconazole (Group D): 38	Male and postmenopausal female patients with uncomplicated EC	Single dose of IZc or fluconazole for at least 14 days of treatment (days 1 to EOT), or a single dose of IZc (day 1) with a 5-day washout period between the next doses (days 7, 14 and 21)	Completed; Full
E/S	WSA-CS-002 (9766-CL-0102)/ Germany	PK, efficacy and safety/tolerability of 2 escalating dose regimens of IZs in patients with neutropenia who are undergoing chemotherapy for AML	Phase 2, randomized, open-label, sequential group comparison of 2 dose levels of IZs	**Low Dose:** IZs, equivalent to ISA: 400/200/200 mg on day 1 and 200/200 mg on day 2 and 200 mg/day to EOT; iv **High Dose:** IZs, equivalent to ISA: 800/400/400 mg on day 1 and 400/400 mg on day 2 and 400 mg/day to EOT; iv	IZs: 23 (Low dose: 11; High dose: 12)	Male and female patients > 18 years old undergoing therapy for AML	Up to 28 days	Completed; Full
E/S	WSA-CS-003 (9766-CL-0103)	Efficacy and safety of IZs (po vs iv)	Phase 3, open-label study of IZs	IZs, equivalent to ISA: (iv and po): 200 mg (q8h) on days 1-2 and 200 mg (q12h) on day 3 to EOT	146 patients (59 with renal impairment, 87 with no renal impairment)	Male and female patients ≥ 18 years old with IA and renal impairment or with IFD caused by rare moulds,	Up to 180 days (additional duration allowed in amendment 4)	Completed; Full

Type of Study	Study Identifier/ Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
						yeasts or dimorphic fungi		
Human (Patient) PK and Efficacy and Safety Studies								
E/S	WSA-CS-004 (9766-CL-0104)	Efficacy and safety of IZs (iv and po) vs VRC (iv and po)	Phase 3, randomized, double-blind noninferiority study of IZs vs VRC	IZs, equivalent to ISA: (iv and po): 200 mg (q8h) on days 1-2 and 200 mg (q12h) on day 3 to EOT or VRC: 6 mg/kg iv (q8h) on day 1, 4 mg/kg iv (q8h) on day 2, 4 mg/kg iv (q12h) or 200 mg po (q12h) on day 3 to EOT	516 (SAF) ISA: 257 VRC: 259	Male and female patients ≥ 18 years old with IA	Up to 84 days	Completed ; Full

BAL8728: inactive cleavage product; DDI: drug-drug interaction; DXM: dextromethorphan; EC: esophageal candidiasis; EE: ethinyl estradiol; EOT: end of treatment; E/S: efficacy and safety; ESRD: end stage renal disease; FE: food effect; HV: healthy volunteers; ISA: isavuconazole; ISA HCL: isavuconazole hydrochloride; IZc: isavuconazonium hydrochloride; IZs: isavuconazonium sulfate; LPV: lopinavir; MAD: multiple ascending dose; MEGX: monoethylglycinexylidide; MMF: mycophenolate mofetil; NE: norethindrone; PD: pharmacodynamics; PK: pharmacokinetics; PT: prothrombin time; PT AUC: prothrombin time area under the curve; RTV: ritonavir; SAD: single ascending dose; SAF: safety population.

2.4.2. Pharmacokinetics

Eight studies in healthy subjects, 5 studies in special patients groups and 25 interaction studies were performed to support the pharmacokinetics of isavuconazonium/isavuconazole. In addition, the results of 2 QT studies, and 5 phase 2/3 studies were also submitted for assessment. Moreover, 20 reports covering *in vitro* data and 5 reports with population pharmacokinetics data were also submitted.

The prodrug isavuconazonium sulfate has a high solubility of about 1 g/ml over the pH range of 1 to about 7 and water. The prodrug is administered as a racemate, which is rapidly converted ($t_{1/2}$ less than 1.5 min) into the active moiety isavuconazole (single enantiomer). Small differences in the hydrolysis rate were observed between the 2 diastereromers, but these differences are unlikely to significantly affect the pharmacokinetic profiles of the active drug, isavuconazole.

Analytical methods

Fully validated methods have been applied for the analysis of isavuconazole, isavuconazonium and BAL8728 in human plasma or urine. The methods were considered accurate and precise. In addition, stability data showed that the analytes were stable under sampling handling conditions.

Regarding the analysis of study samples, CHMP agreed that the principles of the guidance on bioanalytical method validations were followed. Also for the analytes used in the interaction studies, fully validated methods have been applied, showing a good accuracy and precision.

Bioequivalence

For the i.v. formulation, isavuconazonium hydrochloride and isavuconazonium sulfate were used as pro-drugs. Isavuconazonium hydrochloride was only used in 2 early phase one studies. Considering that the formulations are i.v. formulations, no concerns regarding bioavailability due to the use of the different salt were expressed.

For the capsule formulation, isavuconazonium hydrochloride and isavuconazonium sulfate were also used as pro-drugs. Isavuconazonium hydrochloride was only used in a few early phase I studies. The only excipient added in these formulations was lactose. The capsule formulation was changed and isavuconazonium sulfate used as prodrug. This formulation was only used in 3 interaction studies and in a QT study. The capsule formulation was reformulated and this formulation was similar to the proposed commercial to be marketed formulation and used in the majority of the phase I studies and in the pivotal phase III studies.

Disintegration time was comparable between the capsules. After disintegration isavuconazonium is very rapidly dissolved, as shown by dissolution data at pH 1.2, 4.5 and 6.8. A cross study comparison of pharmacokinetic data for the 3 formulations did not indicate a difference in bioavailability.

Absorption

After oral administration, the pro-drug isavuconazonium is rapidly converted into the active moiety isavuconazole. Isavuconazonium is almost undetectable after oral administration. Maximum isavuconazole plasma concentrations are observed after about 2-3 h. The absolute bioavailability of the oral formulation is 98%. After oral administration, Cmax is about 78% compared to i.v. administration (infusion 500 ml over 2 h). Based upon comparable exposures after oral and i.v. administration, both formulations can be interchanged.

After i.v. administration, isavuconazonium is rapidly converted into isavuconazole. Very low isavuconazonium plasma levels are observed, which rapidly decline. A high fat, high caloric meal had no clinically relevant

impact on isavuconazole pharmacokinetics after administration as its pro-drug isavuconazonium. Tmax was delayed by 2 h resulting in an 8% lower Cmax and a 10% higher AUC. Based upon these data, isavuconazole can be taken with or without food, as recommended in the SmPC.

After a single i.v. administration, a more than dose proportional increase in AUCinf and Cmax is observed over the 40 – 160 mg dose range, i.e. AUCinf increased 6.3-fold and Cmax increased 5.5-fold. After multiple doses, a more or less proportional increase is observed over a 50 – 600 mg q.d. After a single oral administration, Cmax and AUCinf increased 3.8 and 5.7- fold over a 100 – 400 mg dose range. Proportional increases were observed over the 50 – 600 mg q.d. dose range.

Non-linearity in pharmacokinetics is of less concern, as only one dose is recommended, i.e. a loading dose of 200 mg t.i.d. at day 1 and 2, followed by 200 mg once daily. Isavuconazole did not show time-dependent pharmacokinetics. No unexpected accumulation was observed. Steady state was achieved after about 14 days, which is consisted with an elimination half-life of about 100 - 130 h. However, by applying a loading dose of 200 mg t.i.d. at day 1 – 2, followed by a maintenance dose of 200 mg q.d., steady state was achieved at day 3. Intra-individual variability was not evaluated. The inter-individual variability in Cmax and AUC was generally about 20 – 30%, for i.v. as well as for oral administration. Population pharmacokinetics indicated an overall intersubject variability for AUC of 58% (%CV) and an intra-subject variability of 45 (%CV).

Pharmacokinetics in healthy subjects and patients were comparable. Following the dose scheme recommended in the SmPC, mean isavuconazole trough concentrations of around and above 3 µg/ml were observed, which were above the targeted clinical MIC values of 1-2 µg/ml.

Distribution

Isavuconazole is not actively taken up into red blood cells. It is highly bound to plasma proteins (about 99.3%). Comparable values were observed in patients with mild-severe renal impaired function and in patients with mild-moderate hepatic impairment. Taking into account the high volume of distribution of 450 litres, drug-drug interactions due to protein displacement are not expected.

Based upon animal data, isavuconazole may cross the blood-brain barrier and transfer over the placenta.

Metabolism:

After i.v. administration, isavuconazonium is rapidly converted into isavuconazole, during which the cleavage product BAL8728 is formed. After labelling the C-atom of the cleavage product BAL8728, mean recovery of radioactivity in urine and faeces samples was 98.4% over 168-hour, of which 96% in urine. In urine, 0.62% of the administered dose was recovered as BAL8728.

The main metabolism pathway after intravenous administration to humans was considered to be the cleavage of isavuconazonium, followed by the generation of BAL8728. BAL8728 was predominantly metabolized to M4 followed by glucuronide conjugation (M20). BAL8728 was also metabolized by oxidation and subsequent glucuronide, or cysteine and acetylcysteine conjugation.

After oral administration, isavuconazonium plasma concentrations were almost undetectable. After labelling of the isavuconazole molecule, isavuconazole accounted for about 88% of the labelled plasma levels. BAL8728 plasma levels were not detectable or close to the LLOQ. 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). In faeces, 33% could be recovered as parent over the sampling period of 0 – 144h, next to 18 metabolites each presenting less than 1% of the dose. In urine, only low levels of isavuconazole could be detected. In addition, 12

metabolites were detected, of which metabolites M11 to M14 were the main metabolites, accounting for about 50% of the radioactivity.

The main metabolism pathway of isavuconazonium after oral administration to humans was considered to be cleavage of isavuconazonium, followed by generation of isavuconazole and its oxidation and cleavage of the thiazole ring of isavuconazole. Isavuconazole was metabolized 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.

It should be noted that metabolic profiles in urine were identified up to 144 h after administration, which accounted 30% of the administered radioactive dose for urine, while over the whole 600 h period 45.5% was recovered. For faeces this was 23.7% of the 46.1%.

Elimination

The plasma elimination half-life of isavuconazole is about 100 -130 h. The plasma elimination half-life of the cleavage product BAL8728 is about 1 h. Isavuconazole CL after single i.v. dose was about 2300 ml/h. CL/F after a single oral dose was about 2360 ml/h, indicative for a low (hepatic) clearance. Renal clearance ranged from 7.4 – 14 ml/h.

Special populations

No significant gender effect was observed. In addition, no clinically significant effect of age was observed. Therefore, no dose adjustment in the elderly is required for isavuconazole; this is reflected in the Cresemba SmPC.

Chinese subjects showed to have 15 – 50% higher exposure compared to Western subjects. The cause is unknown. This difference was nevertheless considered as not clinically significant; therefore, no dose adjustment is required for isavuconazole. Limited data in Blacks and African American subjects indicate no difference in pharmacokinetics compared to Caucasians.

Renal clearance of intact isavuconazole and its cleavage product BAL8728 is a minor excretion pathway. Therefore, an impact on clearance due to an impaired renal function is not anticipated. Indeed, in patients with mild, moderate and severe renal impairment, Cmax and AUC were not statistical significant affected. For the cleavage product BAL8728 the AUC in patients with mild and severe renal impairment was about 25 – 30% higher, while in patients with moderate renal impairment no effect was observed. However, BAL8728 plasma levels were still very low.

The effect of dialyzing ESRD subjects 1 hour prior to dosing (day 1) compared to dialyzing the subject just after the 1 hour infusion (day 15) on the pharmacokinetics of isavuconazole was limited. AUC0-72h was about 30% higher post dialysis, independent if predialysis access line or postdialysis access line was evaluated. This effect may be attributed to the hemodilution effect. Predialysis access line or postdialysis access line pharmacokinetics were comparable.

The observation that there is no difference in the plasma concentrations of isavuconazole between the predialysis and postdialysis access lines reflects the very low dialytic removal of the drug which is consistent with its very high protein binding (>99%). Further, the low dialytic removal indicates that supplementation of

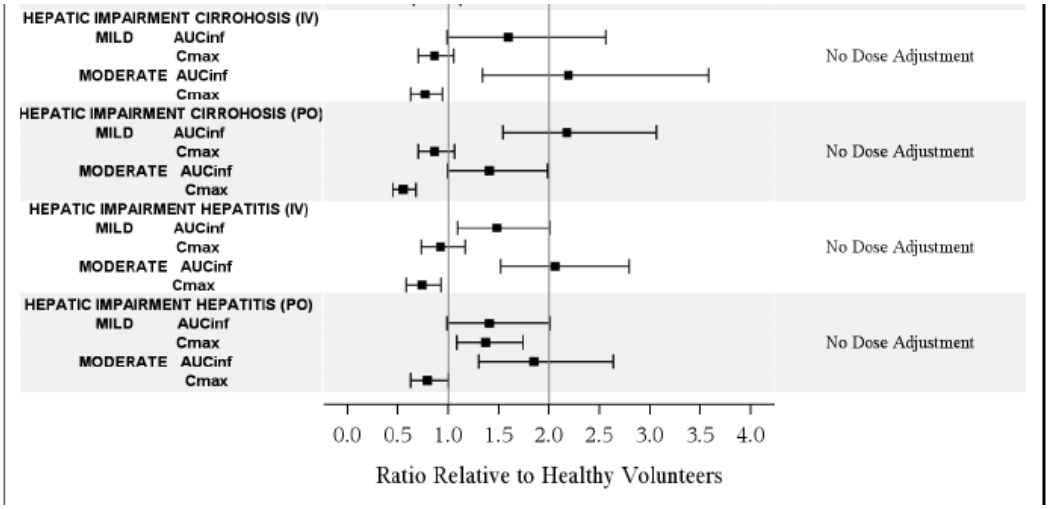
isavuconazole postdialysis will not be required and that an overdose of isavuconazole cannot be managed effectively with hemodialysis.

No dose adjustment based on renal function is required for isavuconazole; this is reflected in the SmPC.

Data have indicated that after i.v. administration total plasma Cl decreased by 30 and 51% in patients with mild and moderate hepatic impairment respectively (cirrhosis due to hepatitis B/C). Comparable results were observed for free plasma Cl (-34 and -63% respectively).

After oral administration total plasma Cl/F decreased by 27 and 42% in patients with mild and moderate hepatic impairment, respectively. For free plasma Cl/F this was -28 and -61%, respectively. Comparable values were observed in patients with liver cirrhosis due to alcohol (see figure below).

Figure 2 Effect of hepatic impairment on the pharmacokinetic parameters of isavuconazole



The CHMP required that the results in mild and moderate hepatic impairment and the lack of data in severe hepatic impairment are reflected in the SmPC.

Weight was one of the continuous covariates explored in the POPPK analysis described in study PK-005. Vp increased with BMI but weight was not *per se* identified as a significant covariate.

Pharmacokinetic interaction studies

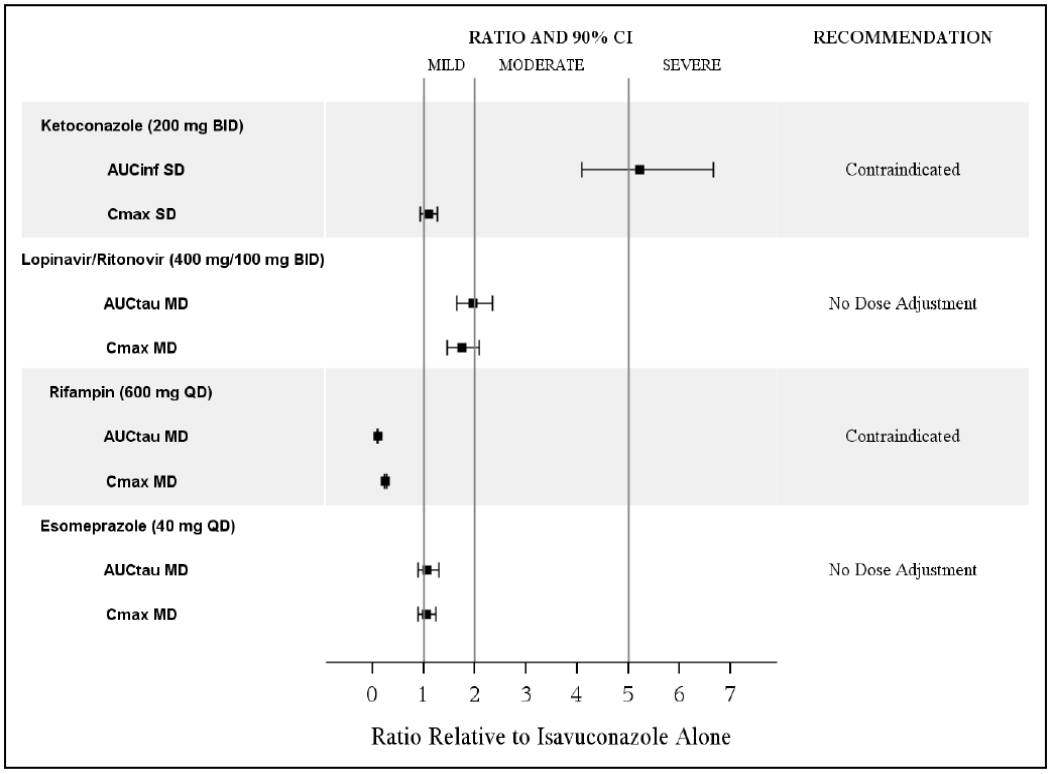
In vitro data indicate that isavuconazonium is a substrate of human butyrylcholinesterase (hBChe). Drug interactions involving competition for BChE have not been reported in the literature. As such, it is not expected that the conversion of isavuconazonium into isavuconazole will be clinically relevant affected by a possible inhibition.

Isavuconazole is a substrate for CYP3A4. There was no indication of a possible impact of genetic polymorphisms on the pharmacokinetics, based on the results of a pilot pharmacogenomic study in subjects receiving isavuconazole.

In addition, isavuconazole may induce CYP2B6. Moreover, isavuconazole may inhibit P-gp, BCRP, OCT2 and UGT. The possible interactions potential with these enzymes have been studied *in vivo* (see figures below).

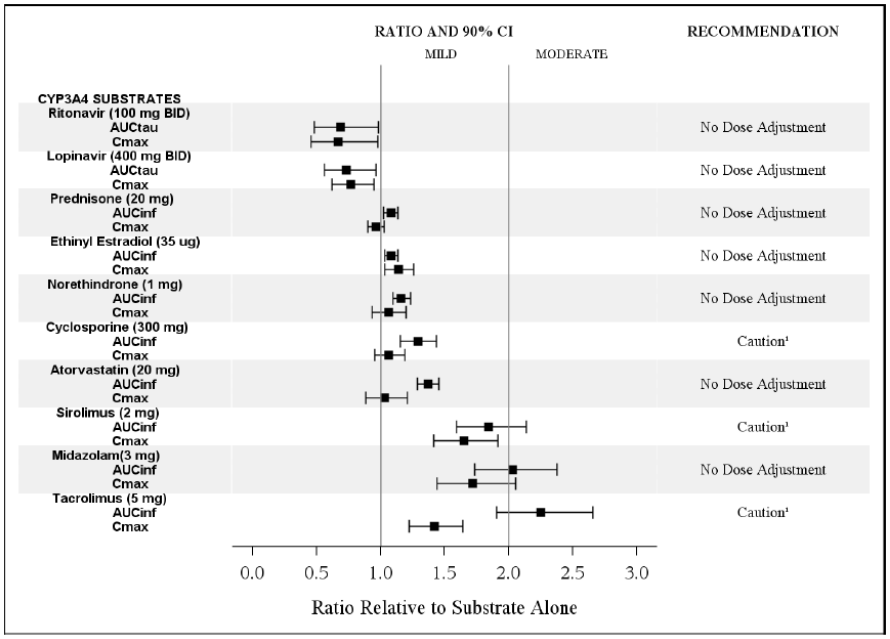
Additional peaks were often observed in the declining phase of individual isavuconazole plasma concentration-time profiles, occurring about 6 to 12 hours postdose, and coincided with a meal or snack. Biliary excretion was 'confirmed' in bile-duct cannulated rats. The enterohepatic recycling concerns excretion and reabsorption of isavuconazole.

Figure 3 Effects of other drugs on the pharmacokinetics of isavuconazole



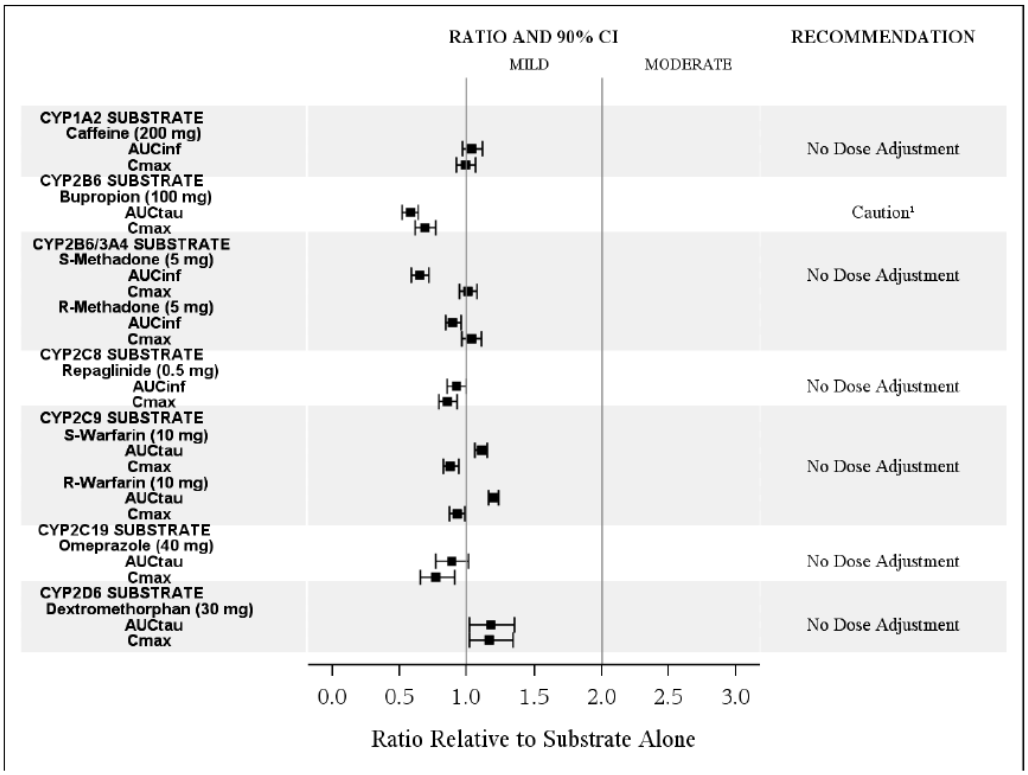
(ketoconazole: strong inhibition CYP3A4, lopinavir/ritonavir moderate inhibition of CYP3A4, rifampicin strong induction of CYP3A4, esomeprazole gastrointestinal pH increase)

Figure 4 Effect of isavuconazole on CYP3A4 substrates



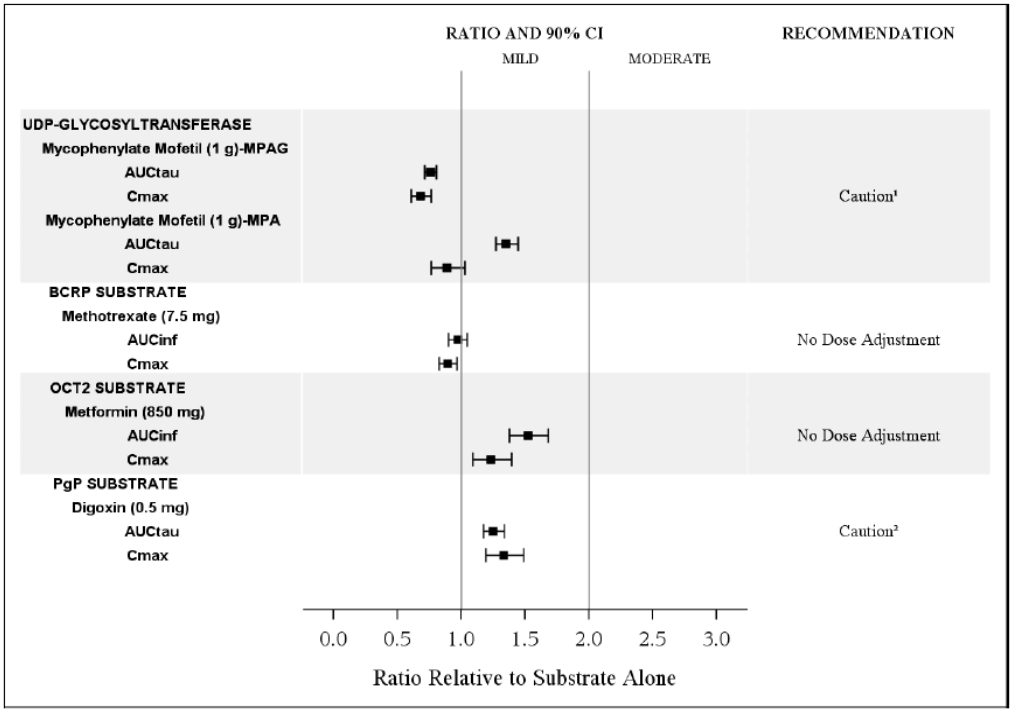
[1] Appropriate therapeutic drug monitoring and dose adjustment of tacrolimus, sirolimus, and cyclosporine may be necessary when co-administered with isavuconazole.

Figure 5 Effect of isavuconazole on other CYP enzyme substrates



1 Isavuconazole decreased the systemic exposure of bupropion. Caution is advised if isavuconazonium is co-administrated with CYP2B6 substrates, especially narrow therapeutic index drugs such as cyclophosphamide.

Figure 6 Effect of isavuconazole on UGT and transporters



1 Due to the unclear association between MPA pharmacokinetics and MPA-related toxicity, no specific dose recommendation can be made. Patients receiving isavuconazonium concurrently with MMF should be monitored for MPA-related toxicities.

2 Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect.

Two-fold and three-fold increases in the maintenance dose have shown an acceptable safety profile both in patients (study 9766-CL-0102) and healthy subjects (study 9766-CL-0017). However, CHMP considered that the patient group used in study 9766-CL-0102 (prophylaxis of patients undergoing chemotherapy for acute myeloid leukemia) was not representative. In addition, in study 9766-CL-0017 a clear increase in the number of AEs was observed at a 600 mg dose, so it cannot be excluded that a doubling of the exposure for a 200 mg dose would result in higher AEs. Therefore, in such cases, caution is advised as adverse drug reactions may increase.

Concomitant administration of lopinavir 400 mg/ritonavir100 mg and Cresemba resulted in decreased exposure of lopinavir with concurrent decreases in the mean AUCs of lopinavir and ritonavir by 27% and 31%, respectively. This could possibly result in loss of antiviral efficacy. No dose adjustment is necessary for isavuconazole when co-administered with lopinavir 400 mg/ritonavir 100 mg every 12 hours.

Co-administration of Cresemba with the strong CYP3A4 inhibitor ketoconazole is contraindicated as a significant increase in plasma exposure of isavuconazole of more than 5-fold is observed. The strong CYP3A4 inhibitor lopinavir/ritonavir, increased the plasma exposure of isavuconazole by about 2-fold, therefore no dose adjustment is necessary, however caution is advised. As other strong CYP3A4 inhibitors are considered to have a similar or a less potent CYP3A4 inhibition, this recommendation is also applicable to these CYP3A4 inhibitors.

Co-administration with moderate CYP3A4 inducers such as efavirenz, nafcillin and etravirine may result in a 70% decrease in isavuconazole plasma levels (based upon literature data using midazolam as reference)

which will result in loss of efficacy. These combinations are contraindicated. As a mild inducer like aprepitant may reduce plasma levels of CYP3A4 substrates by 25%, this may be of concern for isavuconazole efficacy. Therefore, co-administration with mild CYP3A4 inducers such as aprepitant, prednisone and pioglitazone, may result in mild to moderate decreases of isavuconazole plasma levels and co-administration with mild CYP3A4 inducers should be avoided unless the benefit outweighs the risk. This has been included as a warning in SmPC section 4.4.

A single dose of isavuconazonium decreased the exposure of indinavir by 36%. No interaction mechanism could be identified for the observed decrease in indinavir exposure after a single dose of isavuconazonium. The effect after multiple doses of isavuconazonium is unclear, i.e. the effect may be even more pronounced. Further decreases in indinavir concentration may have clinical implications. However, indinavir is almost not used anymore to treat HIV in the EU. Therefore the SmPC conservatively states that careful monitoring for any occurrence of lack of anti-viral efficacy should be applied and the indinavir dose could be increased if required.

Population pharmacokinetic analyses were used to further explore and support the pharmacokinetics. At the time of assessment, no new PopPK analysis has been carried out. Data from study 105 are awaited and will be incorporated in a PopPK analysis. The applicant should submit these data no later than the end of May 2016.

2.4.3. Pharmacodynamics

The pharmacological activity of isavuconazole has been investigated in *in vitro* and *in vivo* (animal and human) studies. *In vivo* data mainly came from two main clinical phase 3 studies:

- Study 9766- CL-0104: a randomized, double blind, non-inferiority, active controlled study (versus voriconazole), which randomized 527 adult patients with proven, probable, or possible IFD caused by *Aspergillus* species or other filamentous fungi.
- Study 9766- CL-0103: an open-label study of isavuconazole in the treatment of renally impaired patients with aspergillosis and in the treatment of patients with invasive fungal disease caused by rare moulds, yeasts or dimorphic fungi. A subpopulation of 37 patients was enrolled, who were confirmed by an independent DRC to have proven or probable mucormycosis.

Mechanism of action

Isavuconazole inhibits fungal lanosterol-14 alpha-demethylase ($P450_{14DM}$), which results in depletion of ergosterol and disruption of the structure and function of the fungal cell membrane. In addition, inhibition of this enzyme leads to the accumulation of toxic methylated intermediates that inhibit fungal growth. Isavuconazole, like other azoles, thus demonstrates a fungicidal effect by blocking the synthesis of ergosterol.

Inhibition of $P450_{14DM}$ extracted from *C. albicans* and rat liver gave IC_{50} values of isavuconazole that were 0.043 and 4.0 mg/L, respectively. Based on the selectivity ratio, isavuconazole is expected to have moderate inhibitory activity against the human P450 enzyme.

Primary and Secondary pharmacology

Primary pharmacology

Aspergillus spp.

Using CLSI methodology to test 1,717 worldwide isolates of *Aspergillus* the isavuconazole MIC_{50} and MIC_{90} were 0.5 and 2 mg/L, respectively (range 0.06 to 32 mg/L). Using EUCAST methodology to test 1,563 isolates the MIC_{50} and MIC_{90} were 1 and 2 mg/L, respectively (range 0.004 to 16 mg/L), see below table:

Table 2 MICs of isavuconazole against *Aspergillus* spp.

Species	Method	Isolates	MIC parameter (mg/L)				
		(n)	MIN	MAX	MIC_{50}	MIC_{90}	GM
All	CLSI	1,717	0.06	32	0.5	2	0.65
	EUCAST	1,563	0.004	16	1	2	0.75
A. fumigatus	CLSI	875	0.12	8	1	1	0.79
	EUCAST	434	0.12	16	1	1	0.8
A. flavus	CLSI	145	0.12	16	1	4	0.89
	EUCAST	233	0.12	4	1	2	1.1
A. niger	CLSI	101	0.12	32	1	2	0.97
	EUCAST	222	0.25	16	2	4	2.24
A. terreus	CLSI	432	0.06	32	0.25	1	0.39
	EUCAST	431	0.06	8	0.5	4	0.65
A. nidulans	CLSI	85	0.12	16	0.5	1	0.39
	EUCAST	206	0.004	8	0.12	0.5	0.19

In a study of isavuconazole using CLSI and EUCAST methodologies, DNA sequencing identified 189 *A. terreus* complex, 15 *A. hortai* and 30 falling in the *Aspergillus terrei* complex. Against all isolates, isavuconazole had a CLSI MIC_{90} of 0.5 mg/L and a EUCAST MIC_{90} of 1 mg/L.

Acquired azole resistance in *Aspergillus* is relatively uncommon, except for fluconazole, and usually involves one or more mutational events in the gene encoding CYP51A. In addition, the CDR1B efflux transporter is associated with non-CYP51A-mediated itraconazole resistance in *Aspergillus fumigatus*. Other mechanisms have been identified in *Candida* species (efflux pumps, over-expression of altered CYP51A and bypass pathways). Little is known about resistance mechanisms in other fungal species.

Sixteen laboratory-derived isavuconazole-resistant mutants did not have point mutations in the *CYP51A* or *CYP51B* gene and showed no or a slight variation in the expression profile of the four efflux pump genes (*MDR*1-4). All of the resistant mutants showed cross-resistance with at least one of itraconazole and voriconazole. There was no clear evidence that acquired isavuconazole resistance reduced fitness in non-clinical infection models.

Aspergillus fumigatus (40) with *CYP51A* mutations conferring azole resistance were tested against isavuconazole using the CLSI methodology. The strains included 31 with alterations in their *CYP51A* sequence at M220 (n=9), G54 (n=6), G138/Y431/G434/G448 (n=5), L98 (n=3) and other mutations (n=8). The remaining nine strains were allocated to the group for wild-type *CYP51A* sequence.

All had MICs > 8 mg/L for itraconazole MICs, of which 77% (24/31) and 68% (21/31) had raised MICs of posaconazole and voriconazole, respectively. The isavuconazole MIC ranges of the *CYP51A*-mutated and wild type isolates were 0.5–>8 and 0.5–2 mg/L, respectively. Strains with alterations L98H, G138C, Y431C, G434C and G448S showed elevated MICs to all triazoles including isavuconazole.

Isavuconazole MICs showed the highest degree of correlation with those for voriconazole (Spearman's correlation coefficient 0.885, $p < 0.001$). Isavuconazole MICs were more likely to be raised in strains of *A.*

fumigatus with reduced susceptibility to other triazoles, and tended to mirror changes in voriconazole susceptibility. There was no correlation between MICs for isavuconazole and ampB (-0.165, p <0.307).

In a study of *A. fumigatus* isolates with various *CYP51A* mutations strains with mutations in the G54 and M220 codons had similar isavuconazole MICs to the wild-type isolates. Among the G54 and M220 mutants 10/80 MICs were >2 mg/L. *A. fumigatus* isolates with TR_{34}/L98H alterations tended to have higher isavuconazole MICs (29/40 were >2 mg/L). The activity of isavuconazole against *A. fumigatus* may be less affected by mutations at codons G54 and M220 compared with TR_{34}/L98H.

The PK/PD relationship of isavuconazole in a neutropenic murine model of invasive pulmonary aspergillosis (IPA) was examined to assess the optimal drug exposure for infection due to wild-type and *CYP51* mutant isolates. A dose-response relationship was observed and higher doses were needed to achieve an antifungal effect against isolates with elevated isavuconazole MICs. The total drug AUC/MIC associated with net stasis for the *CYP51* wild-type group ranged from 415-1111 whereas for isolates F14403 and F14532 (the *CYP51* mutant) it was slightly lower at 361-367. For all isolates where net stasis was achieved, the median static dose total drug AUC/MIC was 503. The 1 $\log_{10}$ kill total drug AUC/MIC was ~2-fold higher than the static dose PD target, with a median value of 1111. AUC/MIC was a strong predictor of observed outcome (R^2 = 0.75).

The PK/PD relationship for isavuconazole was investigated in a validated dynamic *in vitro* model of the human alveolus using two wild-type and two mutant strains of *Aspergillus fumigatus*. The galactomannan index (GMI) was used as a quantitative biomarker to evaluate the antifungal efficacy of isavuconazole. Exposure-response relationships with a trough concentration of 0.2-0.5 mg/L were observed for green fluorescent protein (GFP) and non-GFP expressing wild types with near maximal suppression of GM release. In contrast, only the highest concentration of isavuconazole suppressed GM in the F/16216 mutant and no suppression was noted for the F/11628 mutant strain. An AUC/MIC ratio of 11.40 resulted in a 90% probability of galactomannan suppression <1.

From the two phase 3 studies, 136 baseline fungal isolates from 102 isavuconazole-treated patients (studies 9766-CL-0103 and 9766-CL-0104) and 28 baseline fungal isolates from 25 voriconazole-treated patients (study 9766-CL-0104) were tested for susceptibility to isavuconazole and other antifungal drugs. The most common genus from both studies was *Aspergillus spp*. with *A. fumigatus* (n=37, isavuconazole: studies 9766-CL-0104/9766-CL-0103; n=17 voriconazole: study 9766-CL-0104) as the most common species. Although MIC values for isavuconazole were generally similar to voriconazole MIC values, it is noted that regarding some *Aspergillus* isolates, isavuconazole MIC values of 8-32 were reported (this was irrespective of the testing method used (CLSI or EUCAST). MICs for posaconazole were in general lower, see table below:

Table 3 MIC Values for isavuconazole and Other Antifungal Drugs for Baseline Fungal Isolates from isavuconazole-Treated Patients per EUCAST Methodology from Study 9766-CL-0104 (mITT population)

Organism Genus species (No. isolates collected)	MIC †	AmB	CAS‡	ISA	POS	VOR
Aspergillus spp. (51)	MIC Range (mg/L)	0.5-32	0.12-1	0.25-32	0.25-1	0.25-32
	MIC_{50}	4	0.12	1	0.5	1
	MIC_{90}	4	0.25	2	1	4
Aspergillus flavus (9)	MIC Range (mg/L)	0.5-4	0.12-0.25	0.25-2	0.25-1	1-4
Aspergillus fumigatus (28)	MIC Range (mg/L)	2-4	0.12-1	0.25-32	0.25-1	0.25-32
	MIC_{50}	4	0.25	0.5	0.5	0.5
	MIC_{90}	4	0.25	2	1	4
Aspergillus niger (7)	MIC Range (mg/L)	1-2	0.12-0.25	1-8	0.5-1	0.5-4
Aspergillus terreus (6)	MIC Range (mg/L)	0.5-8	0.12-1	0.25-2	0.25-1	0.5-32
Aspergillus westerdijkiae (1)	MIC Range (mg/L)	32	1	4	1	32

AmB: amphotericin B; CAS: caspofungin; EUCAST: European Committee for Antimicrobial Susceptibility Testing; ISA: isavuconazole; MIC: minimum inhibitory concentration; mITT: modified intent-to-treat; POS: posaconazole; ULOQ: upper limit of quantification; VOR: voriconazole.

mITT: All ITT patients who have proven or probable invasive fungal disease as determined by the data review committee.

If a MIC value is reported as >ULOQ, then the MIC value is imputed as single two-fold dilution above the ULOQ and used in this summary.

† The MIC50 and MIC90 are not reported if the number of isolates is less than 10.

‡ Sensitivities to CAS are measured as minimum effective concentrations (MEC).

Mucorales *species*

MIC data were entered on a total of 374 worldwide isolates of Mucorales from 5 genera. Using CLSI methodology isavuconazole exhibited MIC_{50} and MIC_{90} values of 1–4 and 2–32 mg/L, respectively.

Table 4 MIC distributions for isavuconazole against Mucorales

Genus	Species	MIC parameter (mg/L)					
		Isolates (n)	MIN	MAX	MIC_{50}	MIC_{90}	GM
Absidia spp.	All	67	0.12	32	1	8	1.57
	A. corymbifera	44	0.12	8	1	8	1.37
	Absidia sp.	23	0.5	32	1	32	2.06
Cunninghamella spp.	All	13	0.25	32	4	32	4.45
Mucor spp.	All	68	0.12	32	4	16	3.65
	M. circinelloides	18	2	8	4	8	3.7
Rhizomucor spp.	All	18	0.12	8	1	4	1.08
	All (EUCAST)	9	2	16	16	16	10.08
Rhizopus spp.	All	134	0.12	32	1	8	1.48
	R. arrhizus	28	0.12	8	2	4	2.15
	R. microsporous	41	0.5	32	1	2	1.05
	R. oryzae	11	0.5	4	1	4	1.46
	Rhizopus sp.	52	0.12	32	1	16	1.53
	Rhizopus spp. (MFC)	14	1	32	8	32	7.61

All isolates were tested using CLSI methodology except for *Rhizomucor* spp. MFC was determined for 14 *Rhizopus* spp.

Several other studies have been conducted to determine the *in vitro* activity of isavuconazole. Some of the most pertinent are mentioned above. In each case it was clear that for some Mucorales the MIC_{50} values exceed the breakpoints proposed for *A. fumigatus*. Overall, isavuconazole has shown variable *in vitro* activity against isolates of the Mucorales order (*Absidia* spp., *Cunninghamella* spp., *Mucor* spp., *Rhizomucor* spp. and *Rhizopus* spp.), often studied in low numbers. Isavuconazole tended to be most active against *Rhizomucor* and *Rhizopus* spp. in vitro (MIC_{90}: 4–16 mg/L) and had the lowest *in vitro* activity against *Cunninghamella* spp. (MIC_{90}: 16–32 mg/L).

Additional MIC data on Mucorales (Arendrup 2015 and Cuenca Estrella 2015) were submitted. MICs using the EUCAST method (n=154) and CLSI method are shown in the following tables. There is a clear difference in MIC when both methods are compared, which is due to methodological differences, resulting in 1-2 dilutions higher MICs with the EUCAST method. The MIC pattern presented within the initial application is generally in line with that reported by Arendrup (2015) and Cuenca Estrella (2015), however MICs were generally higher within the initial application. With the currently recommended posology of isavuconazole, the average isavuconazole plasma trough level is approximately 4 mg/L (phase 3 clinical studies 9766-CL-0103 and 9766-CL-0104). It is therefore expected that plasma levels will be attained that are above the EUCAST MIC of only a few Mucorales species (for instance *Rhizopus* and *Rhizomucor*). *Lichtheimia* species are less susceptible and *Mucor* species are regarded not susceptible to isavuconazole. However, the clinical relevance of these MICs cannot be derived from these data only.

Table 5 Isavuconazole MIC distributions on Mucorales isolates using the EUCAST method (n=154)

Species	MIC (mg/L)								
	≤ 0.06	0.125	0.25	0.5	1	2	4	8	16
Lichtheimia corymbifera (26)	-	1	-	6	12	3	1	2	1
Lichtheimia ramosa (19)	-	1	3	3	4	4	3	1	-
Rhizomucor miehei (2)	-	-	-	-	1	1	-	-	-
Rhizomucor pusillus (18)	-	-	-	7	5	5	-	1	-
Mucor circinelloides (16)	2	-	-	1	-	1	2	7	3
Mucor circinelloides, G-I (5)	-	-	-	-	-	-	2	3	-
Mucor circinelloides, G-II (9)	-	-	-	-	1	-	1	5	2
Rhizopus arrhizus (16)	-	-	-	2	4	5	3	2	-
Rhizopus microsporus (37)	-	-	-	13	19	3	2	-	-
Rhizopus oryzae (6)	-	-	-	1	2	2	1	-	-
Percentage isolates at MIC	**1.32**	**1.32**	**1.97**	**22**	**31**	**16**	**9**	**14**	**4**
Cumulative percentage	**1.32**	**2.64**	**4.61**	**26**	**57**	**73**	**82**	**96**	**100**

Table 6 **Isavuconazole MIC distributions on Mucorales isolates using the CLSI method (n=154)**

Species	MIC (mg/L)								
	≤ 0.06	0.125	0.25	0.5	1	2	4	8	16
Lichtheimia corymbifera (26)	6	3	1	2	10	3	1	-	-
Lichtheimia ramosa (19)	6	2	1	4	3	3	-	-	-
Rhizomucor miehei (2)	-	-	1	-	-	1	-	-	-
Rhizomucor pusillus (17)	2	1	1	6	5	1	1	-	-
Mucor circinelloides (16)	6	-	1	-	3	2	3	1	-
Mucor circinelloides, G-I (5)	-	-	-	-	-	3	1	-	-
Mucor circinelloides, G-II (9)	-	-	-	-	1	-	3	5	-
Rhizopus arrhizus (16)	3	4	6	2	1	-	-	-	-
Rhizopus microsporus (37)	9	6	6	13	3	-	-	-	-
Rhizopus oryzae (6)	-	1	-	-	4	1	-	-	-
Percentage isolates at MIC	**21.1**	**11.2**	**11.2**	**18**	**20**	**8**	**7**	**4**	**0**
Cumulative percentage	**21.1**	**32.2**	**43.4**	**61**	**81**	**89**	**96**	**100**	**100**

Note: one strain of *M. circinelloides* G-I and one strain of *Rhizomucor pusillus* did not grow sufficiently at 24 h or 48 h to read an MIC.

In vivo efficacy was assessed in neutropenic and diabetic ketoacidotic (DKA) mouse models using intratracheal infection with *R. oryzae* 99-880 and treatment with isavuconazole 43, 59, and 116 mg/kg orally TID starting at 8 h for 5 days. The 116 mg/kg group had significantly ($p < 0.05$) higher 21-day survival rates vs. placebo (70% vs. 10%). Isavuconazole was as effective as LAmB in treating pulmonary mucormycosis infections with *R. oryzae* in neutropenic mice. After 21 days, the survival rates for isavuconazole-, LAmB-, and placebo-treated mice were 65%, 40%, and 15%, respectively. Isavuconazole decreased lung and brain fungal burden by approximately one log compared with the placebo group. A similar decrease in lung and brain was noted in the LAmB-treated animals.

The relevance of these animal models for the use of isavuconazole in clinical practice remains however uncertain.

In study 9766-CL-0103 19 baseline organisms of the Mucorales order were tested for susceptibility. The most common species isolates were *Rhizopus oryzae* (9), followed by *Rhizomucor pusillus* (3) and *Lichtheimia (Absidia) corymbifera* (3). Overall, isavuconazole MIC values ranged from 0.25 to 32 mg/L (CLSI and EUCAST). The EUCAST MIC range values for isavuconazole are shown in the following table.

Isavuconazole MIC values for Mucorales were considerably higher than for *Aspergillus spp*., which is considered problematic in the treatment of mucormycosis.

Table 7 MIC Values for ISA and Other Antifungal Drugs for Baseline Isolates from the Mucorales Order per EUCAST Methodology from Study 9766-CL- 0103 (mITT)

Organism Genus (No. isolates collected)	MIC†	AmB	CAS‡	ISA	POS	VOR
Rhizopus oryzae (9)	MIC Range (mg/L)	0.25-4	32-128	0.25-32	0.5-32	16-32
Actinomucor elegans (1)	MIC Range (mg/L) (mg/L)	2	128	4	0.5	32
Lichtheimia (Absidia) corymbifera (3)	MIC Range (mg/L)	0.25-2	32-128	8-16	0.5-1	32-64
Rhizomucor pusillus (3)	MIC Range (mg/L)	0.5-1	32-64	4- 8	1	32
Rhizopus azygosporus (1)	MIC Range (mg/L)	2	1	0.5	1	2
Rhizopus microsporus (1)	MIC Range (mg/L)	2	64	4	8	16
Mucor circinelloides (1)	MIC Range (mg/L)	2	64	32	32	16

AmB: amphotericin B; CAS: caspofungin; CLSI: Clinical and Laboratory Standards Institute; ISA: isavuconazole; MIC: minimum inhibitory concentration; mITT: modified intent-to-treat; POS: posaconazole; ULOQ: upperlimit of quantification; VOR: voriconazole.

mITT: All ITT patients who have proven or probable invasive fungal disease as determined by the data review committee.

If a MIC value is reported as >ULOQ, then the MIC value is imputed as single two-fold dilution above the ULOQ.

† The MIC_{50} and MIC_{90} are not reported if the number of isolates is less than 10.

‡ Sensitivities to CAS are measured as minimum effective concentrations (MEC).

Relationship between plasma concentration and effect

Aspergillus

Probability of target attainment analysis (PTA) was estimated for a range of MICs using Monte Carlo simulations, taking into account the mean population estimates from the best 2-compartment model with covariates. Concentration-time profiles (n=5000) were simulated to steady state based on the phase 3 regimen (200 mg q8h for 48 h and then QD). The total drug AUC/MIC targets estimated in the non-clinical models ranged from 11.2 to 503 when MICs were based on CLSI methodology and from 11.4 to 24.7 when based on EUCAST methodology. The above suggested that the phase 3 regimen would suffice to treat *Aspergillus spp.* with MICs up to 1 mg/L under CLSI methodology and 2 mg/L under EUCAST methodology.

Exposure-response analyses were based on data from 232 patients with aspergillosis who were treated with isavuconazole in the phase 3 study 9766-CL-0104. Separate models were developed for mortality at day 42, DRC adjudicated overall response at EOT and DRC adjudicated clinical response at EOT for both ITT and mITT populations. Mortality was modelled as a binary outcome; the overall and the clinical responses were modelled as ordinal and also as binary responses.

AUC, concentration at steady state, concentration at day 7, concentration at day 14 and concentration after loading dose were the PK parameters analysed against efficacy endpoints. None of these primary exposure parameters were found to be statistically significant for any of the efficacy endpoints.

The applicant concluded that the absence of any relationship between exposure and response indicated that patients had plasma levels above the AUC/MIC breakpoint and factors other than exposure had a greater

impact on response than exposure to isavuconazole. Modelling confirmed that in the phase 3 population, exposures were adequate to treat organisms seen in the studies. Lack of association between exposure and response would be expected if exposures exceed the AUC/MIC target for organisms within the wild type population with MIC_{90} of 1 or 2 mg/L for *Aspergillus* species.

During the procedure, EUCAST has recommended and CHMP has endorsed the following clinical breakpoints for *Aspergillus* species that were included in SmPC section 5.1:

- *Aspergillus fumigatus:* S ≤ 1 mg/L, R > 1 mg/L
- *Aspergillus nidulans:* S ≤ 0.25 mg/L, R > 0.25 mg/L
- *Aspergillus terreus:* S ≤ 1 mg/L, R > 1 mg/L

S=susceptible, R=resistant

There are currently insufficient data to set clinical breakpoints for other *Aspergillus* species.

Mucorales

Positive cultures and MIC testing results were available for *Mucorales* from only fifteen patients. Of the patients that were infected with pathogens with MICs of ≤ 4mg/L, 5 out of 7 (71%) had a complete/partial/stable response and in 2 out of 7 (29%) patients fungal disease progressed. Of the patients that were infected with pathogens with MICs of ≥ 8 mg/L, 2 out of 8 (25%) had a complete/partial/stable response and in 6/8 (75%) patients fungal disease progressed.

In 24/37 patients fungal pathogens from the families of *Mucoraceae* (Genera *Actinomucor*, *Mucor*, *Rhizomucor* and *Rhizopus*), *Cunninghamellaceae* (Genus *Cunninghamella*) and *Lichtheimiaceae* (Genus *Lichtheimia* [former *Absidia*]) were identified. The most common pathogen was *Rhizopus oryzae* (7/24, 29%). Other pathogenes identified were *Mucor NOS* (5), *Rhizomucor pusillus* (4), *Lichtheimia corymbifera* (2), *Rhizopus azygosporus* (1), *Rhizopus microsporus* (1), *Rhizomucor* (1), *Mucor amphibiorum* (1), *Actinomucor elegans* (1), *Cunninghamella* (1).

From the available data, no clear relationship appears evident between fungal species and clinical outcome. In case of the patients infected with the most common identified species *Rhizopus oryzae*, 4/7 failed on isavuconazole therapy, while 2/7 cured completely and 1/7 cured partial. The four patients infected by *Rhizomucor pusillus* all failed on therapy. MICs of *Rhizomucor pusillus* identified in study 9766-CL-0103 (n=4) were considerably higher than those reported in the tables presenting the data of Arendrup (2015) and Cuenca Estrella (2015).

No recommendations for clinical breakpoints for Mucorales species were made by EUCAST.

Secondary pharmacology

Isavuconazole produced a limited blockade of the hERG potassium channels *in vitro* (IC50 = 5.82 ìM or 2.55 ìg/mL = 49-fold unbound Cmax at steady state with 200 mg QD), which is similar to the IC50 for ketoconazole (5.46 ìM).

A QT study was conducted in 161 subjects aged 18-55 years as follows:

Table 8 Dose regimen by treatment group

Day	Treatment Groups			
	Isavuconazole		Placebo (n = 40)	Moxifloxacin (n = 40)
	200 mg (n = 40)	600 mg (n = 40)		
Days 1-2	200 mg oral isavuconazole tid	200 mg oral isavuconazole tid	placebo oral tid	placebo oral tid
Days 3-12	200 mg oral isavuconazole qd	600 mg oral isavuconazole qd	placebo oral qd	placebo oral qd
Day 13	200 mg oral isavuconazole	600 mg oral isavuconazole	placebo oral	400 mg oral moxifloxacin

On days -2, -1 and 13 a continuous ECG was recorded for ~24 h. ECGs extracted on days -1 and 13 were measured automatically with a manual over-read by a trained reader at a central ECG laboratory in a blinded manner. Blood PK samples were collected on days 11 and 12 (within 15 minutes pre-dose) and then on day 13 pre-dose [0 hour] and at timed intervals up to 24 h post-dose. Moxifloxacin was assayed in samples obtained at these same times on day 13.

Of 161 healthy subjects enrolled, 148 (91.9%) completed the study and were included in the ECG analysis.

On day 13 the mean Cmax and AUC24 were higher in the 600 mg vs. 200 mg isavuconazole group compared to the 200 mg isavuconazole treatment group. Trough levels on days 11-13 showed that isavuconazole was approaching steady state.

For the isavuconazole 200 mg and 600 mg treatment groups, the mean change from placebo baseline-adjusted in QTcF decreased by 9 to 13 ms and by 19 to 25 ms, respectively, within 1 h and 24 h post-dose.

The assay sensitivity was assessed at 2 h (median tmax for moxifloxacin) at which time the effect size was 11.03 ms with a lower bound of 7.14 ms. The lower bound of the maximum treatment difference between placebo and moxifloxacin at the nominal assessment time was > 5 ms, so assay sensitivity was confirmed.

No subjects had QTcF > 450 ms or an increase from baseline >30 ms in the isavuconazole groups. Decreases from baseline in QTcF > 30 ms were observed in 13 (40.6%) in the 600 mg group and in 7 (18.9%) in the 200 mg group vs. one (2.6%) subject in the placebo group. No subjects had an increase or decrease from baseline in QTcF > 60 ms on day 13.

Table 9 Number and Percentage of Subjects with Extreme QTcF Values at any Time Point on Day 13

Parameter	Placebo (n = 39)† n (%)	Isavuconazole 200 mg (n = 37)† n (%)	Isavuconazole 600 mg (n = 32)† n (%)	Moxifloxacin (n = 40)† n (%)
Extreme values‡				
< 360 msec	1 (2.6)	4 (10.8)	8 (25.0)	3 (7.5)
< 330 msec	0	0	0	0
< 300 msec	0	0	0	0
> 450 msec	2 (5.1)	1 (2.7)	0	6 (15.0)
> 480 msec	0	0	0	0
> 500 msec	0	0	0	0
Change from baseline§				
>30 msec increase	3 (7.7)	0	0	4 (10.0)
>60 msec increase	0	0	0	0
>30 msec decrease	1 (2.6)	7 (18.9)	13 (40.6)	1 (2.5)
>60 msec decrease	0	0	0	0

It was concluded that multiple doses of 200 mg and 600 mg isavuconazole did not prolong the QTcF interval. There was a negative relationship between ddQTcF and isavuconazole plasma concentrations with predicted mean ddQTcF at Cmax for the 200 mg and 600 mg treatment groups of -13.84 and -26.80, respectively.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The absolute bioavailability of the oral formulation is 98%. Compared to that obtained after i.v. administration (500ml/2h) the isavuconazole Cmax after oral administration is about 22% lower, which is considered not clinically relevant. Based upon comparable exposures after oral and i.v. administration, both formulations can be interchanged. Moreover, food did not affect isavuconazole exposure, so it can be taken with or without food. A high distribution volume is observed (about 450 litres), indicating that isavuconazole is well distributed. Isavuconazole is extensively metabolized, however, it is a low clearance medicine and in plasma, exposure accounted mainly for intact drug. In addition, applying a loading dose of 200 mg t.i.d. for 2 days, followed by a maintenance dose of 200 mg q.d. resulted in a rapid achievement of steady state at day 3 and high trough levels of around and above 3 µg/ml. The trough values were above the targeted clinical MIC values of 1-2 µg/ml of especially *Aspergillus*. For Mucorales higher levels seems to be needed. However, a dose–response relationship for both was not identified (see section on pharmacodynamics).

Renal impairment had no influence on the pharmacokinetics of isavuconazole and as such it can be given to this patient group without a need to adjust the dose. In patients with mild and moderate hepatic impairment clearance after i.v. administration decreased by 30 and 50%, respectively, resulting in increased exposures of about 60 and 120%. After oral dosing, comparable results were observed. No dose adjustment is necessary, but an increase in AEs may be expected due to the increased exposure. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh C). Therefore the Cresemba SmPC indicates that the isavuconazole use in these patients is not recommended unless the potential benefit is considered to outweigh the risks.

With regard to interactions, the isavuconazole PK is mainly affected by inhibition and induction of CYP3A4. The strong inhibitor ketoconazole increased isavuconazole exposure more than 5-fold, and is contraindicated. The strong CYP3A4 inhibitor lopinavir/ritonavir, increased the plasma exposure of isavuconazole by about 2-fold, therefore no dose adjustment is necessary, however caution is advised. This recommendation is also

applicable to other strong CYP3A4 inhibitors, as they are considered to have a similar or a less potent CYP3A4 inhibition compared to lopinavir/ritonavir. Inducers may decrease plasma exposure to a great extent. As such, strong and moderate inducers are contraindicated, and mild inducers should be avoided unless the benefit outweighs the risk. Moreover, isavuconazole mainly affect CYP3A4 substrates (increase, but also decreases observed), CYP2B6 substrates (decreases due to induction), UGT substrates (decreases due to induction), BCRP substrates (increase due to inhibition) and P-gp substrates (increases due to inhibition) resulting in warnings. In general the interaction potential is sufficient elucidated.

In comparison to voriconazole, isavuconazole is more sensitive for CYP3A4 inhibitors. However, both increase CYP3A4 substrates, but voriconazole is a strong CYP3A4 inhibitor whereas isavuconazole is a moderate inhibitor. Both increase tacrolimus levels to the same extent, i.e. about 2.2-fold. With regard to CYP2B6 and UGT substrates, isavuconazole is less favorable, as being an inducer of these substrates.

Pharmacodynamics

The mechanism of action is that of other triazoles. The selectivity ratio for isavuconazole was similar to that reported for voriconazole, indicating that it will likely have moderate inhibitory activity against the human P450 enzyme with attendant implications for the safety profile.

Invasive aspergillosis

MIC breakpoint and probability of target attainment analysis (*Aspergillus spp*.)

In the dose fractionation experiments, the AUC/MIC targets for *Aspergillus spp*. were described as total drug ratios (median 503 for stasis and 1111 for 1-log kill). The PTA was estimated based on this AUC/MIC ratio of 503 for stasis and based on alternative targets derived from other in-vivo studies as well as from an in-vitro model with reduction in galactomannan to < 1 as an endpoint.

It was unknown why the focus was on the total drug and not on the free drug, but the applicant has adequately explained the reasons for using total drug concentration for PK/PD analyses. The precision of the validated method does not allow sufficient differentiation between the average free fractions of 1.05% and 0.74% (1.4-fold) in mouse and human plasma, respectively.

PTA was estimated based on these (very) different targets and separately for EUCAST vs. CLSI MICs and the results were very different for CLSI MICs using the three targets assessed, such that the PTA would suggest that the highest treatable MIC could be anywhere from 0.06 to 4 µg/mL. The applicant has explained the differences between the three models (one *in vitro* and 2 *in vivo)*, but it was considered that this did not really address which model provided the most relevant PD target. It was also not accepted that the neutropenic mouse *overestimated* the PD target. Generally speaking the PK/PD analyses were deemed of a rather poor quality and although the efficacy in the treatment of aspergillosis is recognised, it could not be excluded that a different dose regimen could have provided even better results. CHMP agreed nevertheless that this issue should not be further pursued and should be considered resolved.

The exposure-response analyses are based on PK samples from the very small PK sub-population, which means that there was inadequate sampling in the study for exposure-response analyses. As a result of these inadequate attempts to characterise the PK/PD relationship, the selection of the final dose regimen tested in phase 3 could only really be supported by the PK properties of isavuconazole and by the rather crude comparisons between plasma levels and MICs.

From the 8 patients infected with *Aspergillus* with elevated MICs to isavuconazole (≥ 8 mg/L) and who failed to isavuconazole therapy, all presented trough values below 8 mg/l total drug concentration. The average

isavuconazole plasma trough level is approximately 4 mg/L, however, the data suggest a strong inter-individual variation with regard to trough levels, even after 14 and 42 days of treatment.

During the procedure, EUCAST has recommended and CHMP has endorsed the following clinical breakpoints for *Aspergillus* species that were included in SmPC section 5.1:

- *Aspergillus fumigatus:* S ≤ 1 mg/L, R > 1 mg/L
- *Aspergillus nidulans:* S ≤ 0.25 mg/L, R > 0.25 mg/L
- *Aspergillus terreus:* S ≤ 1 mg/L, R > 1 mg/L

S=susceptible, R=resistant

There are currently insufficient data to set clinical breakpoints for other *Aspergillus* species.

The association of azole trough levels and clinical response has been discussed at length in the international literature and it is generally agreed that the dose-response relation for azoles is complex and ambiguous. Experimental PD models were performed to establish the exposure-response relationship associated with efficacy (PD index) and the target exposure was estimated and associated with the optimal exposure-response (E-R) relationship (PD target). For isavuconazole, the PD index suggested to be associated with efficacy as AUC/MIC [Lepak, et. al 2013]. For isavuconazole, Monte Carlo simulations have shown PTA of 95% for *Aspergillus fumigatus* with MICs that are common in the wild type isolates and below the epidemiological cut off values, which gives some support for probability of efficacy.

MIC breakpoint and probability of target attainment analysis (Mucorales)

Pharmacodynamic studies for the assessment of PD targets and indices have not been established for Mucorales organisms and MIC data from patients in the clinical trials are sparse. In addition, epidemiological cut-off values (ECVs) for organisms of the Mucorales order have not been established to date. Therefore, it is not possible to establish clinical interpretive breakpoints for organisms of the Mucorales order at this time.

In this context it is pertinent to note that isavuconazole demonstrates variable *in vitro* activity against individual species of the *Aspergillus* genus and against isolates of the Mucorales order (*Absidia* spp., *Cunninghamella* spp., *Mucor* spp., *Rhizomucor* spp. and *Rhizopus* spp.). Using the CLSI methodology the isavuconazole MIC_{50} and MIC_{90} against *Aspergillus spp*. were 1 and 4 µg/mL, respectively, with a range from 0.12-32 µg/mL. Among the Mucorales isavuconazole was most active against *Rhizomucor* and *Rhizopus,* for which the MIC_{90} was 4–16 µg/mL, and least active against *Cunninghamella* spp. (MIC_{90}: 16–32 µg/mL).

The applicant has submitted additional MIC data on Mucorales (source: Arendrup 2015 and Cuenca Estrella 2015). Although the MIC pattern presented within the initial application was generally in line with the MIC pattern reported by Arendrup 2015 and Cuenca Estrella 2015, the MICs in the original application were generally considerably higher.

In study 9766-CL-0103 there were 22 isolates of the Mucorales order tested for susceptibility, including *Rhizopus oryzae* (10), *Rhizomucor pusillus* (5) and *Lichtheimia (Absidia) corymbifera* (3). The MIC values ranged from 0.25 to 32 µg/mL, with similar results using CLSI and EUCAST methods. This variability is an important issue to consider, especially with regard to a claim for treatment of mucormycosis.

It is claimed in the clinical study report of study 9766-CL-0103 that successful outcomes were seen for organisms with MIC values as high as 8 µg/mL. This claim is not applicable to the organisms of interest. Specifically for Mucorales, CLSI MICs were compared to outcomes only for 3 Lichtheimia spp. (2 clinical and 3 microbiological failures; all MICs 8 µg/mL or more), 1 Mucor spp. (failure; MIC > 8 µg/mL), 3 Rhizomucor spp. (2 clinical and 3 microbiological failures; all MICs 8 µg/mL or more) and 11 Rhizopus spp. (10 clinical

failures and 8 microbiological failures; MICs from 0.5 to >8 µg/mL). The results based on EUCAST MICs were the same. With the currently recommended posology of isavuconazole, the average isavuconazole plasma trough level is approximately 4 µg/mL (phase 3 clinical studies 9766-CL-0103 and 9766-CL-0104). It is therefore expected that plasma levels will be attained that are above the EUCAST MIC of only a few Mucorales species.

The CHMP agreed that the applicant's proposal to apply a threshold trough level of 4 mg/L isavuconazole to determine the coverage of isavuconazole against Mucorales species in study 9766-CL-0103 was not acceptable. It was concluded that there was no clear relationship between the MIC of isavuconazole and clinical succes/failure in mucormycosis. Moreover the sparse available MIC values of pathogens in study 9766-CL-0103 were considerable higher (up to 32 µg/mL) when compared to those observed in the epidemiology studies (Arendrup 2015, Cuenca Estrella 2015). Since no dose response study was performed in mucormycosis, CHMP agreed that no recommendations with regard to any target trough levels could be made. The limitations of the clinical and *in vitro* data on Mucorales species are being described in the SmPC sections 4.4 and 5.1.

Resistance development

Several mechanisms of resistance have been described for the triazole class of antifungals, including mutations in the CYP51A gene that leads to alterations in the target enzyme (14-α-sterol-demethylase), upregulation of efflux pumps and mutations in the promoter region of CYP51A which leads to overexpression of the protein product.

A total of eighteen isolates collected from the phase 3 studies (9766-CL-0104 and 9766-CL-0103) of which 15 with elevated MICs to isavuconazole (≥ 8 mg/L) and 3 wild-type organisms from each genus for comparison were tested to identify the presence of any of the classic triazole resistance mechanisms [study 9766-PH-0127]. The results indicated that the mechanisms underlying the increased MIC to isavuconazole are similar to those observed for other triazoles in *Rhizopus*, *Fusarium* and *Aspergillus* isolates. These organisms exhibiting reduced susceptibility to isavuconazole also showed elevated MICs to most other azoles that were tested, suggesting cross-resistance can occur among these azoles. The SmPC is mentioning the possibility of cross-resistance in section 5.1.

The applicant was requested to provide a detailed analysis of underlying resistance mechanisms, including development of point mutations known to be associated with triazole resistance development, in addition to efflux mechanisms and to incorporate data on cross resistance between isavuconazole and voriconazole into section 5.1 of the SmPC. The applicant clarified that the resistance mechanisms are likely to be similar to azoles in general, particularly with cyp51A and cyp51B gene mutations being most relevant.

Two patients from the 2 studies had baseline and follow up MICs available for what was potentially the same isolate. In both cases MIC increased with at least 2 dilution steps. The applicant was asked to describe these patients in details, especially with regard to possible mechanisms of resistance development. From the data provided, it was not possible to draw any conclusions on the risk for selection of reduced susceptibility to isavuconazole from the available data. An appropriate proposal for the monitoring of resistance to isavuconazole in the post-approval period was included in the risk management plan.

Secondary Pharmacology

The outcome of QTc prolongation study 017 led to the inclusion of a contraindication regarding use in familial short QT syndrome in the Cresemba SmPC. CHMP requested the applicant to mention the findings of the

study, which convey the magnitude of the effect, in SmPC section 4.4. The applicant has amended the SmPC adequately.

2.4.5. Conclusions on clinical pharmacology

Regarding pharmacodynamics

Aspergillus

For isavuconazole, the PD index suggested to be associated with efficacy as AUC/MIC like for most azoles. Monte Carlo simulations have shown a PTA of 95% for *Aspergillus fumigatus* with MICs that are common in the wild type isolates and below the epidemiological cut-off values. As for other azoles, the dose-response relation for isavuconazole is complex. The efficacy results of the comparative phase 3 study 9766-CL-0104 versus voriconazole are however taken into consideration.

EUCAST has recommended clinical breakpoints *for Aspergillus fumigatus*, *Aspergillus nidulans* and *Aspergillus terreus*. There are currently insufficient data to set clinical breakpoints for other *Aspergillus* species. The CHMP endorsed the EUCAST recommendations.

Mucorales

It was concluded that the available microbiological data were inadequate to support a conclusion that isavuconazole, when used at the proposed posology, is suitable for the treatment of all Mucorales species. Moreover, the data suggested that some of the genera/species may be inherently insusceptible to isavuconazole. A pathogen-specific indication was not acceptable either. Further qualifications in sections 4.4 and 5.1 in the SmPC were implemented.

2.5. Clinical efficacy

Four clinical studies were performed. This application is mainly based on the results from two pivotal clinical trials, **9766-CL-0104** (invasive aspergillosis) and **9766-CL-0103** (mucormycosis):

Study ID	Design Control Type	Treatments	Enrolled/ Completed	Gender Mean Age (Range)	Inclusion Criteria	Primary Endpoint(s)
0104 Americas, Europe, Middle East, Africa, SE Asia, Pacific rim	Phase 3, randomized, multicentre, double-blind, non-inferiority, active controlled	Isavuconazole Loading Dose: 200 mg, IV q8h on days 1 and 2; Maintenance: 200 mg IV or oral q24h Voriconazole Loading dose: 6 mg/kg IV q12h on day 1; Maintenance dose: 4 mg/kg IV or 200 mg oral q12h	258/118 258/120	Male: 56.2% Female: 43.8% 51.1 (17-82) Male: 63.2% Female: 36.8% 51.2 (18-87)	Proven, probable or possible IFD caused by *Aspergillus* species or other filamentous fungi	Crude rate of all-cause mortality through day 42

Study ID	Design Control Type	Treatments	Enrolled/ Completed	Gender Mean Age (Range)	Inclusion Criteria	Primary Endpoint(s)
0103 EU, Americas, Asia and Middle East	Phase 3, open-label, uncontrolled, multicentre	Isavuconazole Loading dose: 200 mg, IV or oral q8h on days 1 and 2; Maintenance dose: 200 mg IV or oral q24h	146/72	Male: 68.5% Female: 31.5% 49.9 (18-92) (ITT)	As above in patients with CLCr <50 mL/min or proven/probable IFD due to moulds, yeasts or dimorphic fungi (other than *Aspergillus fumigatus* or *Candida* species) primary, refractory or intolerant to prior treatment	Outcome of treatment evaluated by the DRC at day 42

Phase 2 study 9766-CL-0101 was conducted in "uncomplicated oesophageal candidiasis" patients and study 9766-CL-0102 in "prophylaxis of patients undergoing chemotherapy for AML" patients; these studies are therefore considered as supportive only (for safety).

2.5.1. Dose response studies

No formal dose-response studies were conducted in support of any of the sought indications. The proposed dosing regimen was merely based on *in vitro* MIC data and on non-clinical studies in neutropenic rats and mice. Further considerations were to maximize both the exposure to isavuconazole (AUC/MIC) and the trough levels to recommend the dosage to be administered daily and not intermittently. To achieve steady-state levels more rapidly (e.g. within 3 to 4 days), a loading dose regimen on days 1 and 2 was administered. A minimum infusion duration of 1 hour (1.5 to 2 hours in this study to match the comparator) was recommended to minimize the risk of local intolerance at the injection site.

2.5.2. Main studies

Title of Study

Study 9766-CL-0104 A phase III, double-blind, randomized study to evaluate safety and efficacy of isavuconazole (BAL8557) versus voriconazole for primary treatment of invasive fungal disease caused by Aspergillus species or otherfilamentous fungi (the SECURE Study)

Methods

Study 9766-CL-0104 was a randomized, double-blind, double-dummy, non-inferiority, active-controlled study (versus voriconazole), which randomized 527 adult patients with proven, probable, or possible IFD caused by *Aspergillus* species or other filamentous fungi. Stratification factors included geographic region, allogeneic bone marrow transplant (BMT) status and uncontrolled malignancy status.

The chosen NI design (demonstration of non-inferiority towards a reference drug) is considered acceptable by CHMP and in line with the CHMP Guidance on antifungal agents (CHMP/EWP/1343, 2010). Voriconazole is a well-established comparator and the preferred antifungal drug in the treatment of invasive aspergillosis.

Study Participants

Eligible patients were aged ≥ 18 years, including females not at risk of pregnancy, and had proven, probable or possible IFD caused by *Aspergillus* species or other filamentous fungi. The EORTC/MWG definitions were applied.

If invasive diagnostic procedures were not successful in establishing the diagnosis or were not possible, a serum galactomannan [GM; Platelia *Aspergillus* EIA] single value ≥ 0.7 or two consecutive values ≥ 0.5 - < 0.7 were considered as acceptable mycological evidence for the enrolment as probable IFD (except in patients receiving amoxicillin-clavulanate, piperacillin-tazobactam or Plasma-Lyte™). GM in BAL, pleural fluid or cerebrospinal fluid was not acceptable for enrolment, except for those cases with two BAL GM values ≥ 1.0 (2 aliquots of the same sample), which were enrolled as *possible* IFD. Other diagnostic tests (e.g. PCR or β-D-glucan) were not acceptable for determining patient eligibility.

Important exclusions included:

- High risk for QT/QTc prolongation, including those on concomitant medications that are known to prolong the QT/QTc interval
- Evidence of hepatic dysfunction defined as: total bilirubin ≥ 3 x ULN, ALT or AST ≥ 5 x ULN, known cirrhosis or chronic hepatic failure
- Use of potentially interacting drugs
- Chronic aspergillosis, aspergilloma or allergic bronchopulmonary aspergillosis (ABPA)
- More than 4 cumulative days of itraconazole, voriconazole or posaconazole within the 7 days prior to the first dose of study medication
- Advanced HIV with CD4 count < 200 or AIDS-defining condition
- BW ≤ 40 kg
- CrCL < 50 mL/minute; on or likely to require dialysis

Due to the restrictions on the use of i.v. voriconazole in patients with moderate to severe renal impairment, related to the presence of a cyclodextrin excipient, the study excluded renally impaired patients (estimated creatinine clearance < 50 mL/min). Supportive evidence on the efficacy of isavuconazole in these patients is provided by study 9766-CL-0103 (mucormycosis), which enrolled a subpopulation of renally impaired patients with invasive aspergillosis.

Treatments

The study treatment schedule included i.v. loading doses for 1-2 days followed by i.v. infusion or oral capsules for maintenance treatment until EOT. Isavuconazole was administered in loading dose of 200 mg every 8 hours i.v. for 2 days (6 doses) followed by a maintenance dose of 200mg i.v. or p.o. daily. Voriconazole was administered in a loading dose of 6 mg/kg every 12 hours i.v. for one day (2 doses) followed by a maintenance regime of 4 mg/kg i.v. or 200 mg orally every 12 hours.

Study 9766-CL-0104 precluded the use of therapeutic drug monitoring (TDM) to adjust for the voriconazole dose. The applicant was asked to discuss the implications of this for the overall efficacy/safety comparison in study 9766-CL-104, in particular to discuss the efficacy observed with voriconazole for the subsets that did and did not undergo an early switch from iv to p.o voriconazole. From the applicant's response it was understood that patients that switched early to oral treatment (≤ Day 7) had a better prognosis than patients who did not. A detailed reanalysis of the efficacy and safety data based on proxy variables which may have affected the drug levels of voriconazole (such as BMI and ethnicity) did not suggest any confounding of the main study outcomes.

Therapeutic drug monitoring of voriconazole (and posaconazole) has been described in recent published literature (Pascual A. 2012[1]. Park WB, 2012[2] and (Ashbee HR 2014[3]). Whether or not voriconazole was used suboptimal in part of the patients, remains unclear. However, also patients treated with isavuconazole could theoretically benefit from TDM. The reasons of the applicant not to consider TDM at the time of the conduct of pivotal study 9766-CL-004 (in 2006), "since TDM was not well established yet" and "TDM of voriconazole would potentially have jeopardised the blinding of the study" are considered understandable and acceptable by CHMP.

The switch from i.v. to oral administration of study drug was to be made as early as possible from day 3 onward. Patients remained on therapy until they had reached a treatment endpoint or until they had received treatment for a maximum period of 84 days. Treatment was to continue for at least 7 days after resolution of all clinical symptoms and physical findings of infection. Non-study systemic antifungal medication is allowed only after the day 42 visit, unless the patient is a failure prior to the day 42 visit.

Objectives

The primary objective of the study was to compare all-cause mortality through day 42 following primary treatment with isavuconazole versus voriconazole in patients with IFD caused by *Aspergillus* species or other filamentous fungi.

The secondary objectives of the study were to characterize the safety and tolerability while assessing additional efficacy of treatment with isavuconazole versus voriconazole.

Exploratory objectives were to summarize the concentration-time profiles and to characterize pharmacokinetic trough values of isavuconazole and metabolite(s) in patients from a pharmacokinetic (PK) substudy.

Outcomes/endpoints

The primary efficacy endpoint was crude rate of all-cause mortality through day 42 in the ITT-Population.

Secondary efficacy endpoints were DRC-assessed overall response at EOT (key secondary analysis) and at days 42 and 84, all-cause mortality through day 84, DRC attribution of mortality to IFD, investigator assessment of clinical, mycological and radiological response, impact of the use of potentially mould active systemic antifungal therapy (AFT), and the results of minimum inhibitory concentration (MIC) testing.

All-cause mortality through day 42 in the ITT population was further analyzed for the various intrinsic and extrinsic factors including several subgroups (age, gender, race, ethnicity, BMI, eGFR-MDRD category and neutropenia) and by stratification factors relating to underlying disease (i.e. uncontrolled malignancy versus allogeneic BMT/HSCT) which is considered appropriate. The reason for stratification by region was based on the similarities in the health care systems and the provision of standard of care.

The applicant's choice of having mortality as the primary endpoint was criticized during several scientific advices as it was not considered in accordance with the *Guideline on the clinical evaluation of antifungal agents for the treatment and prophylaxis of invasive fungal disease* (CHMP/EWP/1343/01 Rev 1, 2010) which recommends "overall clinical response" as the primary outcome measure. Mortality may result from causes unrelated to IFD in these severe ill patients and attribution of mortality associated with IFD is very difficult in

[1] Pascual A, Csajka C, Buclin T et al. Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: population pharmacokinetics-based analysis of adult patients with invasive fungal infections. Clin Infect Dis 2012; 55: 381–90.
[2] Park WB, Kim NH, Kim KH et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. Clin Infect Dis 2012; 55: 1080–7.
[3] Ashbee HR et al. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. J Antimicrob Chemother 2014; 69: 1162–1176.

these medically complex cases. For this reason "DRC-assessed overall response at EOT" was proposed as the key efficacy endpoint for the CHMP.

"DRC-assessed overall response at EOT (in mITT-Population)" is a combined endpoint of clinical, mycological and radiological responses at EOT. Study data were independently assessed by a blinded Drug Review Committee (DRC) consisting of experts in IFD that provided an independent adjudication of each patient's IFD at enrolment, responses at EOT, day 42 and day 84 and attributable mortality. Review of patient data by the DRC was in the form of patient profiles and did not include the investigator assessments or AEs. Independent radiology experts provided a qualitative assessment of images, including location of infection, characteristics of LRTD and an overall outcome assessment of percent improvement from baseline at EOT, day 42 and day 84. These data were included in the patient data reviewed by the DRC. The criteria used to assess if a patient had proven, probable or possible IFD at entry of the study were fully in line with the consensus criteria of EORTC/MSG.

Treatment "success" was defined as complete response or partial response.

Treatment "failure" was defined as stable response or progression of IFD. Patients who were missing or not evaluable at the endpoint were considered failures. This conservative approach is endorsed.

- The most important populations for the assessment of efficacy are considered the Modified Intent-to-Treat (mITT) population which consists of the ITT patients with proven or probable invasive fungal disease as determined by DRC and the Mycological Intent-to-Treat (myITT). The myITT consist of mITT patients with the following pathogen causing invasive fungal disease (IFD) as assessed by DRC:
- Aspergillus species only, or
- Aspergillus species plus other mould species, or
- No pathogen (identified by the DRC for those patients with aspergillosis with only serum GM as mycological evidence).

Sample size

The sample size calculation was based on all-cause mortality through day 42. Approximately 255 patients per group were to be enrolled to ensure at least 80% power to demonstrate that the upper bound of the 95% confidence interval (CI) for a treatment difference in favour of the comparator was no larger than 10% (see below). This was based on a one-sided, large sample, normal approximation and non-inferiority test at a 2.5% significance level. It was also assumed that both voriconazole and isavuconazole would have a 20% mortality rate in the primary efficacy population. The methods for analysis of the primary endpoint were considered appropriate.

Randomisation

In this study, patients were randomized 1:1 to receive either isavuconazole or voriconazole.

Blinding (masking)

The sponsor, clinical research organization (CRO) staff, investigators, patient and study coordinator(s) were blinded to randomization of study drug.

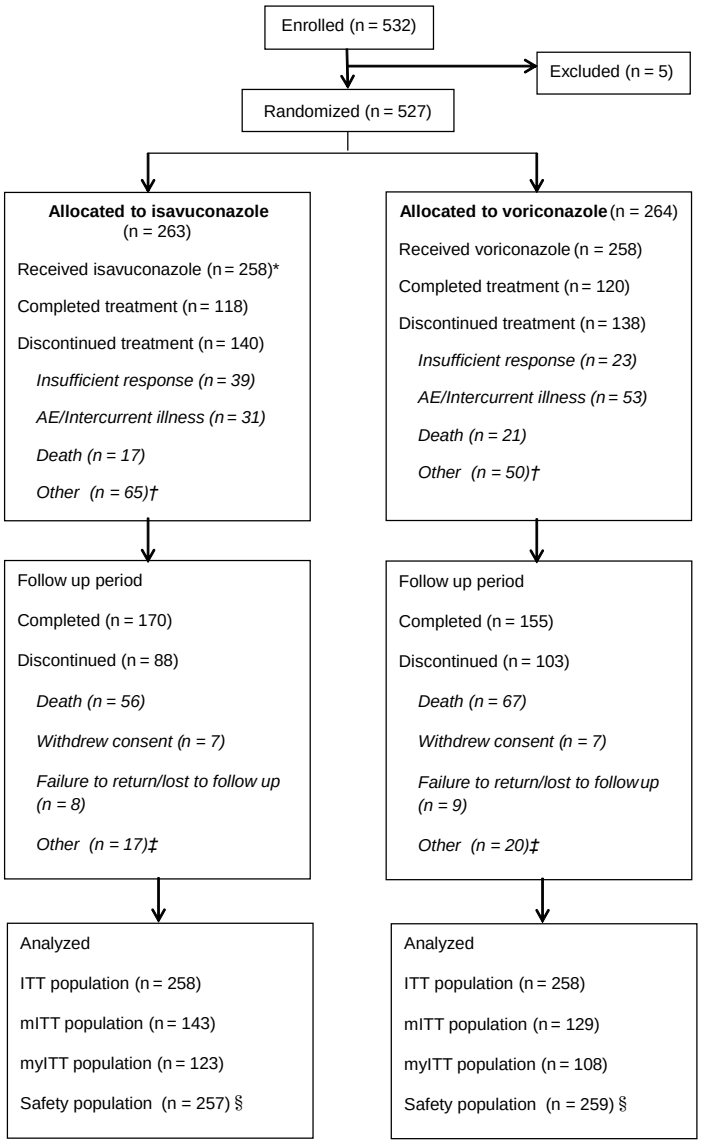
Statistical methods

For the primary endpoint "all-cause mortality through day 42", the protocol pre-specified non-inferiority margin (NIM) value was 10% and was based on the sponsor's meta-analysis. In the absence of historical

placebo-controlled data, the meta-analysis estimated that all-cause mortality through day 42 in untreated patients was 84.8% (95% CI 75.1%, 94.5%). This estimation was supported by a mortality rate of 100% in untreated patients reported by Denning [1996]. The historical all-cause mortality rate through day 42 for voriconazole was 18.8% (95% CI 12.4%, 25.1%) based on Herbrecht *et al*., 2002. A conservative estimate of M1 for voriconazole vs. placebo for all-cause mortality through day 42 was 50.0%. On this basis the sponsor considered that the 10% NIM provided statistically robust evidence that isavuconazole was superior to placebo and preserved > 80% of the voriconazole treatment effect.

Results

Participant flow



* One patient received voriconazole for the first 7 days.
† Other includes failure to return/lost to follow up, violation of selection at entry, other protocol deviation, did not cooperate, refused treatment, withdrew consent and admin/other.
‡ Other includes AE/intercurrent illness, and admin/other.

§ One patient was included in the isavuconazole treatment group for the ITT population and was included in the voriconazole treatment group for the safety population. They were randomized to the isavuconazole treatment group, received voriconazole treatment for the first 7 days and then were switched to isavuconazole oral study drug.

Recruitment

Of 532 who consented, there were 527 patients randomised of which 516 patients (97.9%) received at least 1 dose of study drug and were included in the ITT population. Numbers that prematurely discontinued treatment or study were as shown in the below table:

Table 10 Reasons for Discontinuation during Treatment and Follow-up Periods (ITT)

Parameter Category	ISA (n=258)	VRC (n=258)	Total (n=516)
Treatment discontinuation			
Completed	118 (45.7%)	120 (46.5%)	238 (46.1%)
Discontinued	140 (54.3%)	138 (53.5%)	278 (53.9%)
Primary Reason for Discontinuation			
Adverse Event/Intercurrent Illness	31 (12.0%)	53 (20.5%)	84 (16.3%)
Death	17 (6.6%)	21 (8.1%)	38 (7.4%)
Insufficient Therapeutic Response	39 (15.1%)	23 (8.9%)	62 (12.0%)
Failure to Return/Lost-to-follow-up	2 (0.8%)	1 (0.4%)	3 (0.6%)
Violation of Selection at Entry	17 (6.6%)	10 (3.9%)	27 (5.2%)
Other Protocol Violation	10 (3.9%)	6 (2.3%)	16 (3.1%)
Did Not Cooperate	12 (4.7%)	9 (3.5%)	21 (4.1%)
Refused treatment	7 (2.7%)	5 (1.9%)	12 (2.3%)
Withdrew consent	5 (1.9%)	4 (1.6%)	9 (1.7%)
Admin/Other	12 (4.7%)	15 (5.8%)	27 (5.2%)
Discontinuation During Follow-up Period			
Completed	170 (65.9%)	155 (60.1%)	325 (63.0%)
Discontinued	88 (34.1%)	103 (39.9%)	191 (37.0%)
Primary Reason for Discontinuation			
Adverse Event/Intercurrent Illness†	2 (0.8%)	5 (1.9%)	7 (1.4%)
Death	56 (21.7%)	67 (26.0%)	123 (23.8%)
Failure to Return/Lost-to-follow-up	8 (3.1%)	9 (3.5%)	17 (3.3%)
Admin/Other	15 (5.8%)	15 (5.8%)	30 (5.8%)
Withdrew Consent‡	7 (2.7%)	7 (2.7%)	14 (2.7%)

ISA: isavuconazole; ITT: intent-to-treat; VRC: voriconazole.
† This information was collected up to amendment 2.
‡ This information was collected from amendment 3.

An overall high number of protocol violations were reported. The overall number of patients who prematurely discontinued treatment was similar between the two treatment groups: isavuconazole 140/258 (54.3%) versus voriconazole 138/258 (53.5%).

The 3 most common reasons for discontinuation of treatment were intercurrent illness, insufficient therapeutic response and death. Differences were observed between treatment groups for two of the categories. The number of patients who discontinued treatment primarily due to adverse events/intercurrent illness was lower in the isavuconazole treatment group (31/258, 12.0%) than in the voriconazole treatment group (53/258, 20.5%). The number of patients who discontinued treatment primarily due to an insufficient therapeutic response, as assessed by the investigator, was however higher in the isavuconazole treatment group (39/258, 15.1%) than in the voriconazole treatment group (23/258, 8.9%).

In addition, more patients in the isavuconazole treated group died from infections and infestations isavuconazole: 28/257 (10.9%) vs voriconazole: 18/259 (6.9%). Study drug-related TEAE leading to death encompassed 3 patients that died due to "(fungal) infections and infestations" and all were isavuconazole treated.

Conduct of the study

Baseline data

Baseline demographic and underlying disease distributions for the myITT population are also shown below:

Table 11 Study 9766-CL-0104: Patient disposition and analysis sets

Analysis set	Isavuconazole N=263 n (%)	Voriconazole N=264 n (%)	Total N=527 n (%)
ITT	258 (98.1)	258 (97.7)	516 (97.9)
mITT	143 (54.4)	129 (48.9)	272 (51.6)
myITT	123 (46.8)	108 (40.9)	231 (43.8)

ITT=Intent-to-treat; mITT=Modified ITT; myITT=Mycological ITT.
Note: Percentages are based on the randomized population.

Table 12 Study 9766-CL-0104: Treatment discontinuation (mITT and myITT analysis sets)

	mITT			myITT		
	Isavuconazole N=143 n (%)	Voriconazole N=129 n (%)	Total N=272 n (%)	Isavuconazole N=123 n (%)	Voriconazole N=108 n (%)	Total N=231 n (%)
Completed	61 (42.7)	56 (43.4)	117 (43.0)	52 (42.3)	50 (46.3)	102 (44.2)
Discontinued	82 (57.3)	73 (56.6)	155 (57.0)	71 (57.7)	58 (53.7)	129 (55.8)

mITT=Modified ITT; myITT=Mycological ITT.

Table 13 Study 9766-CL-0104: Study drug duration (myITT analysis set)

	Isavuconazole	Voriconazole	Total
Total duration (days)			
n	123	108	231
Mean (SD)	50.1 (33.05)	48.7 (32.2)	49.4 (32.6)
Min	1	1	1
Median	54.0	50.5	52.0
Max	102	88	102
Duration of intravenous dosing only (days)			
n	123	108	231
Mean (SD)	9.35 (10.0)	9.4 (10.2)	9.39 (10.1)
Min	1	1	1
Median	6.0	5.0	6.0
Max	84.0	53.5	84.0

The treatment discontinuation rates in the myITT population were high, but no imbalances between the two treatment groups (isavuconazole and voriconazole) were noticed. Also the study drug duration in the myITT analysis set was comparable between the two groups.

In addition to the analysis sets shown below, there were 468 patients in the ITT-excluding no IFD population (i.e. after excluding those DRC-assessed as not having proven, probable or possible IFD).

Table 14 Patient Disposition and Analysis Sets

Populations for Analysis†	ISA	VRC	Total
Randomized	263 (100%)	264 (100%)	527 (100%)
ITT	258 (98.1%)	258 (97.7%)	516 (97.9%)
mITT	143 (54.4%)	129 (48.9%)	272 (51.6%)
mITT-FDA	147 (55.9%)	128 (48.5%)	275 (52.2%)
PPS-ITT	172 (65.4%)	175 (66.3%)	347 (65.8%)
PPS-mITT	108 (41.1%)	96 (36.4%)	204 (38.7%)
SAF	257 (97.7%)	259 (98.1%)	516 (97.9%)

Percentages were calculated based upon the Randomized population.

The DRC identified 272 (52.7%) mITT patients (proven or probable IFD) vs. 280 (54.3%) according to the investigators. An overall concordance between the two datasets was observed for 420 (81.4%) patients. The DRC determined that most patients had IFD in the LRTD only (81.1% isavuconazole and 82.9% voriconazole).

The DRC reported that no pathogen was identified in 140/272 (51.5%) of the mITT population (i.e. they were included based only on GM results). Among the pathogens found on culture or histology, the most common was *Aspergillus fumigatus.* The DRC assessed 231/272 in the mITT population as having invasive aspergillosis and 139 of these 231 cases were based on GM only-see below table:

Table 15 Disposition of the myITT Analysis Set and Subjects

Populations for Analyis¥	ISA	VRC	Total
myITT	123 (46.8%)	108 (40.9%)	231 (43.8%)
Probable *Aspergillus* by serum GM only	71 (27.0%)	68 (25.8%)	139 (26.4%)
Aspergillus only or *Aspergillus* plus other mould pathogens¥	52 (19.8%)	40 (15.2%)	92 (17.5%)

Percentages were calculated based upon the randomized population
¥Patients with proven or probable aspergillosis by culture or histology

The applicant confirmed the DRC-assigned level of certainty of diagnosis taking into account the centralised laboratory galactomannan results as well as local testing results. Given the nature of galactomannan test and its place in the diagnostic work-up this is considered acceptable by CHMP.

The treatment groups were balanced for demographics and baseline characteristics of ITT Population as shown in the following table:

Table 16 Demographics and Baseline characteristics of ITT population (9766-CL-0104)

Parameter Statistics	ISA (n = 258)	VRC (n = 258)	Total (n = 516)
Age Category			
≤ 45 years	94 (36.4%)	101 (39.1%)	195 (37.8%)
> 45 - ≤ 65 years	108 (41.9%)	99 (38.4%)	207 (40.1%)
> 65 - ≤ 75 years	46 (17.8%)	51 (19.8%)	97 (18.8%)
> 75 years	10 (3.9%)	7 (2.7%)	17 (3.3%)
Sex			
Male	145 (56.2%)	163 (63.2%)	308 (59.7%)
Female	113 (43.8%)	95 (36.8%)	208 (40.3%)
Race			
White	211 (81.8%)	191 (74.3%)	402 (78.1%)
Black or African American	1 (0.4%)	1 (0.4%)	2 (0.4%)
Asian	45 (17.4%)	64 (24.9%)	109 (21.2%)
Other	1 (0.4%)	1 (0.4%)	2 (0.4%)
Missing	0	1	1
Ethnicity			
Hispanic or Latino	22 (8.5%)	9 (3.5%)	31 (6.0%)
Not Hispanic or Latino	236 (91.5%)	248 (96.5%)	484 (94.0%)
Missing	0	1	1
BMI (kg/m^2)			
n	251	249	500
Mean	24.2	23.7	23.9
Median	23.4	23.4	23.4
Min - Max	13.9 - 50.0	14.5 - 38.0	13.9 - 50.0
Geographical Region†			
North America	30 (11.6%)	28 (10.9%)	58 (11.2%)
Western Europe plus Australia and New Zealand	105 (40.7%)	107 (41.5%)	212 (41.1%)
Other Regions	123 (47.7%)	123 (47.7%)	246 (47.7%)
Hematologic malignancy	211 (81.8%)	222 (86.0%)	433 (83.9%)
Prior Allogeneic BMT	54 (20.9%)	51 (19.8%)	105 (20.3%)
Uncontrolled Malignancy at Baseline	173 (67.1%)	187 (72.5%)	360 (69.8%)
Neutropenic‡	163 (63.2%)	175 (67.8%)	338 (65.5%)
Use of Corticosteroids	48 (18.6%)	39 (15.1%)	87 (16.9%)
Use of T-Cell Immunosuppressant	111 (43.0%)	109 (42.2%)	220 (42.6%)
eGFR-MDRD ($mL/min/1.73\ m^2$) < 60 ≥ 60 Missing	 20 (8.0%) 231 (92.0%) 7	 33 (13.2%) 217 (86.8%) 8	 53 (10.6%) 448 (89.4%) 15

The primary underlying diseases were leukaemias and lymphomas, but the diagnostic categories were not well balanced between treatment groups in most cases. Baseline isolated pathogens were evenly distributed over both treatment groups. There were no relevant differences for any prior and concomitant medication between treatment and no relevant differences in the mITT population compared to the ITT population.

Baseline demographic and underlying disease distributions were also presented for the myITT population. From the submitted data, it is concluded that the baseline demographic characteristics for the myITT-population were generally well balanced, as presented in the following table:

Table 17 Study 9766-CL-0104:Demographic characteristics (mITT and myITT analysis sets)

Variable	mITT			myITT		
	Isavuconazole n (%)	Voriconazole n (%)	Total n (%)	Isavuconazole n (%)	Voriconazole n (%)	Total n (%)
Age (years)	143	129	272	123	108	231
Mean	50.8	51.8	51.2	50.9	51.6	51.2
SD	16.48	14.63	15.61	15.73	14.95	15.34
Min	18	18	18	18	18	18
Median	52.0	54.0	54.0	53.0	54.0	54.0
Max	81	77	81	81	77	81
≤ 45	54 (37.8)	44 (34.1)	98 (36.0)	45 (36.6)	36 (33.3)	81 (35.1)
> 45 – ≤ 65	55 (38.5)	63 (48.8)	118 (43.4)	52 (42.3)	54 (50.0)	106 (45.9)
> 65 – ≤ 75	29 (20.3)	21 (16.3)	50 (18.4)	23 (18.7)	17 (15.7)	40 (17.3)
> 75	5 (3.5)	1 (0.8)	6 (2.2)	3 (2.4)	1 (0.9)	4 (1.7)
Other variables						
Male	81 (56.6)	84 (65.1)	165 (60.7)	69 (56.1)	71 (65.7)	140 (60.6)
White	115 (80.4)	92 (71.9)	207 (76.4)	100 (81.3)	75 (69.4)	175 (75.8)
Black/African-American	0	1 (0.8)	1 (0.4)	0	1 (0.9)	1 (0.4)
Asian	27 (18.9)	35 (27.3)	62 (22.9)	22 (17.9)	32 (29.6)	54 (23.4)
Other race	1 (0.7)	0	1 (0.4)	1 (0.8)	0	1 (0.4)
BMI < 25 kg/m^2	93 (66.4)	81 (65.9)	174 (66.2)	81 (66.9)	68 (66.0)	149 (66.5)
BMI ≥ 25–< 30 kg/m^2	32 (22.9)	32 (26.0)	64 (24.3)	27 (22.3)	25 (24.3)	52 (23.2)
BMI ≥ 30 kg/m^2	15 (10.7)	10 (8.1)	25 (9.5)	13 (10.7)	10 (9.7)	23 (10.3)
BMI Missing	3	6	9	2	5	7
North America	19 (13.3)	23 (17.8)	42 (15.4)	17 (13.8)	21 (19.4)	38 (16.5)
Western Europe*	50 (35.0)	42 (32.6)	92 (33.8)	46 (37.4)	33 (30.6)	79 (34.2)
Other Regions	74 (51.7)	64 (49.6)	138 (50.7)	60 (48.8)	54 (50.0)	114 (49.4)
Europe‡	59 (41.3)	47 (36.4)	106 (39.0)	55 (44.7)	39 (36.1)	94 (40.7)
eGFR-MDRD < 60 mL/min/1.73 m^2	13 (9.4)	17 (13.7)	30 (11.4)	11 (9.2)	13 (12.3)	24 (10.7)
eGFR-MDRD ≥ 60 mL/min/1.73 m^2	126 (90.6)	107 (86.3)	233 (88.6)	108 (90.8)	93 (87.7)	201 (89.3)
eGFR-MDRD missing	4	5	9	4	2	6
Allogeneic BMT status	33 (23.1)	27 (20.9)	60 (22.1)	32 (26.0)	22 (20.4)	54 (23.4)
Uncontrolled malignancy	89 (62.2)	89 (69.0)	178 (65.4)	79 (64.2)	78 (72.2)	157 (68.0)
Neutropenic	88 (61.5)	73 (56.6)	161 (59.2)	78 (63.4)	64 (59.3)	142 (61.5)
Haematological malignancy	112 (78.3)	105 (81.4)	217 (79.8)	100 (81.3)	90 (83.3)	190 (82.3)
Corticosteroid use	30 (21.0)	30 (23.3)	60 (22.1)	25 (20.3)	27 (25.0)	52 (22.5)
T-cell immunosuppressant	59 (41.3)	61 (47.3)	120 (44.1)	52 (42.3)	52 (48.1)	104 (45.0)

* Randomization stratum: Belgium, France, Germany, Italy, The Netherlands, Spain, Switzerland, Australia, New Zealand.
‡ Predefined analysis geographic subgroup: Belgium, France, Germany, Hungary, Italy, Poland, Russia, Spain, Switzerland, The Netherlands.

The only exceptions were the imbalances in gender (slightly more women in the isavuconazole group than in the voriconazole group) and in race (considerably less Asian patients in the isavuconazole group than in the voriconazole group). These imbalances however are not considered to have influenced the overall clinical outcome of pivotal study 9766-CL-0104. There were no clinically relevant differences between the two treatment groups for the stratification factors (geographic region, allogeneic BMT/HSCT, and uncontrolled malignancy).

Numbers analysed

The different analysis sets used in this study are described below:

- The ITT population consisted of all randomized patients who received at least one administration of study drug. For this population, data were analysed by the treatment group that patients were randomized to even though they might not be compliant with the protocol or assigned treatment.
- The modified ITT (mITT) population consisted of ITT patients who had proven or probable IFD as determined by the DRC. Patients with appropriate host factor and clinical features were considered to

have probable IFD based on the GM criteria (GMc) set forth in the protocol (i.e., 2 consecutive serum GM values ≥ 0.5 or at least 1 serum GM value ≥ 0.7).

- The safety analysis set (SAF) consisted of all randomized patients who received at least one dose of study drug. For the SAF, data were analysed according to the study drug that patients received as the first dose even if it was different from what they were randomized to.
- The mycological ITT (myITT) population consisted of mITT patients with proven or probable invasive aspergillosis based on cytology, histology, culture or GMc set forth in the protocol and assessed by the DRC.
- The Per Protocol Set (PPS) was a subset of ITT (PPS-ITT) or a subset of mITT (PPS-mITT) patients who did not deviate from the pre-specified Classification Criteria.
- The pharmacokinetic analysis set (PKAS) consisted of a subset of the SAF population who had at least one isavuconazole plasma concentration.

Outcomes and estimation

Efficacy results for primary efficacy endpoint

The primary objective of demonstrating non-inferiority of isavuconazole relative to voriconazole for the primary endpoint "all-cause mortality through day 42 in the ITT population" was met, with the upper bound of the 95% CI of 5.7% around the adjusted treatment difference (isavuconazole - voriconazole: -1.0%) being lower than the pre-specified non-inferiority margin of 10%.

Table 18 All-cause Mortality through Day 42 (ITT Population) in study 9766-CL-0104

	ISA (n = 258)	VRC (n = 258)
All-cause Mortality	48 (18.6%)	52 (20.2%)
Adjusted Treatment Difference (ISA-VRC) (%) 95% CI (%)	-1.0 (-7.759, 5.683)	
Known Deaths	45 (17.4%)	50 (19.4%)
Unknown Survival Status†	3 (1.2%)	2 (0.8%)

The adjusted treatment difference (ISA vs. VRC) was calculated by a stratified CMH method with the strata of Geographical Region, Allogeneic BMT Status and Uncontrolled Malignancy Status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

BMT: bone marrow transplant; CMH: Cochran-Mantel-Haenszel; ISA: isavuconazole; ITT: intent-to-treat; VRC: voriconazole.† A patient with unknown survival status was treated as a death.

The sensitivity analysis using a minimum-risk method for all-cause mortality through day 42 gave almost identical results and a *post hoc* analysis without stratification factors gave 95% CI around the treatment difference (isavuconazole-voriconazole: -1.6%) of (-8.771%, 5.670%). Also across the analysis populations the all-cause mortality through day 42 gave adjusted treatment differences in the range -5.1% to -1.3% and upper bounds of the 95% CIs that ranged from 5.024% to 7.215%.

Table 19 All-cause Mortality Through day 42 for Various Populations in study 9766-CL-0104

	ISA		VRC		Treatment Difference (%) 95% CI (%)†
	n	n (%)	n	n (%)	
mITT	143	28 (19.6)	129	30 (23.3)	−2.6 (−12.184, 6.916)
mITT-FDA‡	147	28 (19.0)	128	28 (21.9)	−2.1 (−11.422, 7.215)
PPS-ITT	172	26 (15.1)	175	31 (17.7)	−2.6 (−10.283, 5.079)
PPS-mITT	108	16 (14.8)	96	19 (19.8)	−5.1 (−15.166, 5.024)
ITT-excluding no IFD§	231	43 (18.6)	237	49 (20.7)	−1.3 (−8.424, 5.830)

In the myITT population all-cause mortality through day 42 was consistent with that of the other populations. In the subset with probable *Aspergillus* by GM only and those with *Aspergillus* only or *Aspergillus* plus other moulds the all-cause mortality was consistently numerically lower in the isavuconazole group.

Table 20 All-cause Mortality Through day 42 (myITT Population and Subjects) in study 9766-CL-0104

	ISA		VRC		Treatment Difference (%) 95% CI (%)
	n	n (%)	n	n (%)	
myITT	123	23 (18.7)	108	24 (22.2)	−2.7 (−12.893, 7.542)†
mITT patients with probable *Aspergillus* by serum GM only	71	15 (21.1)	68	16 (23.5)	−2.4 (−17.792, 12.987)‡
mITT patients with *Aspergillus* only or *Aspergillus* plus other moulds pathogens§	52	8 (15.4)	40	8 (20.0)	−4.6 (−22.816, 13.585)‡

All-cause mortality through day 42 in the ITT population was further analyzed for the various intrinsic and extrinsic factors, including the 3 stratification factors (geographic region, allogeneic BMT and uncontrolled malignancy) and in several subgroups (age, gender, race, ethnicity, BMI, eGFR-MDRD category and neutropenia). Overall no significant differences were observed for the different subgroups. However, the mortality in the regions "Western Europe" and "Europe" was numerically lower than in "Other regions", and applicant was asked to explain this finding.

An overview of Day 42 all-cause mortality by region is listed in the following table:

Table 21 All-cause Mortality through Day 42 in the Subgroups of Patients from Western Europe/Europe and Other Regions

All-cause mortality through Day 42 (ITT population)				
Region/Country (number of sites)	**Isavuconazole % (n/N)**	**Voriconazole % (n/N)**	**Difference* %**	**Combined % (n/N)**
Western Europe plus Australia and New Zealand (23)	**12.4** (13/105)	**23.4** (25/107)	−11	**17.9** (38/212)
Europe (28)	**13.0** (15/115)	**22.2** (26/117)	−9	**17.7** (41/232)
Other Regions (63)	**24.4** (30/123)	**17.9** (22/123)	7	**21.1** (52/246)
Western Europe plus Australia and New Zealand	**12.4 (13/105)**	**23.4 (25/107)**	**−11**	**17.9 (38/212)**
Belgium (5)	**10** (6/61)	**25** (14/55)	−16	**17** (20/116)
Germany (7)	**18** (4/22)	**28** (8/29)	−9	**24** (12/51)
France (3)	**21** (3/14)	**15** (2/13)	6	**19** (5/27)
Italy (1)	**0** (0/1)	**20** (1/5)	−20	**17** (1/6)
Australia (3)	**0** (0/5)	**0** (0/3)	0	**0** (0/8)
New Zealand (1)	**0** (0/1)	NA (0/0)	NA	**0** (0/1)
Netherlands (1)	**0** (0/1)	NA (0/0)	NA	**0** (0/1)
Spain (1)	NA (0/0)	**0** (0/1)	NA	**0** (0/1)
Switzerland (1)	NA (0/0)	**0** (0/1)	NA	**0** (0/1)
Other Regions	**24.4 (30/123)**	**17.9 (22/123)**	**7**	**21.1 (52/246)**
Israel (5)	**18** (6/33)	**8** (2/26)	10	**14** (8/59)
Thailand (5)	**17** (2/12)	**21** (4/19)	−4	**19** (6/31)
India (8)	**42** (5/12)	**29** (5/17)	12	**34** (10/29)
China (10)	**10** (1/10)	**25** (4/16)	−15	**19** (5/26)
Russia (6)	**14** (2/14)	**14** (1/7)	0	**14** (3/21)
S. Korea (5)	**63** (5/8)	**8** (1/12)	54	**30** (6/20)
Brazil (6)	**13** (1/8)	**18** (2/11)	−6	**16** (3/19)
Egypt (3)	**30** (3/10)	**0** (0/3)	30	**23** (3/13)
Argentina (5)	**14** (1/7)	**50** (1/2)	−36	**22** (2/9)
Poland (1)	**NA** (0/0)	**0** (0/6)	NA	**0** (0/6)
Chile (3)	**50** (1/2)	**100** (1/1)	−50	**67** (2/3)
Mexico (1)	**100** (2/2)	**0** (0/1)	100	**67** (2/3)
Malaysia (2)	**33** (1/3)	**NA** (0/0)	NA	**33** (1/3)
Turkey (1)	**NA** (0/0)	**50** (1/2)	NA	**50** (1/2)
Hungary (2)	**0** (0/2)	**NA** (0/0)	NA	**0** (0/2)

* Isavuconazole minus voriconazole.

There were differences in mortality rates between the regions. A review of the demographic data submitted by the applicant revealed no substantial differences that could explain the higher mortality rates in India and South Korea. CHMP agreed with the applicant that the numbers of patients enrolled in these two countries were rather low and that the broad geographic distribution and the larger number of countries in other regions could have contributed to the wider variability in outcomes.

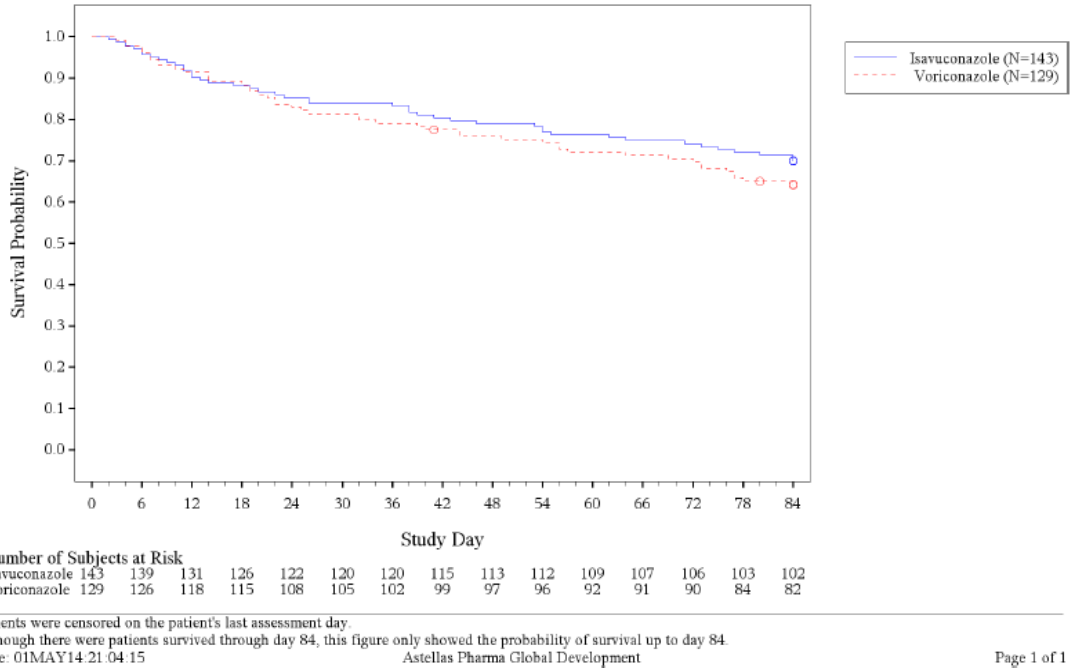
All-cause mortality through day 84 across the various populations supports the results seen in the primary efficacy analysis at day 42 with 29.1% mortality in the isavuconazole group and 31.0% in the voriconazole group (ITT population, treatment difference, -1.4% 95%CI -9.2%-6.3%), see following table. This is also exemplified in the below Kaplan-Meier plot.

Table 22 All-cause Mortality Through Day 84 for Various Populations study 9766-CL-0104

	ISA		VRC		Treatment Difference (%) 95% CI (%)†
	n	n (%)	n	n (%)	
ITT	258	75 (29.1)	258	80 (31.0)	-1.4 (-9.150, 6.340)
mITT	143	43 (30.1)	129	48 (37.2)	-5.5 (-16.059, 5.148)
mITT-FDA‡	147	41 (27.9)	128	43 (33.6)	-4.7 (-15.099, 5.748)
PPS-ITT	172	43 (25.0)	175	48 (27.4)	-2.8 (-11.861, 6.234)
PPS-mITT	108	29 (26.9)	96	31 (32.3)	-5.7 (-17.735, 6.303)
ITT-excluding no IFD	231	67 (29.0)	237	75 (31.6)	-1.9 (-10.055, 6.216)

A patient with unknown survival status was treated as a death.

Figure 7 Kaplan Meier Plot of Time to Death up to Day 84 (mITT population)



Patients were censored on the patient's last assessment day.
Although there were patients survived through day 84, this figure only showed the probability of survival up to day 84.
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The majority of deaths in the isavuconazole and voriconazole treatment groups were reported to be associated with evidence of residual or ongoing IFD at both day 42 (22 and 25 deaths) and day 84 (38 and 37 deaths), see following table:

Table 23 DRC Attribution of Death to IFD (ITT-excluding no IFD Population) study 9766-CL-0104

Attributable Mortality	ISA (n = 231)	VRC (n = 237)
Through Day 42		
Patient Deaths	40 (17.3%)	48 (20.3%)
Directly Due to Consequence of Progressive IFD	17 (7.4%)	16 (6.8%)
Associated with Evidence of Residual or Ongoing IFD	22 (9.5%)	25 (10.5%)
Associated with No Evidence of Residual or Ongoing IFD	1 (0.4%)	2 (0.8%)
Indeterminate Cause	0	5 (2.1%)
Through Day 84		
Patient Deaths	64 (27.7%)	73 (30.8%)
Directly Due to Consequence of Progressive IFD	19 (8.2%)	19 (8.0%)
Associated with Evidence of Residual or Ongoing IFD	38 (16.5%)	37 (15.6%)
Associated with No Evidence of Residual or Ongoing IFD	2 (0.9%)	5 (2.1%)
Indeterminate Cause	5 (2.2%)	12 (5.1%)

The ITT-excluding no IFD population is the ITT population excluding those who were assessed by the DRC as not having adequate evidence of proven, probable or possible IFD. DRC: Data Review Committee, IFD: invasive fungal disease; ISA: isavuconazole; ITT: intent-to-treat; VRC: voriconazole.

The ITT population did not show a marked difference in IFD attributable death.

Efficacy results for the key secondary endpoint

Response rates for DRC overall response at EOT for the mITT population were similar for isavuconazole and voriconazole treated patients (50/143, 35.0% and 47/129, 36.4%, respectively) with an adjusted treatment difference of 1.6% (95%CI: -9.4%, 12.6%):

Table 24 DRC-assessed Overall Response at EOT (mITT Population) study 9766-CL-0104

Outcome Response	ISA (n = 143)	VRC (n = 129)
Success	50 (35.0%)	47 (36.4%)
Adjusted Treatment Difference (VRC-ISA) (%) 95% CI (%)	1.6 (-9.336, 12.572)	
Complete	17 (11.9%)	13 (10.1%)
Partial	33 (23.1%)	34 (26.4%)
Failure	93 (65.0%)	82 (63.6%)
Stable	42 (29.4%)	33 (25.6%)
Progression	51 (35.7%)	49 (38.0%)

The adjusted treatment difference (VRC-ISA) was calculated by a stratified CMH method with the strata of Geographical Region, Allogeneic BMT Status and Uncontrolled Malignancy Status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

BMT: bone marrow transplant; CMH: Cochran-Mantel-Haenszel; DRC: Data Review Committee; EOT: end of treatment; ISA: isavuconazole; mITT: modified intent-to-treat; VRC: voriconazole.

Complete treatment success was achieved in 17 (11.9%) and 13 (10.1%) patients in the isavuconazole and voriconazole treatment groups, respectively. Partial success was achieved in 33 (23.1%) and 34 (26.4%) patients in the isavuconazole and voriconazole treatment groups, respectively (see above table).

DRC-assessed overall response at day 42 and EOT were similar between treatment groups, however at day 84 the failure rate in the isavuconazole group appeared to be higher compared to the voriconazole group (74.8% vs 67.4%), see following table:

Table 25 DRC-assessed Overall Response at Day 84 (mITT Population), study 9766-CL-0104

Outcome Response	ISA (n = 143)	VRC (n = 129)
Success	36/143 (25.2%)	42/129 (32.6%)
Adjusted Treatment Difference (VRC-ISA) (%) 95% CI (%)	8.2 (-1.993, 18.379)	
Complete	14/143 (9.8%)	13/129 (10.1%)
Partial	22/143 (15.4%)	29/129 (22.5%)
Failure	107/143 (74.8%)	87/129 (67.4%)
Stable	30/143 (21.0%)	14/129 (10.9%)
Progression	5/143 (3.5%)	8/129 (6.2%)
Death	43/143 (30.1%)	44/129 (34.1%)
Missing	29/143 (20.3%)	21/129 (16.3%)

The adjusted treatment difference (VRC-ISA) was calculated by a stratified CMH method with the strata of Geographical Region, Allogeneic BMT Status and Uncontrolled Malignancy Status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

For this analysis, any visits that DRC assessed as not done were considered failures. A death before day 42 was also considered a failure at both day 42 and day 84, even if the DRC assessed the patient to be a success prior to death.

The DRC assessments of clinical, mycological and radiological response rates at EOT were similar between the treatment groups for the mITT population. The rates of success for the radiological response were low in both treatment groups mainly due to missing data (no post-baseline radiological assessments at EOT for ~ 22.0% in both treatment groups).

Table 26 DRC-assessed Clinical, Mycological and Radiological Responses at EOT (mITT), study 9766-CL-0104

	ISA (n=143)		VRC (n=129)		Treatment Difference (%)
Success	n	n (%)	n	n (%)	95% CI (%)†
Clinical Response	137	85 (62.0)	121	73 (60.3)	0.4 (-10.640, 11.531)
Mycological Response	143	54 (37.8)	129	53 (41.1)	3.8 (-7.429, 15.087)
Radiological Response	141	41 (29.1)	127	42 (33.1)	5.7 (-4.936, 16.268)

† The adjusted treatment difference (VRC-ISA) was calculated by a stratified CMH method with the strata of Geographical Region, Allogeneic BMT Status and Uncontrolled Malignancy Status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

The DRC-assessed overall response rates at EOT for the myITT population and subsets were generally similar between treatment groups for patients with *Aspergillus* identified by histology or culture. Rates were lower for isavuconazole vs. voriconazole (33.8%, 24/71 vs. 41.2%, 28/68, respectively) for patients with *Aspergillus* identified by GM only-see following table:

Table 27 DRC-assessed Overall Response at EOT (myITT Population and Subsets), study 9766-CL-0104

Outcome Response	ISA (n = 143)	VRC (n = 129)
Success	43/123 (35.0%)	42/108 (38.9%)
Adjusted Treatment Difference (VRC-ISA) (%) 95% CI (%)	4.0 (-7.973, 15.875)†	
Complete	13 (10.6%)	12 (11.1%)
Partial	30 (24.4%)	30 (27.8%)
Failure	80 (65.0%)	66 (61.1%)
Stable	36 (29.3%)	29 (26.9%)
Progression	44 (35.8%)	37 (34.3%)
Success in Subsets of the myITT Population		
mITT Patients with Probable *Aspergillus* by Serum GM Only	24/71 (33.8%)	28/68 (41.2%)
Treatment Difference (VRC-ISA) (%) 95% CI (%)	7.4 (-10.242, 24.989)‡	
mITT Patients with *Aspergillus* Only or *Aspergillus* Plus Other Moulds Pathogens§	19/52 (36.5%)	14/40 (35.0%)
Treatment Difference (VRC-ISA) (%) 95% CI (%)	-1.5 (-23.719, 20.642)‡	

DRC-assessed success rates at EOT were higher in isavuconazole vs. voriconazole patients in Western Europe but lower with isavuconazole in North America and Other Regions (see following table). Success rates for those who did not have uncontrolled malignancy at baseline were lower with isavuconazole. No treatment-by-subgroup interaction was observed except for race (P = 0.085; Wald-Chi-square test). However, most patients were white and had similar success rates with isavuconazole vs. voriconazole. Success rates were numerically lower with isavuconazole in those aged > 65 years.

Table 28 DRC-assessed Overall Response at EOT by Strata (mITT Population), study 9766-CL-0104

Success by Category	ISA (n = 143)	VRC (n = 129)	Treatment Difference (%) 95% CI (%)†
Geographical Region‡			
North America	5/19 (26.3%)	9/23 (39.1%)	12.8 (-20.796, 46.425)
Western Europe plus Australia and New Zealand	19/50 (38.0%)	9/42 (21.4%)	-16.6 (-37.267, 4.125)
Other Regions	26/74 (35.1%)	29/64 (45.3%)	10.2 (-7.742, 28.097)
Allogeneic BMT Status			
Yes	8/33 (24.2%)	7/27 (25.9%)	1.7 (-24.138, 27.505)
No	42/110 (38.2%)	40/102 (39.2%)	1.0 (-13.096, 15.164)
Uncontrolled Malignancy Status			
Yes	32/89 (36.0%)	30/89 (33.7%)	-2.2 (-17.444, 12.950)
No	18/54 (33.3%)	17/40 (42.5%)	9.2 (-13.054, 31.387)

Asian patients had a numerically lower success rate in the isavuconazole group (25.9%, 7/27) than in the voriconazole treatment group (48.6%, 17/35). The applicant was requested to clarify whether there could be an ethnicity effect, especially taken into consideration that drug exposure to isavuconazole in healthy Chinese subjects (study 9766-CL-0038) appeared 15 – 50% higher compared to Western subjects. It was concluded that the observed differences in response rates between Asian and non-Asian patients cannot be explained by drug exposure. From six Asian patients MIC values were available. All MICs were however below 2 µg/mL, so it is considered not likely either that resistance to isavuconazole does explain the results in overall response at EOT. Moreover, the differences in favour of voriconazole were not consistent across the Asian countries; they were apparent in Thailand and South Korea (between group difference in overall response at EOT of 34.3% in favour of voriconazole), but not in China and India (between group difference in overall response at EOT of 6.1% in favour of isavuconazole). Therefore a potential ethnicity effect can not be excluded at present and is included as missing information in the RMP.

The results of analysis of DRC-assessed overall response at EOT by IFD location in the mITT population revealed some differences between the two treatment groups. Voriconazole seemed to perform better in the "mITT patients with LRTD plus other organ" and in "mITT patients with non-LRTD only" subgroups. However, these differences were probably due to some imbalances in the baseline characteristics (less localized disease in the isavuconazole group) but the subgroups were small, limiting any firm conclusions.

DRC-assessed clinical responses at day 42 were isavuconazole 64% vs. voriconazole 57.5% in the myITT population while overall success rates were 35.8% isavuconazole vs. 38% voriconazole. At day 84, DRC-assessed mycological (40/143, 28.0% vs. 47/129, 36.4%) and radiological response (31/141, 22.0% vs. 38/128, 29.7%) were numerically lower in isavuconazole treated patients compared to voriconazole treated patients, whereas the clinical response was similar (isavuconazole: 65/141, 46.1% vs. voriconazole: 55/124, 44.4%).

Very few patients (isavuconazole: 3 patients and voriconazole: 1 patient) received a potentially mould active systemic AFT (any reason for use) up to the EOT and none achieved success for overall response (see following table):

Table 29 Potentially Mould active Systemic AFT Use by Visit (study 9766-CL-0104)

Population Time Point	ISA	VRC
Use for Any Reason		
ITT	(n = 258)	(n = 258)
EOT	3 (1.2%)	1 (0.4%)
Up to Day 42	76 (29.5%)	57 (22.1%)
Up to Day 84	92 (35.7%)	77 (29.8%)
mITT	(n = 143)	(n = 129)
EOT	3 (2.1%)	1 (0.8%)
Up to Day 42	41 (28.7%)	32 (24.8%)
Up to Day 84	55 (38.5%)	44 (34.1%)

Ancillary analyses

A *post hoc* analysis of all-cause mortality and overall response at day 42 and day 84 showed that the use of a potentially mould active systemic AFT did not confound the interpretation of the outcomes based on all-cause mortality and overall response (see following table). Among the patients in the mITT population who received potentially mould active systemic AFT, mortality rates through day 42 were similar between treatments, but mortality rates through day 84 were numerically lower for isavuconazole. For the patients that did not receive potentially mould active systemic AFT, the success rates were similar between treatment groups.

Table 30 Potentially Mould active Systemic AFT Use by Visit (study 9766-CL-0104)

Interaction P value	Systemic AFT Use	ISA (n=258)	VRC (n=258)	Treatment Difference (%) 95% CI (%)†
ITT up to Day 42				
0.208	Yes	25/76 (32.9%)	16/57 (28.1%)	4.8 (-12.571, 22.220)
	No	23/182 (12.6%)	36/201 (17.9%)	-5.3 (-12.985, 2.439)
ITT up to Day 84				
0.335	Yes	37/92 (40.2%)	29/77 (37.7%)	2.6 (-13.476, 18.586)
	No	38/166 (22.9%)	51/181 (28.2%)	-5.3 (-15.043, 4.473)
Interaction P value	**Systemic AFT Use**	**ISA (n=143)**	**VRC (n=129)**	**Treatment Difference (%) 95% CI (%)†**
mITT up to Day 42				
0.575	Yes	14/41 (34.1%)	11/32 (34.4%)	-0.2 (-25.270, 24.813)
	No	14/102 (13.7%)	19/97 (19.6%)	-5.9 (-17.263, 5.539)
mITT up to Day 84				
0.362	Yes	20/55 (36.4%)	23/44 (52.3%)	-15.9 (-37.639, 5.821)
	No	23/88 (26.1%)	25/85 (29.4%)	-3.3 (-17.855, 11.304)

There were 92 patients (52 isavuconazole and 40 voriconazole) with evidence of IFD caused by *Aspergillus spp*. (alone or with another pathogen) that was not based solely on GM. The CSR stated that there were 99 *Aspergillus spp*. tested for isavuconazole susceptibility as well as 5 *Fusarium spp.*, 4 *Lichtheimia (Absidia) corymbifera*, 2 *Penicillium spp.* and 1 *Rhizopus oryzae*. Using the CLSI methodology the isavuconazole MIC_{50} and MIC_{90} against *Aspergillus spp*. were 1 and 4 mcg/mL, respectively (range 0.12 to 32 mcg/mL) (see following table). The lowest isavuconazole MICs were seen against *A. fumigatus*. The EUCAST MIC values were similar. At the EOT and at days 42 and 84 there were no trends in response by MIC.

Table 31 MIC Values for Fungal Isolates per CLSI Standard (ITT Population), study 9766-CL-0104

Organism Genus species (No. isolates)	MIC	AmB	CAS‡	ISA	VRC	POSA
Aspergillus spp. (99)	MIC Range	0.5, 32	0.25, 2	0.12, 32	0.12, 32	0.12, 2
	MIC_{50}	1	0.25	1	1	0.5
	MIC_{90}	4	0.5	4	2	1
Aspergillus flavus (22)	MIC Range	0.5, 4	0.25, 1	0.25, 4	0.5, 16	0.12, 1
	MIC_{50}	1	0.25	1	2	0.5
	MIC_{90}	4	0.25	4	2	1
Aspergillus fumigatus (62)	MIC Range	0.5, 8	0.25, 2	0.12, 32	0.12, 32	0.12, 2
	MIC_{50}	1	0.25	1	1	0.25
	MIC_{90}	4	0.5	2	2	0.5
Aspergillus niger (7)	MIC Range	0.5, 4	0.25, 0.25	2, 4	2, 4	0.5, 1
Aspergillus terreus (7)	MIC Range	1, 8	0.25, 2	0.25, 4	0.25, 16	0.12, 0.5
Aspergillus westerdijkiae (1)	MIC Range	32, 32	2, 2	2, 2	32, 32	1, 1

During the procedure, CHMP asked the applicant to explain the difference between the numbers of isolates tested and the number of patients listed as having *Aspergillus* not based solely on GM, to explain why outcomes were not presented for all patients from whom the 99 isolates tested were obtained and to show outcomes by MIC for myITT patients. From the applicant's responses it appeared that the numbers were based on different datasets:

- 92 patients were those diagnosed with *Aspergillus spp*. with or without other moulds in the MyITT set, irrespective of isolate presence at baseline and/or follow up.
- 99 reflects the number of *Aspergillus spp*. isolates in the ITT dataset in 70 patients with baseline and post baseline isolates; 67 of these patients were part of the myITT dataset, providing 93 *Aspergillus spp*. isolates.

The applicant has further clarified the origin of the numbers, by providing new tables presenting how patients and isolates from different datasets can be extrapolated from each other.

Fifteen patients had isolates tested post-baseline (after day 7) at the central laboratory. MICs of isavuconazole in 5/15 were within 1 dilution step of the baseline MIC. For the other 10, the following were noted:

- One patient (isavuconazole; baseline *A. fumigatus* MIC 0.25 mcg/mL) received 76 days ISA and was responding at day 42 but on day 70 had worsening signs and symptoms, including radiography and positive GM index. *A. fumigatus* was isolated from a respiratory sample collected on day 70 for which the ISA MIC was 1 mcg/mL. The patient had received additional treatment for cancer by day 50.
- Another patient (isavuconazole) had an isolate on day 9 for which the EUCAST but not the CLSI MIC had increased 5 dilution steps. The MIC was back within range for isolates collected on day 43.
- Six patients had only post-baseline isolates tested with CLSI MICs from 0.25 to 4 mcg/mL.
- Two patients had MIC values from multiple fungal isolates and had a new organism isolated while on therapy. Both were considered failures based on DRC assessment. One of them (isavuconazole) had *A. terreus* at baseline (day -3: ISA CLSI MIC 0.5 mcg/mL) as well as *A. westerdijkiae* (CLSI MIC value 2 mcg/mL). *Lichtheimia corymbifera* (ISA CLSI MIC 16 mcg/mL) grew on subsequent baseline cultures (day 6 and day 13). The second patient (voriconazole) had *Fusarium fujikuroi* isolated (CLSI MIC 4 mcg/mL) on day -1 and on day 42 had a new isolate of *Rhizopus oryzae* (CLSI MIC > 32 mcg/mL).

Title of Study

Study 9766-CL-0103: Open-Label Study of Isavuconazole in the Treatment of Patients with Aspergillosis and Renal Impairment or of Patients with Invasive Fungal Disease Caused by Rare Moulds, Yeasts or Dimorphic Fungi (the VITAL study)

Methods

Study 9766-CL-WSA-CS-0103 was a phase 3, open-label, multicentre study in which isavuconazole was investigated in three different patient populations. A pharmacokinetic substudy was conducted and the study investigated the efficacy and safety of isavuconazole in the treatment of

- patients with invasive fungal disease caused by rare moulds, yeasts or dimorphic fungi.
- invasive aspergillosis in patients with renal impairment;

Study Participants

The inclusion criteria and definitions of treatment outcomes (clinical, mycological and radiological response) were in compliance with the recommendations of the EORTC/MSG guideline (2008). The exclusion criteria and criteria for the study drug discontinuation were generally the same as in study 0104, except that under a protocol amendment the total duration allowed was extended from 84 days to 180 days and that some patients could be treated for > 180 days under country-specific amendments.

Main inclusion criteria

Male and female patients aged ≥ 18 years of age, with proven, probable or possible IFD caused by *Aspergillus* species, rare molds, yeasts, or other dimorphic fungi (i.e. fungal pathogens other than *Aspergillus fumigatus* or *Candida* species) were enrolled into the study.

Main exclusion criteria

Patients with a known history of allergy, hypersensitivity, or any serious reaction to the azole class of antifungals or to any component of the study drug, at high risk for QT prolongation or with risk factors for Torsades de Pointes or use of concomitant medications that are known to prolong QT interval, with evidence of hepatic dysfunction or concomitant use of astemizole, cisapride, rifampin/rifampicin, rifabutin, ergot alkaloids, long acting barbiturates, ritonavir, efavirenz, carbamazepine, pimozide, quinidine, neostigmine, terfenadine, ketoconazole, valproic acid or St. John's Wort in the 5 days prior to first administration of study drug were excluded from the study.

Treatments

Isavuconazole was administered during the study as either IV or oral.

An IV isavuconazole loading regimen was administered during the first 48 hours (200 mg q8h) followed by a maintenance dose from day 3 to EOT (200 mg q24h). The first maintenance dose (day 3) was not to have been administered earlier than 12h after the last loading dose. Infusions were given over a period of at least 1 hour.

Oral isavuconazole was taken without regard to food intake. An oral isavuconazole loading regimen was administered during the first 48 hours (2 x 100 mg capsules q8h) followed by a maintenance dose from day 3 to EOT (2 x 100 mg capsules qd).

Objectives

The primary objective was to describe the efficacy of isavuconazole in the treatment of eligible patients with any of the following:

a) Proven, probable or possible invasive aspergillosis with CrCL < 50 mL/min; primary treatment
b) Proven or culture positive probable IFD due to moulds, yeasts or dimorphic fungi other than *Aspergillus fumigatus* or *Candida* species; primary treatment, refractory or intolerant of prior therapy (based on renal function, AEs or inadequate plasma concentrations)
c) Proven or probable zygomycosis documented by culture or histology/cytology

In the final analysis renal, impairment was re-defined as eGFRMDRD < 60 mL/min/1.73 m^2.

The secondary objective of the study was to characterize the safety and tolerability while assessing additional efficacy of treatment with isavuconazole. Exploratory endpoints were the concentration-time profiles of study drug and metabolite(s) if warranted in patients from the PK substudy and characterization of pharmacokinetic trough values of study drug and metabolite(s) if warranted.

Outcomes/endpoints

The primary outcomes were:

- Overall response evaluated by DRC at EOT, day 42 and day 84, by pathogen causing IFD as determined by the DRC;

The secondary efficacy outcomes included:

- Clinical response, mycological response and radiological response assessed by the DRC at EOT, day 42 and day 84 and EOT;
- Mortality rate of patients at multiple time points.

The study protocol identified the DRC-assessed overall response as the primary endpoint, given the variety of fungal infections where mortality may or may not be appropriate. In mucormycosis, the applicant has chosen mortality as the most relevant endpoint to be able to compare the results from Study 9766-CL-0103 to those reported in literature (for instance with standard care liposomal amphotericin B). However, as in study 9766-CL-0104, the "DRC - assessed overall response at EOT", a combined endpoint of clinical, mycological and radiological responses at EOT, is considered the most important endpoint for the CHMP.

Study visits were scheduled in line with study 0104. Overall response was assessed by the DRC as success (complete or partial) or failure (stable or progression) as follows:

Success-complete: Resolution of all clinical symptoms and physical findings associated with IFD; resolution of radiological abnormalities (≥ 90% response in some cases); presumed or documented eradication

Success-partial: Resolution of some clinical symptoms and physical findings associated with IFD; improvement of radiological abnormalities (at least 25% response at Week 6 or 50% at week 12); presumed or documented eradication

Failure-stable: Minor or no change in clinical symptoms and physical findings and radiographic abnormalities associated with IFD but no evidence of progression

Failure-progression: Evidence of progression based on clinical, radiologic and mycological criteria. Worsening or new clinical symptoms and physical findings and/or radiographic abnormalities associated with IFD; alternative systemic antifungal treatment required.

The DRC assessed the attributable mortality with categorisation, as in study 9766-CL-0104.

PK intensive data were obtained over 24h on day 7 or preferably day 14 in a subset. Trough samples were collected from all patients at days 7, 14, 28, 42, 84, and every 4 weeks thereafter.

Overall outcomes and clinical, radiological and mycological responses were evaluated by the DRC at day 42, day 84 and EOT. Rules applied were similar to those in study 9766-CL-0104. Investigators evaluated clinical, radiological and mycological responses at EOT, day 42 and day 84.

The key secondary efficacy endpoint of DRC-assessed overall response at EOT was analysed for the mITT Mucorales population and the mITT-*Aspergillus* population.

Sample size

Approximately 100 patients, with proven or probable IFD were to be enrolled in the study, later increased to 150 to enrol at least 30 renally impaired patients with IFD and "adequate" numbers with mucormycosis.

Randomisation

This study was not randomised.

Blinding (masking)

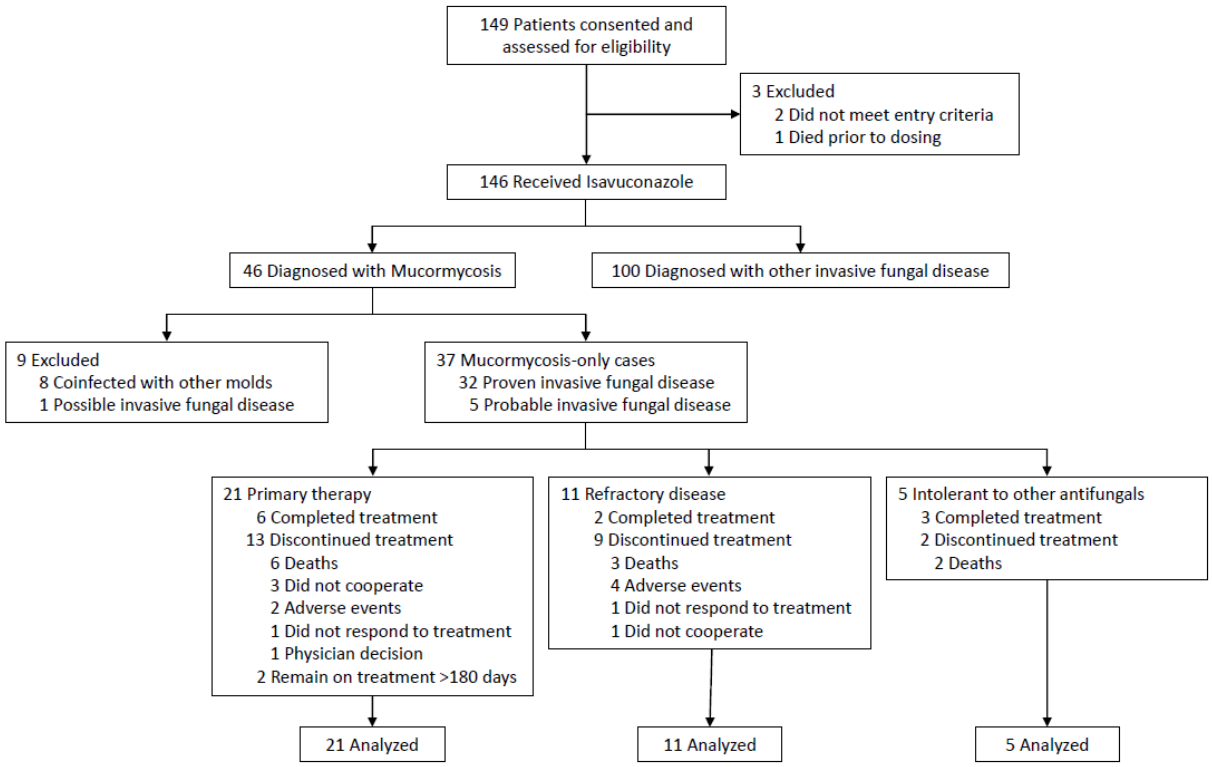
This was an open-label study.

Statistical methods

No statistical hypothesis was tested in this non-randomised open-label study.

Results

Participant flow



Recruitment

Patients were enrolled in this multicentre study at 34 centres in the US, EU, South America, Asia and the Middle East. Of the 149 patients enrolled, 146 (98%) evaluable patients of which 59/146 (40.4%) were renally impaired (RI). The mITT—Mucorales population consisted of 37 patients and the mITT—*Aspergillus* population of 24 patients (20 renally impaired [NI] and 4 non-renally impaired [NRI]) (see table below):

Table 32 Patient Disposition and Analysis Set (study 9766-CL-0103)

	RI (n = 59)	NRI (n = 90)	Total (n = 149)
Signed informed consent			149
Enrolled	59 (100.0%)	90 (100.0%)	149 (100.0%)
Intent-to-Treat (ITT)	59 (100.0%)	87 (96.7%)	146 (98.0%)
Modified Intent-to-Treat (mITT)	54 (91.5%)	86 (95.6%)	140 (94.0%)
mITT-Mucorales	11 (18.6%)	26 (28.9%)	37 (24.8%)
mITT-*Aspergillus*	20 (33.9%)	4 (4.4%)	24 (16.1%)
mITT-Other filamentous fungi (not *Aspergillus* or Mucorales)	9 (15.3%)	8 (8.9%)	17 (11.4%)
mITT-Mold species not otherwise specified	5 (8.5%)	2 (2.2%)	7 (4.7%)
mITT-Dimorphic fungi	2 (3.4%)	27 (30.0%)	29 (19.5%)
mITT-*Non-Candida* yeast	4 (6.8%)	7 (7.8%)	11 (7.4%)
mITT-Mixed infection	3 (5.1%)	12 (13.3%)	15 (10.1%)
Safety (SAF)	59 (100.0%)	87 (96.7%)	146 (98.0%)
Pharmacokinetics (PKAS)	54 (91.5%)	84 (93.3%)	138 (92.6%)

Renal impairment was defined at baseline as eGFR < 60 mL/min/1.73 m^2 by the MDRD formula.

eGFR: estimated glomerular filtration rate; ITT: intent-to-treat; MDRD: Modification of Diet in Renal Disease;

mITT: modified ITT; NRI: not renally impaired; PKAS: All ITT patients who have at least one isavuconazole plasma concentration; RI: renally impaired; SAF: Safety Analysis Set.

Overall, the number of ITT patients discontinuing treatment was 47.3% (57.6% for RI and 40.2% NRI) whereas 40.4% (45.8% RI and 36.8% NRI) did not complete the required follow-up period-see following table:

Table 33 Primary Reason for Treatment Discontinuation (ITT Population)

	RI (n = 59)	NRI (n = 87)	Total (n = 146)
Treatment Discontinuation			
Completed	23 (39.0%)	49 (56.3%)	72 (49.3%)
Discontinued	34 (57.6%)	35 (40.2%)	69 (47.3%)
Primary reason for discontinuation			
Death	13 (22.0%)	9 (10.3%)	22 (15.1%)
Adverse event/intercurrent illness	10 (16.9%)	8 (9.2%)	18 (12.3%)
Insufficient therapeutic response	3 (5.1%)	7 (8.0%)	10 (6.8%)
Did not cooperate	0	5 (5.7%)	5 (3.4%)
Violation of selection at entry	1 (1.7%)	3 (3.4%)	4 (2.7%)
Other protocol violation	3 (5.1%)	1 (1.1%)	4 (2.7%)
Admin/other	2 (3.4%)	2 (2.3%)	4 (2.7%)
Failure to return/lost to follow-up	2 (3.4%)	0	2 (1.4%)
Discontinuation During Follow-up Period			
Completed	30 (50.8%)	52 (59.8%)	82 (56.2%)
Discontinued	27 (45.8%)	32 (36.8%)	59 (40.4%)
Primary reason for discontinuation			
Death	23 (39.0%)	22 (25.3%)	45 (30.8%)
Failure to return/lost to follow-up	2 (3.4%)	5 (5.7%)	7 (4.8%)
Admin/other	2 (3.4%)	2 (2.3%)	4 (2.7%)
Withdrew consent†	0	3 (3.4%)	3 (2.1%)
Ongoing‡	2 (3.4%)	3 (3.4%)	5 (3.4%)

Conduct of the study

Baseline data

Baseline demographics are shown in the following table:

Table 34 Summary of Demographics and Baseline Characteristics (ITT Population), study 9766-CL-0103

Parameter Category/Statistic	RI (n = 59)	NRI (n = 87)	Total (n = 146)
Age (years)			
n	59	87	146
Mean (SD)	52.9 (18.05)	47.8 (15.62)	49.9 (16.78)
Min	19	18	18
Median	57.0	50.0	52.0
Max	92	79	92
Sex			
Male	38 (64.4%)	62 (71.3%)	100 (68.5%)
Female	21 (35.6%)	25 (28.7%)	46 (31.5%)
Race			
White	48 (81.4%)	60 (69.0%)	108 (74.0%)
Black or African American	3 (5.1%)	7 (8.0%)	10 (6.8%)
Asian	8 (13.6%)	16 (18.4%)	24 (16.4%)
Other	0	4 (4.6%)	4 (2.7%)
Ethnicity			
Hispanic or Latino	2 (3.4%)	20 (23.0%)	22 (15.1%)
Not Hispanic or Latino	57 (96.6%)	67 (77.0%)	124 (84.9%)
Geographic region			
North America	30 (50.8%)	26 (29.9%)	56 (38.4%)
Western Europe	7 (11.9%)	10 (11.5%)	17 (11.6%)
Other Regions†	22 (37.3%)	51 (58.6%)	73 (50.0%)
Therapy status			
Primary Therapy	33 (57.9%)	60 (69.8%)	93 (65.0%)
Refractory	17 (29.8%)	21 (24.4%)	38 (26.6%)
Intolerant	7 (12.3%)	5 (5.8%)	12 (8.4%)
Missing	2	1	3
Hematologic malignancy	31 (52.5%)	32 (36.8%)	63 (43.2%)
Allogeneic BMT/HSCT	16 (27.1%)	10 (11.5%)	26 (17.8%)
Uncontrolled malignancy	18 (30.5%)	28 (32.2%)	46 (31.5%)
Neutropenic	14 (26.9%)	24 (46.2%)	38 (36.5%)
Corticosteroid use	20 (33.9%)	15 (17.2%)	35 (24.0%)
T-cell immunosuppressant use	32 (60.4%)	29 (51.8%)	61 (56.0%)

The median age of patients in the ITT population was 52 years (range: 18 - 92 years).

Among the 121 patients (82.9%) with a primary underlying disease or condition, the most common was AML (29 patients [19.9%]) followed by CLL (9 [6.2%]); all others occurred in < 10 patients.

The median age of mITT-Mucorales patients was 50 years (range: 22 - 79 years). Overall, 81.1% of mITT-Mucorales patients were male and 67.6% of patients were white. Overall, 59.5% of mITT-Mucorales patients had a hematologic malignancy, 35.1% of mITT-Mucorales patients had a prior allogeneic BMT and 27.0% was neutropenic (absolute neutrophil count < 0.5 x 10^9/L or < 500/mm^3). The most commonly reported primary underlying diseases were AML, ALL and diabetes mellitus.

Numbers analysed

- The ITT and mITT populations were defined as in study 9766-CL-0104.
- The mITT-Mucorales population included DRC-classified Mucorales only
- The mITT-*Aspergillus* population included DRC-classified *Aspergillus* only or no pathogen identified, but met serum GM and/or BAL GM criteria (see Study 9766-CL-0104)

Outcomes and estimation

Duration of treatment

For the ITT population, the median total duration of treatment was 94 days (range: 1-882 days). Overall, 100 patients (68.5%) received IV isavuconazole and 126 (86.3%) received oral isavuconazole with median durations of 9.5 and 136.8 days, respectively.

For the mITT-Mucorales population, the overall median duration of treatment was 84 days: 10 days for i.v. dosing and 80 days for oral therapy. There were 7 patients (18.9%) who were treated for longer than 180 days. Overall, 51.4% of patients were treated for ≥ 84 days. The median duration for i.v. dosing was 9.5 days, and 142.8 days for oral dosing. One patient had received study drug for 258 days and another for 882 days. Cumulative adherence ≥ 80% during the loading period occurred in 95.9% of patients. For 81 who received IV isavuconazole in the maintenance phase the cumulative adherence ≥ 80% was 98.8% and for 125 who received oral isavuconazole 90.1% were ≥ 80% adherent. Four sites did not use the correct filters and 6 patients received isavuconazole without a filter.

Isavuconazole was administered during the study 9766-CL-0103 as either i.v. or oral. Patients who started on oral therapy or patients who had already switched from i.v. to oral therapy may have switched back to i.v. therapy at any time if the investigator felt it was necessary, e.g., it was in the patient's best interest or for the appropriate clinical management of the patient. A total of 9 out of 37 (24%) patients were switched back from i.v. to oral therapy. Reasons for switching back were however considered comprehensible. No impact on clinical outcomes is expected from multiple switches between formulations as the intravenous and oral formulations are bioequivalent.

The all-cause mortality through day 42 in the ITT population was 18.5% (22.0% RI and 16.1% NRI) whereas rates through day 84 were 24.7% overall (30.5% RI and 20.7% NRI) patients. There were 33 (22.6%) reported patient deaths by day 84 and 3 LTFU patients who were counted as having died.

Mucorales

Of 38 assessed by the DRC as having Mucorales only, 37 had a proven (32) or probable (5) infection. Of these 37, 21 received isavuconazole as primary therapy while 11 were refractory and 5 were intolerant to prior AFT. One of the 38 had a possible infection and was excluded from the mITT analysis while 8 others were excluded because they had Mucorales plus another fungal pathogen. The median duration of treatment was 84 days but 7 received > 180 days. As of the cut-off date 24/37 (64.9%) had discontinued treatment, see following table:

Table 35 Primary Reason for Treatment and Study Discontinuation (mITT-Mucorales Population), study 9766-CL-0103

	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Treatment Discontinuation				
Completed	6 (28.6%)	2 (18.2%)	3 (60.0%)	11 (29.7%)
Discontinued	13 (61.9%)	9 (81.8%)	2 (40.0%)	24 (64.9%)
Primary reason for discontinuation				
Death	6 (28.6%)	3 (27.3%)	2 (40.0%)	11 (29.7%)
Adverse event/intercurrent illness	2 (9.5%)	4 (36.4%)	0	6 (16.2%)
Did not cooperate	3 (14.3%)	1 (9.1%)	0	4 (10.8%)
Insufficient therapeutic response	1 (4.8%)	1 (9.1%)	0	2 (5.4%)
Admin/other	1 (4.8%)	0	0	1 (2.7%)
Discontinuation during follow-up period				
Completed	7 (33.3%)	3 (27.3%)	2 (40.0%)	12 (32.4%)
Discontinued	12 (57.1%)	8 (72.7%)	3 (60.0%)	23 (62.2%)
Primary reason for discontinuation				
Death	10 (47.6%)	6 (54.5%)	2 (40.0%)	18 (48.6%)
Admin/other	0	1 (9.1%)	1 (20.0%)	2 (5.4%)
Withdrew consent†	1 (4.8%)	1 (9.1%)	0	2 (5.4%)
Failure to return/lost to follow-up	1 (4.8%)	0	0	1 (2.7%)
Ongoing‡	2 (9.5%)	0	0	2 (5.4%)

Through day 42, death occurred in 14 patients (37.8%) while 16 (43.2%) had died by day 84 (see following table). The Kaplan-Meier estimates were 64.9% to day 42, 59.2% to day 84, 56.4% to day 120 and 52.9% to day 180.

Table 36 All-cause Crude Mortality Trough Day 42 and Day 84 (mITT-Mucorales Population, study 9766-CL-0103

Outcome	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
All-cause Mortality Through Day 42†	7 (33.3%)	5 (45.5%)	2 (40.0%)	14 (37.8%)
Deaths	7 (33.3%)	4 (36.4%)	2 (40.0%)	13 (35.1%)
Unknown Survival Status	0	1 (9.1%)	0	1 (2.7%)
All-cause Mortality Through Day 84†	9 (42.9%)	5 (45.5%)	2 (40.0%)	16 (43.2%)
Deaths	9 (42.9%)	4 (36.4%)	2 (40.0%)	15 (40.5%)
Unknown Survival Status	0	1 (9.1%)	0	1 (2.7%)

† A patient with the last known survival status was before day 42 or before day 84 or missing and the last assessment day was before day 42 or before day 84 was counted as death

A vast majority of deaths were considered by the DRC to be due to or associated with IFD, see following table:

Table 37 DRC-assessed Attribution of IFD to Death by Therapy Status (mITT-Mucorales Population), study 9766-CL-0103

Timepoint Attributable Mortality	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Through Day 42				
Patients Died	7 (33.3%)	4 (36.4%)	2 (40.0%)	13 (35.1%)
Directly Due to Consequence of Progressive IFD	6 (28.6%)	2 (18.2%)	0	8 (21.6%)
Associated with Evidence of Residual or Ongoing IFD	1 (4.8%)	2 (18.2%)	2 (40.0%)	5 (13.5%)
Through Day 84				
Patients Died	9 (42.9%)	4 (36.4%)	2 (40.0%)	15 (40.5%)
Directly Due to Consequence of Progressive IFD	6 (28.6%)	2 (18.2%)	0	8 (21.6%)
Associated with Evidence of Residual or Ongoing IFD	2 (9.5%)	2 (18.2%)	2 (40.0%)	6 (16.2%)
Associated with No Evidence of Residual or Ongoing IFD	1 (4.8%)	0	0	1 (2.7%)

Two patients were continuing in the study and thus the DRC did not assess their efficacy outcome at EOT. As requested, the applicant has provided an update on the status of these two patients as was requested. One patient was considered completely cured. The other patient was responding clinically and continuing isavuconazole treatment.

For the other 35 the DRC-assessed overall success rate at EOT was 11/35* (31.4%), with 5 patients with complete success and 6 with partial success. When the 10 stable patients were included as successes the rate was 60.0% (21/35).

Table 38 DRC-assessed Overall Response at EOT (mITT-Mucorales Population), study 9766-CL-0103

Outcome Response	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n =37)
Success	6/19 (31.6%)	4/11 (36.4%)	1/5 (20.0%)	11/35 (31.4%)
Complete	3/19 (15.8%)	2/11 (18.2%)	0	5/35 (14.3%)
Partial	3/19 (15.8%)	2/11 (18.2%)	1/5 (20.0%)	6/35 (17.1%)
Failure	13/19 (68.4%)	7/11 (63.6%)	4/5 (80.0%)	24/35 (68.6%)
Stable	6/19 (31.6%)	2/11 (18.2%)	2/5 (40.0%)	10/35 (28.6%)
Progression	7/19 (36.8%)	5/11 (45.5%)	2/5 (40.0%)	14/35 (40.0%)

* Two patients were continuing in the study and thus the DRC did not assess their efficacy outcome at EOT.

The DRC assessed 45.2% as having a successful clinical response at EOT.

Table 39 DRC-assessed Success Rates for Clinical, Mycological, and Radiological Response at EOT by Therapy Status (mITT-Mucorales Population), study 9766-CL-0103

	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Clinical Response	10/18 (55.6%)	2/9 (22.2%)	2/4 (50.0%)	14/31 (45.2%)
Mycological Reponses	6/19 (31.6%)	4/11 (36.4%)	2/5 (40.0%)	12/35 (34.3%)
Radiological Response	3/18 (16.7%)	2/10 (20.0%)	1/5 (20.0%)	6/33 (18.2%)

At day 42 and day 84, the clinical responses were considerably higher than the mycological responses. Because the mycological responses were predominantly 'presumed' based, and therefore depending on the clinical and radiological outcomes, the lower number of mycological responses compared to clinical responses is explained by the very low radiological response rate.

Investigator success rates at EOT were consistently higher for clinical, mycological and radiological outcomes (54.5%, 41.7% and 26.5%, respectively) vs. DRC-assessed rates. For primary patients, the investigator success rates at EOT were also higher (65.0%, 42.9% and 30.0%, respectively).

Prior Medications and Nonmedication Procedures (ITT Population, 9766-CL-0103)

In the ITT population, 69.9% of the patients received prior antifungal therapy (AFT). Amongst the most common used classes of prior AFTs were antimycotics for systemic use (68.5%) and triazole derivatives (53.4%). For patients who required primary therapy for invasive aspergillosis, prior use of potentially mould active systemic AFT was allowed per protocol, as long as it was not administered more than 4 cumulative days within 7 days prior to first administration of study drug. These patients also could have prophylactically received 14 consecutive days of amphotericin B product or an echinocandin and developed new evidence of IFD and still have been eligible for enrolment.

If all primary cases received prior amphotericin it could have impact the study results because response rates in primary treatment and salvage therapy are not necessarily the same (Skiada et al, Haematol. 2013[4]. A tabular overview summarising all patients with prior use of amphotericin is listed in the following table:

[4] Skiada et al. Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL 3) H

Table 40 Summary of patients with prior amphotericin B use

Pt No	Age/ Gender	Underlying Condition	Days on ISA	Duration of amB[1] (days)	Stop day[2] amB	Comment
Primary therapy						
010702	48/M	CKD; Renal transplant	3	1	−1	Eligible for study under primary therapy definition
011508	49/M	TCP-Leukaemia	29	1	1	Eligible for study under primary therapy definition
011514	56/F	AML	33	4	−1	Eligible for study under primary therapy definition
014202	57/M	CLL	27	3	−1	Eligible for study under primary therapy definition
015401	49/M	ALL	363	4	−2	Eligible for study under primary therapy definition
911905	73/M	Diabetes mellitus	4	1	−2	Eligible for study under primary therapy definition
960101	55/M	NHL	179	3	−1	Eligible for study under primary therapy definition
970401	77/M	Hairy cell leukaemia	15	3	1	Eligible for study under primary therapy definition
970402	76/M	MDS	5	4	−1	Eligible for study under primary therapy definition
970403	25/M	AML	1238	2	−1	Eligible for study under primary therapy definition
970412	29/M	KTWS	68	1	1	Eligible for study under primary therapy definition
Refractory						
014103	52/M	Lupus nephritis	33	17	−1	Pulmonary MM refractory to L-amB
070201	28/M	AML	18	6[a]	−1	Pulmonary MM refractory to amB + POS (D15/D1)
110509	41/F	AML-Relapse	22	16	1	Sinus MM refractory to amB + POS (D4/D1)
110510	53/M	LBC-Lymphoma	15	35	−1	Pulmonary/Sinus MM refractory to L-amB
320403	50/F	COPD	182	80	−1	Pulmonary MM refractory to amB
320407	54/M	COPD	86	35	−1	Pulmonary/DST MM refractory to amB + POS (D21/D1)
490401	44/M	Ulcerative Colitis	84	92	−8	Sinus MM refractory to L-amB
490402	60/M	AML	87	14	−2	Pulmonary MM refractory to L-amB
970302	22/M	AML-Relapse	19	11	1	DST MM refractory to amB
970404	27/F	AML-Relapse	735	19	−1	Pulmonary and ear refractory to amB + POSA (D7/D2)
Intolerant						
010502	51/M	Multiple myeloma	132	9	−1	Renal failure due to amB
011501	57/M	CLL	28	202	1	Renal failure due to amB
014804	23/M	Thalassaemia, SCA	85	12	−3	Renal tubular acidosis due to amB

[1] Refers to amphotericin B use within 30 days of baseline; [2] stop day relative to baseline
[a] Patient also received 15 days of prior posaconazole treatment (stopped at study day -1)
Abbreviations: ALL=acute lymphblastic leukaemia; AML=acute myeloid leukaemia; amB=amphotericin B; CKD=chronic kidney disease; CLL=chronic lymphocytic leukaemia; COPD=chronic obstructive pulmonary disease; D=study day; DST=deep soft tissue; KTWS=Klippel-Trenaunay-Weber Syndrome; L-amB=liposomal amphotericin B; LBC Lymphoma=large B-cell lymphoma; MDS=myelodysplastic syndrome; MM=mucormycosis; NHL=non-Hodgkin's lymphoma; POS=posaconazole; SCA=sickle cell anaemia; TCP Leukaemia=T-call prolymphocytic leukaemia.

This tabular overview explains on which base investigators decided patients entering the study (ie, if they were to be regarded as primary patients, if they had failed to or were intolerant to treatment with other antifungal drugs) and whether the patients had received pre-study amphotericin and/or other antifungal drugs active against mucormycosis (i.e. posaconazole). The reasons for inclusion of the patients are considered justified and in compliance with the study protocol.

A total of eight patients (5.5%) underwent surgery and 10 patients (6.8%) underwent debridement as part of their treatment of IFD.

Concomitant Medications and Nonmedication Procedures (ITT Population, 9766-CL-0103)

In the ITT population, 97.3% received at least one concomitant drug. The 3 most commonly used classes of concomitant medications in the ITT population were analgesics (87.0%), ophthalmologicals (84.9%), and antibacterials for systemic use (77.4%). The 3 most commonly used classes of concomitant AFT were antimycotics for systemic use (40.4%), antifungals for dermatological use (30.8%) and gynecological antiinfectives and antiseptics (30.8%). Whether these antifungals were potentially active against Mucorales was however unknown. In the ITT population, 76.0% of patients underwent concomitant non-medication

procedures most commonly packed red blood cell transfusion (43.2%), platelet transfusion (37.7%), and central venous catheterization (16.4%). The contribution of isavuconazole to antifungal treatment was considered difficult to determine when 40.4% of the patients took concomitant systemic antifungals.

Only 1 out of 21 patients had a concomitant systemic Mucorales active antifungal treatment (patient who had 1 day of L-amB on Day 4).

Design of the pivotal study in Mucormycosis (9766-CL-0103); External control data to put the mortality and clinical response rates into context

Compassionate use

The following shortcomings of study 9766-CL-0103 were highlighted during the procedure:

- Design was uncontrolled;

The applicant pointed out during the procedure that no randomized controlled studies had been published that compared different Mucorales-active antifungal treatments head-to-head in mucormycosis (including "standard care drug" L-amB). All studies in L-Amb were uncontrolled and performed in a limited number of patients who had a wide range of baseline characteristics and underwent a range of other interventions (e.g. surgery, correction of predisposing conditions). CHMP agreed that the fact that only uncontrolled data were available was not critical. Nevertheless, it was considered that the external control data were inadequate to put the clinical response rates into context and therefore the indication "treatment of mucormycosis" could not be approvable.

- There were inadequate external control data to put the mortality rates and clinical response rates into context;

At CHMP request, the applicant provided additional analyses to put all-cause mortality rates and overall response rates observed in study 9766-CL-0103 in the context of external control data. These external control data are mainly based on (liposomal-) amphotericin-B, which is considered acceptable.

It was already concluded that the ACM data from study 9766-CL-0103 were correctly put into the context of external control data on mortality, and that the survival benefits provided by isavuconazole in the treatment of mucormycosis seems similar to the survival benefits provided by liposomal amphotericine-B.

In order to put the overall response rates observed in study 9766-CL-0103 in the context of external control data, the Applicant submitted data on five clinical amphotericin-B-based studies. The conclusion of the applicant that, based on study methodology, only the studies by Shoham (Shoham 2010), Xhaard (Xhaard 2012) and Lanternier (Lanternier 2012) were considered appropriate for an external comparison of overall response rates with study 9766-CL-0103, was agreed by CHMP, since these studies were largely consistent with EORTC/MSG definitions. These three studies were considered as a narrow but acceptable basis for the discussion on the overall response rates observed in study 9766-CL-0103 and to put these in external context of AmB in the treatment of this very rare disease.

The overall success rates (32% to 42%) reported in the three studies were similar to the reported overall success rate of 32% for patients with primary therapy in study 9766-CL-0103. The Ambizygo study by Lanternier (2012), which was the only interventional study that used a similar DRC assessment as study 9766-CL-0103 with high dose L amB (10 mg/kg per day), showed very similar response rates and mortality.

From the sparse data available, it appears that the overall response rates in study 9766-CL-0103 are consistent with that observed in external control studies performed with amphotericin-B, the only approved antifugal drug in the treatment of mucormycosis.

During the procedure, and taking into account the CHMP concerns, the applicant decided to change the indication applied for to treatment of adult patients "with mucormycosis for whom amB is inappropriate".

Although the absolute number of patients with a refractory status was low in study 9766-CL-0103, most (10 out of 11) had received prior amB based treatments, and 3 of the 5 patients with an intolerant therapy status had received prior amB (these patients were discontinued from amB due to severe renal side effects). These 13 patients were considered relevant for the above proposed indication. Of the amB-refractory patients 60% had a complete, partial, or stable response and 2 of the 3 patients intolerant to amB-based therapies who survived more than 3 months also had a stable response.

The reported adverse event related overall discontinuation rate in the Ambizygo study (Lanternier 2012) was about 20% (L amB 3mg/kg/day) and 32% in the AmbiLoad study in aspergillosis with a higher regimen of 10 mg L-amB /kg/day (Cornely 2007). AmB-based therapies are known for the risk of development of (severe) renal side-effects. Isavuconazole was well tolerated in patients (10 out of 37) enrolled in study 9766-CL-0103 who had a baseline creatinine-clearance of < 60 mL/min. Isavuconazole (available as IV and oral dosage forms) offers an added treatment option for renally impaired patients with invasive aspergillosis and mucormycosis.

Ancillary analyses

- Compassionate use of isavuconazole

The four reported cases on isavuconazole as compassionate use give some further support for the proposed indication "Patients with mucormycosis for whom amphotericin B is inappropriate". These patients were are all pre-treated with amB-based regimens, in most cases posaconazole was added to the regime. In two of the patients CNS was also involved, which has a poor prognosis. Two patients were intolerant to L-amb and developed renal impairment. The patients appeared to benefit from treatment with isavuconazole. Moreover, isavuconazole was well tolerated, enabling long term treatment.

Literature review on Mucorales

The applicant reviewed the literature on mortality and/or clinical efficacy data with amphotericin B and posaconazole in mucormycosis.

Ten of 39 publications of some relevance presented all-cause mortality – 5 in mixed underlying conditions, 2 in such patients treated with posaconazole and 3 in which patients were treated with amphotericin B formulations. The publications were reviewed for factors that are known to influence prognosis and outcomes in patients with mucormycosis and then compared with patients in study 9766-CL-0103.

Table 41 Summary of Publications Reporting Mortality in Patients with Mixed Underlying Conditions

Author	Number of M Patients Reported	Line of Therapy	Proportion of Study Population with:					Mortality† (%) (n/N)
			HM (%)	Surg (%)	Diss (%)	CNS (%)	DM (%)	
Herbrecht, 2001	21	R, I	48%	59%	29%	5%	29%	ABCD 35% (9/20)‡
Chakrabarti, 2009	75	N/K	9%	75%	5%	N/K	33%	All AmB forms 45% (24/53§)
Shoham, 2010	28	P	54%¶	46%	14%	N/K	7%	L-AmB 61% (17/28)
Skiada, 2011	230	P, R, I	44%	40%	15%	21%	17%	All AmB forms 39% (32/82)†† L-AmB 32% (20/62)
Lanternier, 2012a	34	P	53%	71%	18%	N/K	18%	L-AmB 42% (13/31)‡‡
Greenberg, 2006	24	P, R, I	58%	71%	17%	58%	21%	Posaconazole 38% (9/24)
van Burik, 2006	91	R, I	53%	70%	N/K	12%	33%	Posaconazole 38% (35/91)
Gleissner, 2004	120	N/K	94%	43%	32%	N/K	10%	AmB 61.3% (38/62) L-AmB 37.5% (6/16)
Pagano, 2004	59	P, R, I	100%	12%	7%	19%	17%	AmB/L-AmB 80% (47/59)
Kara, 2009	20	P, R, I	100%	100%	N/K	N/K	N/K	AmB/L-AmB 55% (11/20)

† Timepoint for mortality varies across studies.
P = primary, R = refractory to other therapies, I = intolerant to other therapies, N/K = not known, HM = haematological malignancies, Diss = disseminated infection, CNS = patients with central nervous system infection, DM = diabetes mellitus, ACBD = amphotericin B colloidal dispersion, AmB= Amphotericin B, ABLC = Amphotericin B Lipid Complex Injection

Despite the limitations, the 7 publications reported mortality rates in the range of 32% to 61%, with most of the reports showing mortality between 35% and 45% compared to 38% and 43% mortality rates observed through day 42 and day 84, respectively, in study 9766-CL-0103. The only publication that used the 12 week endpoint reported a mortality rate of 42%, which compares closely with day 84 in study 9766-CL-0103.

In addition, patients in study 9766-CL-0103 assessed by the DRC as having received isavuconazole as primary therapy for proven or probable mucormycosis were matched with patients from the Fungiscope Registry Database who received primary therapy with amphotericin B for proven or probable mucormycosis. The registry contains > 150 cases of mucormycosis diagnosed and treated between 2003 and 2013. At least 1 matching case was found for all of the 21 cases in study 9766-CL-0103 included in the mortality assessment. Nevertheless, there were differences in several factors between the cases and controls:

Table 42 Baseline Fungal Disease Characteristics

Parameter Category/Statistic	9766-CL-0103 Cases (n = 21)	Fungiscope Matched Controls (n = 33)
Categorization of IFD		
Proven	18 (85.7%)	20 (60.6%)
Probable	3 (14.3%)	13 (39.4%)
Severity of Disease		
CNS Involvement (yes)	6 (28.6%)	8 (24.2%)

Parameter Category/Statistic	9766-CL-0103 Cases (n = 21)	Fungiscope Matched Controls (n = 33)
Disseminated Disease (yes)	8 (38.1%)	8 (24.2%)
Location of IFD		
LRTD Only	1 (4.8%)	10 (30.3%)
LRTD Plus Other Organ	8 (38.1%)	7 (21.2%)
Non LRTD Only	12 (57.1%)	16 (48.5%)
Non-LRTD Location		
Biliary System	0	1 (3.0%)
Bone	4 (19.0%)	5 (15.2%)
CNS	6 (28.6%)	8 (24.2%)
Deep Soft Tissues	1 (4.8%)	6 (18.2%)
Eye	7 (33.3%)	4 (12.1%)
GI Tract	2 (9.5%)	5 (15.2%)
Kidneys	2 (9.5%)	1 (3.0%)
Liver	2 (9.5%)	3 (9.1%)
Sinus	13 (61.9%)	11 (33.3%)
Skin	2 (9.5%)	5 (15.2%)
Spleen	1 (4.8%)	2 (6.1%)
Other	2 (9.5%)	2 (6.1%)

The controls had a mean duration of treatment with amphotericin B of 27 days vs. isavuconazole patients 149 days, but 12 controls were switched to posaconazole so that the mean treatment duration for controls was 77 days. The crude mortality rates were similar at day 42.

Table 43 All-Cause Crude Mortality through Day 42

	9766-CL-0103 Cases		Fungiscope Matched Controls	
Outcome	**(n = 21)**	**95 % CI**	**(n =33)**	**95 % CI**
Deaths	7 (33.3%)	(14.588, 56.968)	13 (39.4%)	(22.907, 57.861)

The 95% confidence intervals are based on an exact binomial distribution.

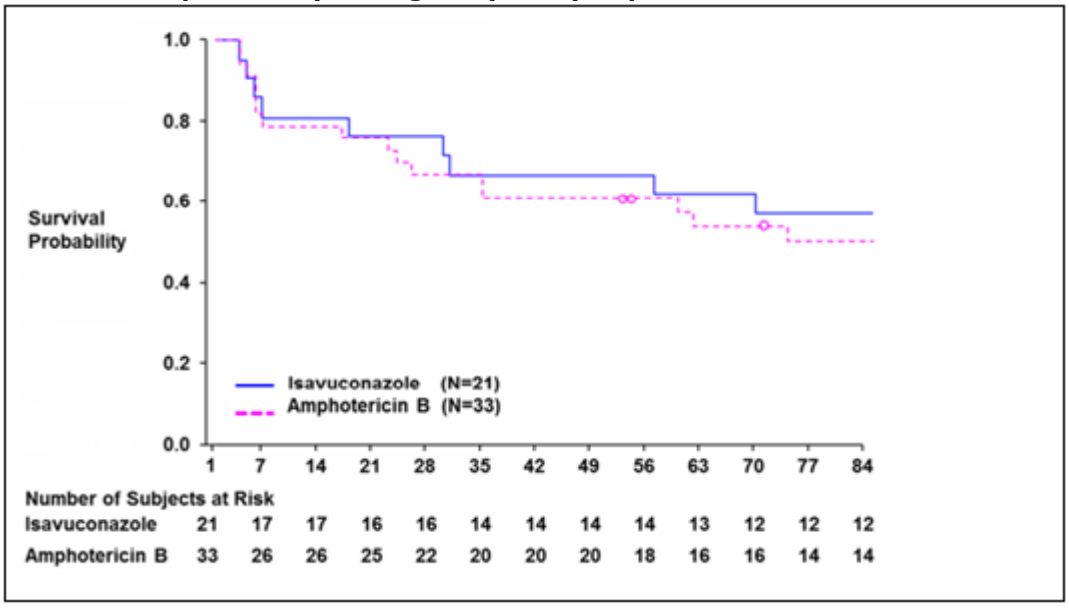
The day 84 survival estimates for study 9766-CL-0103 cases were similar to those for the matched controls (57.1% vs. 49.7% for controls).

The overall response rate at EOT in Mucorales is low and the all-cause mortality through day 42 and day 84 was high. These results are not unexpected, since most of these patients were very ill and were infected with pathogens that generally are resistant to most antifungal drugs.

In order to put the mortality rates of isavuconazole (at day 42 and day 84) into the context of the external control data, an analysis on overall mortality has been submitted, based on an extensive overview of literature in support of amphotericin-B, which is considered as first-line treatment in mucormycosis. L-amB is being preferred to amphotericin deoxycholate (amB-DC) due to its lower toxicity, and to lipid complex amphotericin (ABLC) based on available clinical data.

The following figure presents the survival probability through day 84 from the Kaplan-Meier survival analysis using the last known survival status. The day 84 survival estimates for the patients from study 9766-CL-0103 were comparable to those for the matched-control cases of amphotericin B (57.1% for 9766-CL-0103 patients, 49.7% for the matched controls).

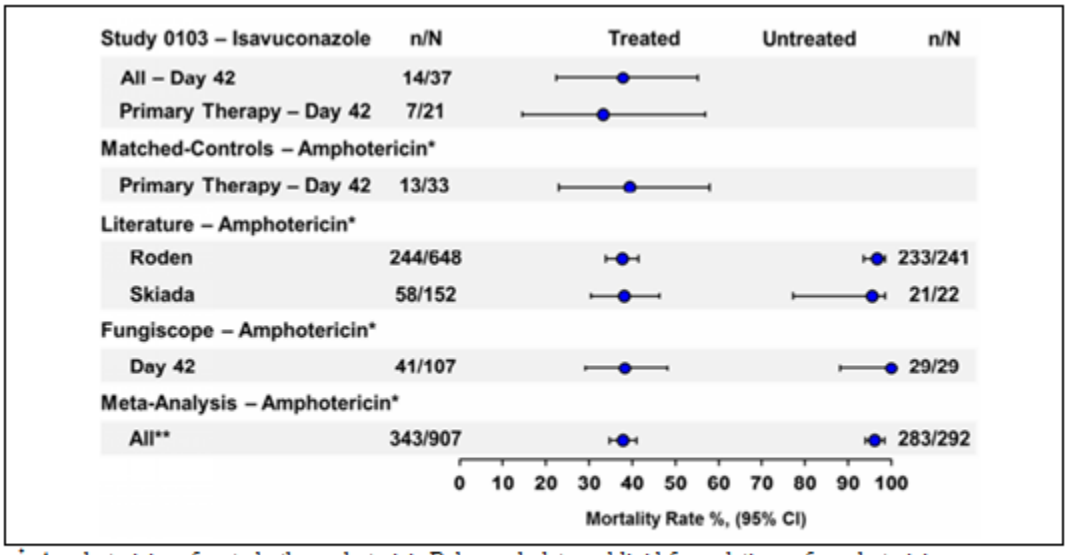
Figure 8 Survival probability through Day 84 by Kaplan-Meier method



As presented above, the day 84 survival estimates for the patients from study 9766-CL-0103 seem comparable to those of the matched control cases of amphotericin B.

Furthermore, to compare the results from study 9766-CL-0103 with the data obtained from the Fungiscope registry and from published observational studies that reported ACM in untreated patients and in amB-treated patients, the applicant has combined various data sources in a meta-analytic approach, which is shown below:

Figure 9 Mortality in amphotericin B-treated, isavuconazole-treated and untreated patients with mucormycosis



* Amphotericin refers to both amphotericin B deoxycholate and lipid formulations of amphotericin.
** The meta-analysis is based on data from Roden 2005 and Skiada 2011 (see Table 15), and Fungiscope data (**Module 5.3.5.4 Fungiscope Matched-Case Control Study**). The number of treated patients=907; the number of untreated patients=292.

The Fungiscope matched-control analysis as provided by applicant underlines a significant treatment benefit of amB compared to untreated patients, and the analysis shows that the treatment effect with isavuconazole in respect to improving survival of patients seems comparable to that of amphotericin-B.

The use of (liposomal) amphotericine-B in mucormycosis is without doubt the best documented. A clinically significant benefit of amphotericin-B treatment compared to untreated patients is shown. Liposomal amphotericine B is the only antifungal medicine that is registered for first line treament of mucormycosis (EU and USA) and is considered as the "standard of care". All-cause mortality in study 9766-CL-0103 (isavuconazole) appears to be compable to all-cause mortality as reported in literature for the use of liposomal amphotericine-B as first line treatment in mucormycosis.

Efficacy results in mITT-*Aspergillus* Population in RI and NRI patients, study 9766-CL-0103

- The DRC assessed 24 patients as having only an *Aspergillus* infection (9 proven and 15 probable). Of the 24, 20 were classed as RI patients. The most common were *Aspergillus fumigatus* (41.7%) and *Aspergillus flavus* (20.8%). *Aspergillus* infection was confined to the LRTD in 62.5%.
- All-cause mortality to day 42 was 3/24 (12.5%) and to day 84 it was 6 (25.0%) deaths.
- The DRC-assessed overall success rate at EOT was 34.8%, at which time 56.5% had a successful clinical response, 39.1% had a successful mycological response and 21.7% had a successful radiological response.
- Overall success rates were 29.2% at day 42 and also at day 84. At day 84, 41.7% had a clinical success, a third had a mycological response and 20% had a radiological response.

Patients with invasive aspergillosis and renal impairment

Patients in study 9766-CL-0103 and a small number in 9766-CL-0104 had invasive aspergillosis and renal impairment (eGFR-MDRD < 60 mL/min/1.73 m^2). Data were pooled across the 143 in the myITT population in 0104 and mITT-*Aspergillus* population in 0103 with known renal status.

Table 44 Summary of Patients by Renal Status (Pooled mITT Invasive Aspergillosis Patients)

	Total Patients with IA†	**NRI Pooled IA mITT group**	**RI Pooled IA mITT group**	**Renal Status Unknown‡**
Study 9766-CL-0104	123	108	11	4
Study 9766-CL-0103	24	4	20	0
Pooled Dataset	147	**112**	**31**	4

IA: invasive aspergillosis; mITT: modified intent-to-treat; myITT: mycological intent-to-treat; NRI: not renally-impaired; RI: renally-impaired.
† Study 9766-CL-0104: isavuconazole-treated patients in the myITT population (mITT patients with proven or probable invasive aspergillosis based on cytology, histology, culture or GM criteria set forth in the protocol); Study 9766-CL-0103: mITT-*Aspergillus* population (mITT patients who the DRC classified as *Aspergillus* only).
‡ Patients with an unknown renal status were not included in the pooled analysis.

The mean age was higher in the RI group (58.4 vs. 49.1 years) while haematologic malignancy and neutropenia were less prevalent in the RI group (64.5% vs. 80.4% and 32.3% vs. 67.0%, respectively). The

majority of the non-RI had *Aspergillus* diagnosed by GM only (51.8%) vs. 22.6% of the RI patients but *Aspergillus fumigatus* was commonest in both groups (25.9% and 32.3%, respectively).

The numerically lower mortality in the RI patients at day 42 only may relate to the small number of patients in this group or differences in the baseline disease characteristics, see following table:

Table 45 All-cause Mortality through Day 42 and Day 84 by Renal Status (Pooled mITT Aspergillosis Patients)

Outcome	NRI Pooled IA (mITT) (n = 112)	RI Pooled IA (mITT) (n = 31)
All-Cause Mortality through Day 42†		
n (%)	21 (18.8%)	4 (12.9%)
All-Cause Mortality through Day 84‡		
n (%)	32 (28.6%)	8 (25.8%)

At EOT, the DRC-assessed overall response success rates were similar for RI and non-RI groups (36.0% and 32.3%, respectively). The clinical response success rates were also similar (60.4% and 58.1%, respectively) with mycological response success rates of 39.6% and 35.5% and radiological response success rates of 32.4% and 16.1%, respectively.

Other pathogens

There were 79 patients with other pathogens, including 73 with proven and 6 with probable IFD. The DRC assessed overall response at day 42, 84 and EOT are summarized in the following two tables:

Table 46 DRC-assessed Overall Response at Day 42 and Day 84 (All Other mITT Populations), study 9766-CL-0103

Timepoint Outcome Response	Other Filamentous Fungi (n = 17)	Mould Species NOS (n = 7)	Dimorphic Fungi (n = 29)	Non-*Candida* Yeast (n = 11)	Mixed Infections (n = 15)
At Day 42					
Success	8 (47.1%)	2 (28.6%)	12 (41.4%)	4 (36.4%)	2 (13.3%)
Complete	2 (11.8%)	2 (28.6%)	0	1 (9.1%)	0
Partial	6 (35.3%)	0	12 (41.4%)	3 (27.3%)	2 (13.3%)
Failure	9 (52.9%)	5 (71.4%)	17 (58.6%)	7 (63.6%)	13 (86.7%)
Stable	5 (29.4%)	2 (28.6%)	14 (48.3%)	4 (36.4%)	7 (46.7%)
Progression	0	2 (28.6%)	0	0	1 (6.7%)
Death	2 (11.8%)	0	2 (6.9%)	1 (9.1%)	2 (13.3%)
Missing	2 (11.8%)	1 (14.3%)	1 (3.4%)	2 (18.2%)	3 (20.0%)
At Day 84					
Success	7 (41.2%)	2 (28.6%)	13 (44.8%)	4 (36.4%)	2 (13.3%)
Complete	1 (5.9%)	1 (14.3%)	1 (3.4%)	1 (9.1%)	1 (6.7%)
Partial	6 (35.3%)	1 (14.3%)	12 (41.4%)	3 (27.3%)	1 (6.7%)
Failure	10 (58.8%)	5 (71.4%)	16 (55.2%)	7 (63.6%)	13 (86.7%)
Stable	5 (29.4%)	1 (14.3%)	12 (41.4%)	4 (36.4%)	6 (40.0%)
Progression	0	0	1 (3.4%)	0	0
Death	3 (17.6%)	1 (14.3%)	2 (6.9%)	1 (9.1%)	4 (26.7%)
Missing	2 (11.8%)	3 (42.9%)	1 (3.4%)	2 (18.2%)	3 (20.0%)

Table 47 DRC-assessed Overall Response at EOT (All Other mITT Populations), study 9766-CL-0103

Outcome Response	Other Filamentous Fungi (n = 17)	Mould Species NOS (n = 7)	Dimorphic Fungi (n = 29)	Non-*Candida* Yeast (n = 11)	Mixed Infection (n = 15)
Success	11 (64.7%)	2 (28.6%)	18 (64.3%)	8 (72.7%)	2 (14.3%)
Complete	7 (41.2%)	1 (14.3%)	5 (17.9%)	3 (27.3%)	0
Partial	4 (23.5%)	1 (14.3%)	13 (46.4%)	5 (45.5%)	2 (14.3%)
Failure	6 (35.3%)	5 (71.4%)	10 (35.7%)	3 (27.3%)	12 (85.7%)
Stable	3 (17.6%)	2 (28.6%)	5 (17.9%)	2 (18.2%)	5 (35.7%)
Progression	3 (17.6%)	3 (42.9%)	5 (17.9%)	1 (9.1%)	7 (50.0%)

Summary of main studies

The following tables summarise the major efficacy results from the two pivotal phase 3 studies (study 9766-CL-0104 and 9766-CL-0103, supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 48 Summary of efficacy for trial 9766-CL-0104 (Invasive Aspergillosis)

Title: A Phase III, Double-Blind, Randomized Study to Evaluate Safety and Efficacy of BAL8557 Versus Voriconazole for Primary Treatment of Invasive Fungal Disease Caused by Aspergillus Species or Other Filamentous Fungi. Clinical Study Report Phase 3 (SECURE Study)		
Study identifier	Study 9766-CL-0104 (WSA-CS-004)	
Design	randomized (1:1), multicenter, double-blind, noninferiority, comparative group study	
	Duration of main phase:	Total study: March 2007 to March 2013 Patients remained on therapy until they had reached a treatment endpoint or until they had received treatment for a maximum period of 84 days. Treatment was to continue for at least 7 days after resolution of all clinical symptoms and physical findings of infection. Mean duration of treatment for both treatment was 47 days.
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Non-inferiority	
Treatments groups	Isavuconazole i.v. + oral	Loading dose: 200 mg administered q8h i.v. for 2 days Maintenance dose: 200 mg once per day i.v. **or** oral number randomized: 258 (ITT)
	Voriconazole i.v. + oral	Loading dose: 6 mg/kg administered q12h i.v. for 1 day Maintenance dose: 4 mg/kg q12h i.v. **or** 200 mg q12h oral number randomized: 258 (ITT)
Endpoints and definitions	Primary endpoint	Crude rate of all cause mortality through day 42 (ITT)
	Key Secondary endpoint	DRC assessed overall response at EOT (mITT)
	Secondary endpoint	DRC assessed overall response at days 42 and 84 (mITT)

	Secondary endpoint	DRC assessed Clinical, mycological and radiological response at EOT, and days 42 and 84 (mITT, myITT)	
	Secondary endpoint	All cause mortality through day 84 (ITT)	
Database lock			
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT: 516; mITT: 272; myITT: 231; (PPS-ITT: 347; PPS-mITT: 204, results not shown below)		
Descriptive statistics and estimate variability	Treatment group	Isavuconazole	Voriconazole
	Number of subject (ITT)	258	258
	Primary endpoint: (All cause mortality through day 42, ITT)	48/258 (18.6%)	52/258 (20.2%)
	% treatment difference; (95% CI)	-1.0 (-7.759, 5.683)	
	Key secondary endpoint: (DRC assessed overall response at EOT) (mITT)	50/143 (35.0%)	47/129 (36.4%)
	% treatment difference; (95% CI)	1.6 (-9.336, 12.572)	
	Secondary endpoint: (DRC assessed overall response at Day 42, mITT)	51/143 (35.7%)	46/129 (35.7%)
	% treatment difference; (95% CI)	-0.5 (-11.277, 10.329)	
	Secondary endpoint: (DRC assessed overall response at Day 84) (mITT)	36/143 (25,2%)	42/129 (32,6%%)
	% treatment difference; (95% CI)	8.2 (-1.993, 18.379)	
	Secondary endpoint: (DRC assessed overall response at EOT, myITT)	43/123 (35.0%)	42/108 (38.9%)
	% treatment difference; (95% CI)	4.0 (-7.973, 15.875)	
	Secondary endpoint: (All-cause mortality through day 42, mITT)	28/143 (19.6)	30/129 (23.3%)
	% treatment difference; (95% CI)	-2.6 (-12.184, 6.916)	
	Secondary endpoint: (All-cause mortality through day 84, mITT)	43/143 (30.1%)	48/129 (37.2%)
	% treatment difference; (95% CI)	-5.5 (-16.059, 5.148)	

Table 49 Summary of efficacy for trial 9766-CL-0103 (Mucormycosis)

Title: Open-Label Study of Isavuconazole in the Treatment of Patients with Aspergillosis and Renal Impairment or of Patients with Invasive Fungal Disease Caused by Rare Moulds, Yeasts or Dimorphic Fungi.		
Study identifier	Study report 9766-CL-01013/WSA-CS-003.	
Design	This was a phase 3, descriptive, open-label, multicenter study.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Total study: April 2008 to January 2014 Patients were treated up to a maximum of 84 days. All patients enrolled under Amendments 3 and 5 and were eligible to receive treatment for a maximum of 180 days. not applicable Country-specific Amendment 4 allowed patients who were deriving clinical benefit to continue on treatment beyond 180 days.
Hypothesis	Exploratory/descriptive	
Treatments groups	Isavuconazole i.v. + oral	Loading dose: 200 mg administered q8h i.v. **or** oral for 2 days. Maintenance dose: 200 mg once per day i.v. or oral. number enrolled: 146 (ITT)
Endpoints and definitions	Primary endpoint	The primary objective of the study was to describe the efficacy of isavuconazole in the treatment of: invasive aspergillosis in patients with renal impairment AND In patients with IFD caused by rare moulds, yeasts or dimorphic fungi.
	Secondary endpoint	The secondary objective of the study was to characterize the safety and tolerability while assessing additional efficacy of treatment with isavuconazole.
	Exploratory endpoint	To summarize the concentration-time profiles of study drug and metabolite(s) if warranted in patients from the pharmacokinetic substudy.
	Exploratory endpoint	To characterize pharmacokinetic trough values of study drug and metabolite(s) if warranted.
Database lock		
Results and Analysis		
Analysis description	**Primary Analysis**	
Analysis population and time point description	ITT (n=146) mITT-*Aspergillus* Population (n=24): RI (n-=20) + NRI (n=4)* mITT-Mucorales Population (n=37): Primary (n=21) + Refractory (n=11) + Intolerant (n=5	
Descriptive statistics	Treatment group: Isavuconazole	

Endpoints: ITT	All-cause Mortality through Day 42 and Day 84
Endpoints: mITT-*Aspergillus* Population	All-cause Mortality through Day 42 and Day 84 DRC Assessed Overall Response at EOT by renal status DRC Assessed Overall Response at Day 42 and Day 84 DRC Assessed Clinical/Mycological/Radiological Response at EOT, Day 42 and Day 84
Endpoints: mITT-Mucorales Population	All-cause Mortality through Day 42 and Day 84 DRC Assessed Overall Response at EOT DRC Assessed Overall Response at Day 42 and Day 84 DRC Assessed Clinical/Mycological/Radiological Response at EOT, Day 42 and Day 84

Only results of the subgroup analyses considered most important are summarized below:

mITT-*Aspergillus* Population (n=24), Endpoints:	**Total**	**RI‡**	**NRI**
All-cause Mortality through Day 42	12.5 (3/24)	15.0 (3/20)	0 (0/4)
All-cause Mortality through Day 84	25 (6/24)	25.0 (5/20)	25.0 (1/4)
DRC Assessed Overall Response at EOT	34.8 (8/23)	30.0 (6/20)	66.7 (2/3)

mITT-Mucorales Population (n=37), Endpoints:	**Total**	**Primary**	**Refractory**	**Intolerant**
All-cause Mortality through Day 42	37.8 (14/37)	33.3 (7/21)	45.5 (5/11)	40.0 (2/5)
All-cause Mortality through Day 84	43.2 (16/37)	42.9 (9/21)	45.5 (5/11)	40.0 (2/5)
DRC Assessed Overall Response at EOT	31.4 (11/35)	31.6 (6/19)	36.4 (4/11)	20.0 (1/5)

* RI = Renally Impaired; NRI = Non Renally Impaired

Analysis performed across trials (pooled analyses and meta-analysis)

Clinical studies in special populations

Paediatric population

No children were included in the phase 1, phase 2 or phase 3 studies and no children were treated with isavuconazole. Only male and female patients aged ≥ 18 years, at time of signing the informed consent form were included in the clinical trials.

Of note, in accordance with Article 7 of Regulation (EC) No. 1901/2006 as amended ('paediatric' regulation) isavuconazonium (sulfate) has an agreed Paediatric Investigation Plan (procedure number EMEA-001301-PIP-12) for the conditions "Treatment of invasive aspergillosis" and "Treatment of mucormycosis" in children from birth to less than 18 years of age with a deferral in place. [EMA Decision No., P/0135/2013, dated 14 June 2013].

Older subjects

No specific efficacy study was performed in older people.

An overview of the age distribution of patients across the various age categories is listed in the following table:

Table 50 Study 9766-CL-0104: Age distribution in the Safety, mITT and myITT populations

Age category (years)	Safety population*			mITT population			myITT population		
	ISA N=257	VRC N=259	Total N=516	ISA N=143	VRC N=129	Total N=272	ISA N=123	VRC N=108	Total N=231
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≤ 45	94 (36.4)	101 (39.1)	195 (37.8)	54 (37.8)	44 (34.1)	98 (36.0)	45 (36.6)	36 (33.3)	81 (35.1)
> 45 to ≤ 65	108 (41.9)	99 (38.4)	207 (40.1)	55 (38.5)	63 (48.8)	118 (43.4)	52 (42.3)	54 (50.0)	106 (45.9)
> 65	56 (21.7)	58 (22.5)	114 (22.1)	34 (23.8)	22 (17.1)	56 (20.6)	26 (21.1)	18 (16.7)	44 (19.0)
≤ 65	202 (78.3)	200 (77.5)	402 (77.9)	109 (76.2)	107 (82.9)	216 (79.4)	97 (78.9)	90 (83.3)	187 (81.0)
> 65 to ≤ 75	46 (17.8)	51 (19.8)	97 (18.8)	29 (20.3)	21 (16.3)	50 (18.4)	23 (18.7)	17 (15.7)	40 (17.3)
> 75	10 (3.9)	7 (2.7)	17 (3.3)	5 (3.5)	1 (0.8)	6 (2.2)	3 (2.4)	1 (0.9)	4 (1.7)

* The voriconazole group in the Safety population (N=259) includes one patient more than in the ITT population (N=258).

The distribution was comparable for the safety, the mITT and myITT populations (for both treatment groups).

No dose adjustments are recommended in older subjects.

Renally impaired patients

Supportive evidence on the efficacy of isavuconazole in renally-impaired patients with invasive aspergillosis is provided by study 9766-CL-0103, which enrolled a subpopulation of patients with invasive aspergillosis and renal impairment. On the basis of the results of study 9766-CL-0103, no dose adjustments are recommended in renally impaired patients.

Hepatically impaired patients

For isavuconazole, statistical results indicate that after i.v. administration, total plasma Cl decreased by 30 and 51% in patients with mild and moderate hepatic impairment, respectively. Comparable results were observed for free plasma Cl (-34 and -63% respectively). After oral administration total plasma Cl/F decreased by 27 and 42% in patients with mild and moderate hepatic impairment, respectively. For free plasma Cl/F this was -28 and -61%, respectively. A limited number of subjects were included and a large variability is observed, which may result in patients to be under dosed, but also that patients may have larger exposures than the mean 2-fold increase. Considering the limited available data, and the fact that no severe AEs were identified, CHMP agreed that a dose adjustment was not necessary, but considered necessary to include an adequate warning in the SmPC.

Supportive studies

The phase 2 study 9766-CL-0101 was conducted in "uncomplicated esophageal candidiasis" and study 9766-CL-0102 was conducted in "prophylaxis of patients undergoing chemotherapy for AML". CHMP agreed that

while these studies could not be considered of relevance for the claimed indications, they could be considered as supportive for safety only. The key design features of both phase 2 studies are summarized in the tabular overview of the performed clinical studies.

Pivotal studies no 9766-CL-0103 and 0104: the use of in-line filters
In the phase 3 studies in-line filters were to be used but some sites used the wrong pore size and some patients received unfiltered drug. The final advice regarding use of in-line filters requires further discussion in terms of the potential clinical effects of their use vs. their omission. The applicant was asked to clarify. From the applicant's response the following is concluded:

Efficacy

On the basis of the available data no conclusions with regard to any consequences for the clinical efficacy of Cresemba can be drawn.

Safety

From the two analyses performed, for both studies separately, no occurrence of an embolic or thrombotic-type AE was observed. However, no definitive conclusions with regard to safety of Cresemba iv can be drawn on the basis of the available information.

According to the applicant, the review of the safety data from patients (n=27) administered intravenous isavuconazole without an in-line filter and from an additional 21 patients administered the drug with an incorrect filter, did not suggest a causal relationship between the absence of an in-line filter and pulmonary events or systemic infusion reactions.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies
Isavuconazonium sulfate is an antifungal agent and the prodrug of the active moiety isavuconazole. Isavuconazole, a triazole, demonstrates a fungicidal effect by blocking the synthesis of ergosterol, a key component of the fungal cell membrane.

CRESEMBA is indicated in adults for the treatment of

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

Invasive aspergillosis and mucormycosis are both very rare life threatening fungal infections that are seen predominantly in immunocompromised patients. There are only a few treatment options available. There is an urgent medical need for new effective antifungal drugs.

No formal dose-finding studies were conducted. Despite different *in vitro* and *in vivo* models to simulate the relation between MIC and AUC, no conclusions could be drawn with regard to the adequate dose–effect relation. All the evidence was therefore to be derived from the two pivotal phase 3 trials, study 9766-CL-0104 in invasive aspergillosis and study 9766-CL-0103 in mucormycosis.

Treatment of Invasive Aspergillosis

This indication rests on a single pivotal study (9766-CL-0104) against an appropriate comparator (voriconazole) used at the approved dose regimen and with an allowance for up to 12 weeks treatment. The study was not confined to infections due to *Aspergillus* and it allowed recruitment of patients with possible IFD but only those with proven or probably IFD were included in the mITT population and only mITT patients with aspergillosis were included in the mITT population. Therefore these, and particularly the latter, are the critical analysis populations. Those with chronic infections or aspergillomas were excluded, which effectively resulted in the majority of patients having some degree of immunosuppression at baseline. These basic design features of the study were generally appropriate.

The EORTC/MSG criteria were used for patient categorisation and a DMC was used to determine the IFD diagnosis at baseline as well as the patient and mycological responses to treatment. The use of galactomannan as a marker of infection was in accordance with EORTC/MSG recommendations of 2008 and the testing was repeated at central laboratories using a single commercial assay.

About half of all patients had IFD (mITT) and just under half had aspergillosis (myITT); clearly not all of these patients completed treatment. In addition, the majority of patients had only GM evidence of a pathogen and only about one third of the MITT population had other evidence of aspergillosis although in most of these it was found alone.

In the mITT population the outcomes at EOT by CLSI MICs were presented for 41 isavuconazole and 24 voriconazole cases involving *Aspergillus spp.* Numbers for outcomes presented by EUCAST MICs are 47 and 25 in respective groups. Such small numbers cannot support what is anyway a crude analysis of outcomes by MIC. The paucity of isolates with MIC documented, along with the inadequate PK sampling in this study, also means that good quality analyses of exposure-response that take into account individual patient AUC/MIC ratios (i.e. POPPK-predicted AUC from individual sparse PK data and the MIC documented for that patient's pathogen) are impossible. Due to the combined lack of appropriate PK/PD analyses and the paucity of clinical and mycological data for those who actually had a pathogen isolated it is difficult to conclude on the highest MIC of isavuconazole that may be treatable with the recommended dose regimen. EUCAST recommended clinical breakpoints for *Aspergillus fumigatus*, *Aspergillus nidulans* and *Aspergillus terreus*. There are currently insufficient data to set clinical breakpoints for other *Aspergillus* species. CHMP endorsed the EUCAST recommendations.

The baseline demographic and underlying disease distributions for the mITT and myITT populations showed some features that occurred more and some less often in the isavuconazole group.

Day 42 mortality rates were consistently similar between treatments. In the myITT population, which is the primary population of interest to support the indication claimed (123 isavuconazole and 108 voriconazole cases) the observed mortality rates were numerically lower for isavuconazole. These numerical differences between treatments persisted for mortality rates at day 84.

The DRC-assigned overall success rates at EOT were generally comparable or slightly numerically lower for isavuconazole. The DRC-assigned success rates at days 42 in the mITT and myITT populations were broadly comparable between treatments. Nevertheless, in the myITT patients with aspergillosis that was not diagnosed based solely on GM the responses were 19/52 (36.5%) vs. 14/40 (35%). For analyses in these and other relatively small subsets, which are very small if focussing only on the myITT population, it is difficult to interpret the imbalances observed in both directions according to various other factors.

Asian patients had a numerically lower success rate in the isavuconazole group (25.9%, 7/27) than in the voriconazole treatment group (48.6%, 17/35). The observed differences in response rates between Asian and non-Asian patients cannot be explained by drug exposure. From six Asian patients with MIC values available all were below 2 µg/mL, so it is considered not likely that resistance to isavuconazole does explain the results in overall response at EOT. The differences in favour of voriconazole were not consistent across the Asian countries; they were apparent in Thailand and South Korea, but not in China and India. Therefore no definitive conclusions could be drawn. CHMP agreed that a potential ethnicity effect could not be excluded at present and has agreed to the inclusion of this as missing information in the RMP.

During the procedure, some other concerns were raised by CHMP, one of which related to the relatively high number of protocol violations that were reported in the ITT-population, in particular the number of patients who discontinued treatment primarily due to Insufficient Therapeutic Response that was considerably higher in the isavuconazole treatment group than in the voriconazole treatment group. It was initially not clear whether this imbalance in discontinuation rates would be of the same magnitude in mITT and myITT populations, which are considered more conclusive in this respect. It was clarified that despite the rather high treatment discontinuation rates in mITT and myITT, no imbalance between the two treatment groups (isavuconazole and voriconazole) was noticed. CHMP agreed that there was enough support of the validity of the comparison between treatments in the mITT and myITT populations. These concerns were therefore considered resolved.

Treatment of Mucormycoses

The invasive fungal disease caused by fungi classified as the order of Mucorales (e.g. *Rhizopus*, *Mucor*, *Rhizomucor*) is characterized by high mortality and requires antifungal treatment, debridement and correction of underlying predisposing conditions (e.g. cessation of corticosteroids, correction of neutropenia and metabolic disorders). Proof for the recommended antifungals (amphotericin (primary treatment) and posaconazole (salvage therapy) or combinations) is derived from *in vitro* data and mostly from small retrospective cases series with 20-40 cases. Extrapolation of results from one study to others is hampered by different predisposing conditions, different sites of infection and combined efforts to diminish fungal load and improve the immune system of the host.

The uncontrolled study (study 9766-CL-0103) had several aims and recruited a very mixed population, including some that could be dosed orally from the outset and were managed as outpatients as well as patients with a range of different infection sites. The sub-population of interest is the DRC-classified mITT-Mucorales, which included 32 proven and 5 probable infections of which 21/37 were treated for the first time in this study.

The applicant has put the results of uncontrolled study 9766-CL-0103 into context. The applicant's response was based on external control data of "standard-care drug" liposomal amphotericine-B, which was considered acceptable since the use of (Liposomal) amphotericine-B in mucormycosis is without doubt is the best documented. It is the only antifungal drug that is registered for first line treament of mucormycosis (EU and USA). Based on the presented Fungiscope matched-control analysis, the mortality rate with the use of isavuconazole appears to be comparable to that reported in literature for standard care Liposomal amphotericin B in the treatment of mucormycosis.

In order to put the overall response rates observed in study 9766-CL-0103 in the context of external control data, the applicant also submitted data on five clinical amphotericin-B-based studies, out of which three studies were considered by CHMP as a narrow but acceptable basis for the discussion on the overall response rates observed in study 9766-CL-0103 and to put these in external context of AmB in the treatment of this

very rare disease. The overall success rates (32% to 42%) reported in the three studies were similar as those reported overall success rate of 32% for patients with primary therapy in study 9766-CL-0103. Although sparse, from data available, it appears that the overall response rates in study 9766-CL-0103 were consistent with that observed in external control studies performed with amphotericin-B, the only approved antifugal drug in the treatment of mucormycosis.

To further address the above mentioned issues, the applicant decided during the procedure to change the indication applied for to the treatment of adult "patients with mucormycosis for whom amB is inappropriate". Although the absolute number of patients with a refractory status was low in study 9766-CL-0103, most (10 out of 11) had received prior amB based treatments, and 3 of the 5 patients with an intolerant therapy status had received prior amB (these patients were discontinued from amB due to severe renal side effects). These 13 patients were considered relevant for the above proposed indication. Of the amB-refractory patients 60% had a complete, partial, or stable response, and 2 of the 3 patients intolerant to amB-based therapies who survived more than 3 months also had a stable response.

The reported adverse event related overall discontinuation rate in the Ambizygo study (Lanternier 2012) was about 20% (L amB 3mg/kg/day) and 32% in the AmbiLoad study in aspergillosis with a higher regimen of 10 mg L-amB /kg/day (Cornely 2007). AmB-based therapies are known for the risk of development of (severe) renal side-effects. Isavuconazole was well tolerated in patients (10 out of 37) enrolled in study 9766-CL-0103 who had a baseline creatinine-clearance of < 60 mL/min. Isavuconazole (available as IV and oral dosage forms) offers an added treatment option for renally impaired patients with invasive aspergillosis and mucormycosis.

The four reported cases on isavuconazole as compassionate use further supported the above proposed indication "Patients with mucormycosis for whom amphotericin B is inappropriate". These patients were all pre-treated with amB-based regimens, in most cases posaconazole was added to the regime. In two of the patients CNS was also involved, which has a poor prognosis. Two patients were intolerant to L-amb and developed renal impairment. The patients appeared to benefit from treatment with isavuconazole. Moreover, isavuconazole was well tolerated, enabling long term treatment.

2.5.4. Conclusions on the clinical efficacy

From a clinical perspective the indication "treatment of invasive aspergillosis" is approvable.

The efficacy data submitted in support of mucormycosis give support to the indication "mucormycosis in patients for whom amphotericin B is inappropriate", with the limitations of clinical data described in section 4.4 and 5.1.

2.6. Clinical safety

Adverse Effects Characteristic of the Pharmacological Class

Isavuconazole is a member of the azole class of antifungal agents. Elevated liver transaminases, infusion-related reactions and severe cutaneous adverse reactions (SCAR) are considered important risks for the azole class effects. Additional class effects include anaphylaxis, QT prolongation/torsades de pointes, visual disturbances, psychiatric events and acute pancreatitis events that have been reported with other marketed azole antifungal agents (i.e., voriconazole, posaconazole, fluconazole and itraconazole).

Safety Population

Clinical programme

The integrated safety analyses were conducted in 3 populations: the phase 3 controlled population (Study 9766-CL-0104), the phase 2 and 3 population (isavuconazole treatment only) and the phase 1 population (integrated data from healthy subjects treated in 40 phase 1 studies).

The applicant's evaluation of safety was primarily based on the data from the active-controlled study versus voriconazole (Study 9766-CL-0104).

This approach is agreed, since the two phase 2 studies (9766-CL-0101 and 9766-CL-0102) were evaluating isavuconazole in different patient populations (9766-CL-0101 in patients with uncomplicated esophageal candidiasis [= less severe, non-invasive fungal disease] and 9766-CL-102 in neutropenic patients undergoing chemotherapy with isavuconazole used as profylactic treatment), and therefore considered not to be representative for the phase 3 population.

Furthermore, study 9766-CL-0103 was an open study in a very heterogeneous population consisting of different subpopulations. Moreover the Mucorales subpopulation was administered other concomitant antibiotic and antifungal medication (and surgery/debridement), potentially affecting the incidence of AE's in patients treated with isavuconazole. Phase 1 population is still of interest since it allows the evaluation of safety in a setting not confounded by underlying complex co-morbidities of these severe ill patients.

Patient exposure

A total of 1692 subjects received at least one dose of isavuconazole in clinical studies including 1145 subjects in the 40 phase 1 studies, 144 subjects in the phase 2 studies and 403 subjects in the phase 3 studies.

Table 51 Summary of Treated Subjects in the Isavuconazole Phase 3 Clinical Program

Category	**Isavuconazole**	**Controls**
Phase 3 studies	**403**	**259**
9766-CL-0103/WSA-CS-003	146	0
9766-CL-0104/WSA-CS-004‡	257	259††

‡ Phase 3 Controlled Population; ‡‡ received voriconazole

A total of 1049 healthy subjects received at least one dose of isavuconazole in a total of 40 completed phase 1 clinical studies, including single doses of up to 400 mg and multiple doses of up to 600 mg.

A total of 403 patients with invasive aspergillosis and other filamentous fungi, or rare molds, yeast and dimorphic fungi were enrolled in the 2 phase 3 studies and received at least one dose of isavuconazole 200 mg. Within these phase 3 studies, a total of 288 of 403 patients (71.5%) received isavuconazole for at least 21 days, 269 of 403 patients (66.7%) received isavuconazole for at least 28 days, 144 of 403 patients (35.7%) received isavuconazole for at least 84 days, and 52 of 403 patients (12.9%) received isavuconazole for at least 180 days.

Demographics and other characteristics of the study population

The demographics and underlying diseases of the patients evaluated in the phase 3 controlled population of study 9766-CL-0104 is considered to be representative of the target indication (invasive aspergillosis).

Adverse events

In the overall phase 2 and 3 population, 87.2% of patients treated with isavuconazole experienced a treatment-emergent adverse event (TEAE). Serious adverse events occurred in 42.0% of patients, TEAEs leading to discontinuation occurred in 11.9% of patients, and 19.9% of patients experienced a TEAE that led to death. The majority of events were not considered to be related to study drug.

The lower incidence of TEAEs and study drug-related TEAEs in the phase 2 studies compared with the phase 3 studies is most likely related to less severe disease (esophageal candidiasis) in the majority of patients in the phase 2 studies than in the phase 3 studies, see following table:

Table 52 Overview of Treatment Emergent Adverse Events and Deaths in the Phase 2 and 3 Population

	Phase 2 Isavuconazole (n = 144)	Phase 3 Isavuconazole (n = 403)	Total Isavuconazole (n = 547)
Adverse events	91 (63.2%)	386 (95.8%)	477 (87.2%)
Study drug-related adverse events	35 (24.3%)	169 (41.9%)	204 (37.3%)
Serious adverse events	7 (4.9%)	223 (55.3%)	230 (42.0%)
Study drug-related serious adverse events	2 (1.4%)	41 (10.2%)	43 (7.9%)
Adverse events leading to permanent discontinuation of study drug	9 (6.3%)	56 (13.9%)	65 (11.9%)
Study drug-related adverse events leading to permanent discontinuation of study drug	5 (3.5%)	28 (6.9%)	33 (6.0%)
Adverse events leading to death	3 (2.1%)	106 (26.3%)	109 (19.9%)
Study drug-related adverse events leading to death	1 (0.7%)	8 (2.0%)	9 (1.6%)
All deaths reported after the first dose of study drug†	3 (2.1%)	128 (31.8%)	131 (23.9%)

Study drug-related adverse events include those reported as remotely, possibly or probably related to study drug by the Investigator and those with a missing relationship. An AE with a missing seriousness is considered as serious.

† All reported deaths after first dose of study drug are summarized, regardless of the number of study days after the last dose of study drug.

In the overall phase 1 population, TEAEs occurred in 54.8% of subjects. Serious adverse events occurred in 4 subjects; 3 of these 4 subjects received multiple doses of isavuconazole. Of the 18 subjects who discontinued study drug due to an adverse event, 17 received multiple doses of isavuconazole. A total of 45.3% of subjects had TEAEs that were considered related to study drug; these TEAEs occurred more frequently in subjects who received multiple doses of isavuconazole, see following table:

Table 53 Overview of Treatment Emergent Adverse Events and Deaths in the Phase 1 Population

	Single Dose Isavuconazole (n = 279)	Multiple Dose Isavuconazole (n = 722)	Total Isavuconazole (n = 1001)
Adverse events	123 (44.1%)	426 (59.0%)	549 (54.8%)
Study drug-related adverse events	93 (33.3%)	360 (49.9%)	453 (45.3%)
Serious adverse events	1 (0.4%)	3 (0.4%)	4 (0.4%)
Study drug-related serious adverse events	0	3 (0.4%)	3 (0.3%)
Adverse events leading to permanent discontinuation of study drug	1 (0.4%)	17 (2.4%)	18 (1.8%)
Study drug-related adverse events leading to permanent discontinuation of study drug	1 (0.4%)	16 (2.2%)	17 (1.7%)
Deaths	0	0	0

Study drug-related adverse events include those reported as remotely, possibly or probably related to study drug by the investigator and those with a missing relationship. An AE with a missing seriousness is considered as serious.

All reported deaths after first dose of study drug are summarized, regardless of the number of study days after the last dose of study drug.

Adverse events compared to voriconazole (phase 3 controlled population: Study 9766 CL 0104)

Compared to voriconazole, a statistically significant lower incidence of study drug-related TEAEs (42.4% vs 59.8%, p<0.05) and TEAEs leading to permanent discontinuation of study drug (14.4% vs 22.8%, p<0.05) was observed in the isavuconazole group.

Study drug-related TEAEs leading to permanent discontinuation of study drug also occurred at a lower incidence in the isavuconazole group (8.2%) compared with the voriconazole group (13.5%); the difference was not statistically significant. The proportion of patients with TEAEs in the remaining categories was similar between treatment groups, see following table:

Table 54 Overview of Treatment Emergent Adverse Events and Deaths in the Phase 3 Controlled Population (study 9766-CL-0104)

	Isavuconazole (n = 257)	Voriconazole (n = 259)
Adverse events	247 (96.1%)	255 (98.5%)
Study drug-related adverse events	109 (42.4%)*	155 (59.8%)
Serious adverse events	134 (52.1%)	149 (57.5%)
Study drug-related serious adverse events	28 (10.9%)	29 (11.2%)
Adverse events leading to permanent discontinuation of study drug	37 (14.4%)*	59 (22.8%)
Study drug-related adverse events leading to permanent discontinuation of study drug	21 (8.2%)	35 (13.5%)
Adverse events leading to death	62 (24.1%)	72 (27.8%)
Study drug-related adverse events leading to death	7 (2.7%)	6 (2.3%)
Deaths through 28 days after the last dose of study drug	62 (24.1%)	70 (27.0%)
All deaths reported after the first dose of study drug†	81 (31.5%)	87 (33.6%)

*Statistical significance at ≤ 0.05 (Fisher's exact test). An AE with a missing seriousness is considered as serious.

† All reported deaths after first dose of study drug are summarized, regardless of the number of study days after the last dose of study drug.

Significant differences in TEAE's between the treatment groups observed for the following system organ classes (SOCs): skin disorders [isavuconazole: 86/257 (33.5%) vs voriconazole: 110/259 (42.5)%, P<0.05)], eye disorders [isavuconazole: 39/257 (15.2%) vs voriconazole: 69/259 (26.6%), P<0.05] and hepatobiliary disorders [isavuconazole: 23/257 8.9% vs voriconazole: 42/259 (16.2%), P<0.05) and numerically lower rates (by at least 5%) were reported for psychiatric and cardiac disorders.

These notable differences between treatments by SOC were primarily due to imbalances between treatments for the following individual PTs (isavuconazole vs. voriconazole rates):

- Hepatobiliary disorders SOC: hyperbilirubinaemia (5, 1.9% vs. 10, 3.9%), hepatic function abnormal (4, 1.6% vs. 9, 3.5%), jaundice (1, 0.4% vs. 6, 2.3%) and cholestasis (1, 0.4% vs. 6, 2.3%)
- Eye disorders SOC: visual impairment (4, 1.6% vs. 19, 7.3%), photophobia (2, 0.8% vs. 6, 2.3%), visual acuity reduced (1, 0.4% vs. 6, 2.3%) and retinal haemorrhage (0 vs. 5, 1.9%)
- Skin and subcutaneous tissue disorders SOC: rash (17, 6.6% vs. 28, 10.8%), erythema (9, 3.5% vs. 15, 5.8%), skin lesion (4, 1.6% vs. 8, 3.1%) and drug eruption (3, 1.2% vs. 11, 4.2%)
- Psychiatric disorders: hallucination (6, 2.3% vs. 11, 4.2%), visual hallucination (3, 1.2% vs. 11, 4.2%) and agitation (2, 0.8% vs. 7, 2.7%)
- Cardiac disorders SOC: tachycardia (12, 4.7% vs. 21, 8.1%) and cardiac arrest (1, 0.4% vs. 6, 2.3%)

The 5 most common TEAEs (occurring with an incidence ≥ 5%) in the isavuconazole or voriconazole treatment groups, respectively, were nausea (27.6% vs 30.1%), vomiting (24.9% vs 28.2%), diarrhoea (23.7% vs 23.2%), pyrexia (22.2% vs 30.1%), and hypokalemia (17.5% vs 21.6%).

The majority of patients had TEAEs that occurred within the first 7 days of treatment in both the isavuconazole (75.1%) and voriconazole (84.2%) treatment groups.

More than half of the patients had TEAEs of severe intensity and approximately one third had TEAEs of moderate intensity. Important differences were apparent between isavuconazole and voriconazole for moderate or severe TEAEs in 3 SOCs: hepatobiliary disorders (6.6% vs. 10.8%), skin disorders (11.3% vs. 15.8%) and cardiac disorders (8.6% vs. 14.3%).

Table 55 Treatment Emergent Adverse Events in ≥ 5% of Patients in Either Treatment Group in the Phase 3 Controlled Population (study 9766-CL-0104)

MedDRA v12.1 Preferred Term	Isavuconazole (n = 257)	Voriconazole (n = 259)
Overall	**247 (96.1%)**	**255 (98.5%)**
Nausea	71 (27.6%)	78 (30.1%)
Vomiting	64 (24.9%)	73 (28.2%)
Diarrhoea	61 (23.7%)	60 (23.2%)
Pyrexia	57 (22.2%)	78 (30.1%)
Hypokalaemia	45 (17.5%)	56 (21.6%)
Headache	41 (16.0%)	38 (14.7%)
Constipation	36 (14.0%)	54 (20.8%)
Dyspnoea	34 (13.2%)	29 (11.2%)
Cough	33 (12.8%)	35 (13.5%)
Febrile neutropenia	32 (12.5%)	38 (14.7%)
Chills	27 (10.5%)	23 (8.9%)
Fatigue	27 (10.5%)	18 (6.9%)
Oedema peripheral	26 (10.1%)	31 (12.0%)
Back pain	26 (10.1%)	19 (7.3%)
Abdominal pain	25 (9.7%)	36 (13.9%)
Hypertension	25 (9.7%)	31 (12.0%)
Insomnia	23 (8.9%)	24 (9.3%)
Mucosal inflammation	23 (8.9%)	14 (5.4%)
Decreased appetite	22 (8.6%)	28 (10.8%)
Epistaxis	21 (8.2%)	28 (10.8%)
Hypotension	21 (8.2%)	28 (10.8%)
Anxiety	20 (7.8%)	17 (6.6%)
Pruritus	19 (7.4%)	15 (5.8%)
Rash	17 (6.6%)	28 (10.8%)
Gamma-glutamyltransferase increased	16 (6.2%)	22 (8.5%)
Asthenia	16 (6.2%)	20 (7.7%)
Confusional state	16 (6.2%)	20 (7.7%)
Haemoptysis	16 (6.2%)	17 (6.6%)
Abdominal pain upper	15 (5.8%)	25 (9.7%)
Cytomegalovirus infection	15 (5.8%)	23 (8.9%)
Dyspepsia	15 (5.8%)	13 (5.0%)
Septic shock	15 (5.8%)	10 (3.9%)
Hypomagnesaemia	14 (5.4%)	27 (10.4%)
Respiratory failure	14 (5.4%)	17 (6.6%)
Oropharyngeal pain	14 (5.4%)	14 (5.4%)
Oedema	13 (5.1%)	18 (6.9%)
Alanine aminotransferase increased	13 (5.1%)	17 (6.6%)
Oral herpes	13 (5.1%)	14 (5.4%)
Anaemia	12 (4.7%)	23 (8.9%)
Tachycardia	12 (4.7%)	21 (8.1%)
Blood alkaline phosphatase increased	12 (4.7%)	15 (5.8%)
Thrombocytopenia	11 (4.3%)	25 (9.7%)
Pain in extremity	11 (4.3%)	15 (5.8%)
Aspartate aminotransferase increased	11 (4.3%)	14 (5.4%)
Dizziness	10 (3.9%)	15 (5.8%)
Hyperglycaemia	10 (3.9%)	13 (5.0%)
Erythema	9 (3.5%)	15 (5.8%)
Staphylococcal bacteraemia	7 (2.7%)	13 (5.0%)
Rales	5 (1.9%)	14 (5.4%)
Hypoglycaemia	5 (1.9%)	13 (5.0%)
Visual impairment	4 (1.6%)	19 (7.3%)
Bacteraemia	4 (1.6%)	14 (5.4%)

Sorting order: descending percentage in isavuconazole group for all adverse events.

In contrast, a higher proportion of isavuconazole-treated patients had drug-related TEAEs within the respiratory SOC (6.2% vs. 1.9%), reflecting the rates of dyspnoea. The applicant was requested to clarify this. There were also imbalances in respiratory SAEs. Since these findings stand out the applicant was asked

during the procedure to provide details of these cases, including any (S)AEs, related or otherwise, that occurred in these cases and whether they occurred concomitantly.

Based on the submitted data, CHMP concluded the following:

- The applicant has been requested to clarify the higher proportion of isavuconazole-treated patients that had drug-related TEAEs within the respiratory SOC. The applicant did not provide a rationale, but based on the case descriptions no direct relationship between the intake of isavuconazole and the incidence of serious TEAEs in respiratory SOC was observed.
- On the basis of the analysis of five serious TEAEs of dyspnoea in the isavuconazole group it could not be concluded that the administration of isavuconazole in itself might lead to dyspnoea.
- Based on the case descriptions of nine patients with serious TEAEs in respiratory SOC there appears no direct relationship between intake of isavuconazole and the incidence of the TEAEs. In eight out of the 9 described cases, underlying disease appears to have played an (important) role. The only exemption might be patient 5502-03. The serious TEAE of acute respiratory failure was considered "possibly related" (according the predefined definition) since there was a temporal relationship between administration of isavuconazole and onset of the event, and no clear alternative aetiologies could be identified.
- Dyspnoea occurred during IV infusion of isavuconazole, and may be an element of an infusion reaction syndrome. This is adequately warned for in the SmPC.

Drug-related TEAE's

Fewer isavuconazole-treated patients experienced study drug related TEAEs as determined by the investigators than voriconazole-treated patients (42.4% vs 59.8%, P<0.05) (see below table) and this overall lower rate with isavuconazole vs. voriconazole reflected the following SOCs: hepatobiliary disorders (1.9% vs. 10.0%), investigations (9.7% vs. 18.1%), eye disorders (3.1% vs. 10.8%) and psychiatric disorders (2.3% vs. 11.2%). These differences were primarily influenced by imbalances in rates for the following PTs:

- Hepatobiliary disorders SOC: hepatic function abnormal (2 (0.8%) vs. 9 (3.5%)), hyperbilirubinaemia (1 (0.4%) vs. 6 (2.3%)), cholestasis (0 vs. 3 (1.2%)), hepatic failure (0 vs. 3 (1.2%)) and jaundice (0 vs. 2 (0.8%))
- Investigations SOC: increased GGT (6 (2.3%) vs. 14 (5.4%)), ALP (5 (1.9%) vs. 11 (4.2%)), AST (5 (1.9%) vs. 11 (4.2%)) or ALT (4 (1.6%) vs. 11 (4.2%)) and QT prolonged (1 (0.4%) vs. 8 (3.1%))
- Eye disorders SOC: visual impairment (1 (0.4%) vs. 15 (5.8%)), visual acuity reduced (0 vs. 4 (1.5%))
- Psychiatric disorders SOC: hallucination (1 (0.4%) vs. 11 (4.2%)), visual hallucination (0 vs. 9 (3.5%))

Table 56 Study Drug Related Treatment Emergent Adverse Events by System Organ Class in the Phase 3 Controlled Population (study 9766-CL-0104)

System Organ Class	Isavuconazole (n = 257)	Voriconazole (n = 259)
Overall	**109 (42.4%)***	**155 (59.8%)**
Gastrointestinal Disorders	39 (15.2%)	39 (15.1%)
Investigations	25 (9.7%)*	47 (18.1%)
General Disorders and Administration Site Conditions	25 (9.7%)	21 (8.1%)
Nervous System Disorders	19 (7.4%)	18 (6.9%)
Respiratory, Thoracic and Mediastinal Disorders	16 (6.2%)*	5 (1.9%)
Skin and Subcutaneous Tissue Disorders	14 (5.4%)	20 (7.7%)
Metabolism and Nutrition Disorders	11 (4.3%)	11 (4.2%)
Cardiac Disorders	11 (4.3%)	10 (3.9%)
Vascular Disorders	9 (3.5%)	9 (3.5%)
Eye Disorders	8 (3.1%)*	28 (10.8%)
Infections and Infestations	7 (2.7%)	3 (1.2%)
Psychiatric Disorders	6 (2.3%)*	29 (11.2%)
Hepatobiliary Disorders	5 (1.9%)*	26 (10.0%)
Musculoskeletal and Connective Tissue Disorders	4 (1.6%)	2 (0.8%)
Blood and Lymphatic System Disorders	3 (1.2%)	8 (3.1%)
Renal and Urinary Disorders	3 (1.2%)	4 (1.5%)
Immune System Disorders	2 (0.8%)	2 (0.8%)
Injury, Poisoning and Procedural Complications	2 (0.8%)	1 (0.4%)
Congenital, Familial and Genetic Disorders	1 (0.4%)	1 (0.4%)
Ear and Labyrinth Disorders	1 (0.4%)	1 (0.4%)
Reproductive System and Breast Disorders	0	1 (0.4%)

*Statistical significance at ≤ 0.05 (Fisheri's exact test)
Sorting order: descending percentage in isavuconazole group by system organ class.

The common study drug related TEAEs that occurred in ≥ 2% of patients in either the isavuconazole or voriconazole treatment groups are shown in the following table. The proportion of patients was generally similar between treatment groups. Study drug related TEAEs that occurred in ≥ 5% of patients in either the isavuconazole or voriconazole treatment groups, respectively, were nausea (7.4% vs 8.1%), vomiting (5.1% vs 8.5%), increased GGT (2.3% vs 5.4%) and visual impairment (0.4% vs 5.8%).

Table 57 Study Drug Related Treatment Emergent Adverse Events in ≥ 2% of Patients in Either Treatment Group in the Phase 3 Controlled Population (study 9766-CL-0104)

MedDRA v12.1 Preferred Term	Isavuconazole (n = 257)	Voriconazole (n = 259)
Overall	**109 (42.4%)**	**155 (59.8%)**
Nausea	19 (7.4%)	21 (8.1%)
Vomiting	13 (5.1%)	22 (8.5%)
Dyspnoea	8 (3.1%)	2 (0.8%)
Hypokalaemia	7 (2.7%)	5 (1.9%)
Gamma-glutamyl transferase increased	6 (2.3%)	14 (5.4%)
Headache	6 (2.3%)	5 (1.9%)
Aspartate aminotransferase increased	5 (1.9%)	11 (4.2%)
Blood alkaline phosphatase increased	5 (1.9%)	11 (4.2%)
Rash	5 (1.9%)	7 (2.7%)
Alanine aminotransferase increased	4 (1.6%)	11 (4.2%)
Chills	4 (1.6%)	7 (2.7%)
Hepatic function abnormal	2 (0.8%)	9 (3.5%)
Electrocardiogram QT prolonged	1 (0.4%)	8 (3.1%)
Hallucination	1 (0.4%)	11 (4.2%)
Hyperbilirubinaemia	1 (0.4%)	6 (2.3%)
Visual impairment	1 (0.4%)	15 (5.8%)
Hallucination, visual	0	9 (3.5%)

Study drug-related adverse events include those reported as remotely, possibly or probably related to study drug by the investigator and those with a missing relationship.

Sorting order: descending percentage in isavuconazole group for all adverse events.

Phase 3 uncontrolled population (Study 9766-CL-0103)

The proportion of patients with study drug-related TEAEs in the phase 3 uncontrolled population of study 9766-CL-0103 are shown in the following table:

Table 58 Overview of Treatment Emergent Adverse Events and Deaths in the Phase 3 Uncontrolled Population (study 9766-CL-0103)

	RI (n = 59)	NRI (n = 87)	Total (n = 146)
TEAEs	59 (100.0%)	80 (92.0%)	139 (95.2%)
Study Drug-Related TEAEs	26 (44.1%)	34 (39.1%)	60 (41.1%)
Serious TEAEs	43 (72.9%)	46 (52.9%)	89 (61.0%)
Study Drug-Related Serious TEAEs	4 (6.8%)	9 (10.3%)	13 (8.9%)
TEAEs Leading to Permanent Discontinuation of Study Drug	11 (18.6%)	8 (9.2%)	19 (13.0%)
Study Drug-Related TEAEs Leading to Permanent Discontinuation of Study Drug	5 (8.5%)	2 (2.3%)	7 (4.8%)
TEAEs Leading to Death	21 (35.6%)	23 (26.4%)	44 (30.1%)
Study Drug-Related TEAEs Leading to Death	1 (1.7%)	0	1 (0.7%)
Deaths†	24 (40.7%)	23 (26.4%)	47 (32.2%)
Deaths Through 28 Days after the Last Dose of Study Drug	20 (33.9%)	22 (25.3%)	42 (28.8%)

Overall, more than half of the patients of Phase 3 controlled population of study 9766-CL-0104 had TEAEs of severe intensity and approximately one-third of patients had TEAEs of moderate intensity as determined by the investigators.

Table 59 Treatment-Emergent Adverse Events by Severity (9766-CL-0104)

System Organ Class Preferred Term	Maximum Severity	Isavuconazole (N=257)	Voriconazole (N=259)
Overall	Mild	37 (14.4%)	24 (9.3%)
	Moderate	73 (28.4%)	82 (31.7%)
	Severe	137 (53.3%)	149 (57.5%)
	Total	247 (96.1%)	255 (98.5%)

Moderate or severe TEAEs were reported in the respective isavuconazole and voriconazole treatment groups in the following SOCs: hepatobiliary disorders (6.6% and 10.8%), skin disorders (11.3% and 15.8%) and cardiac disorders (8.6% and 14.3%).

Treatment emergent adverse events were evaluated by study day of onset. The majority of patients had TEAEs that occurred within the first 7 days of treatment in both the isavuconazole (75.1%) and voriconazole (84.2%) treatment groups.

Renally impaired patients

Differences between RI and NRI patients exceeded 10% for the SOCs of blood and lymphatic system disorders, cardiac disorders, gastrointestinal disorders, metabolism and nutrition disorders, nervous system disorders, vascular disorders and renal and urinary disorders, see following table:

Table 60 Study Drug Related TEAEs by SOC for (2% of Patients Overall), (ITT Population), study 9766-CL-0103

MedDRA v12.1 SOC	RI (n = 59)	NRI (n = 87)	Total (n = 146)
Overall	26 (44.1%)	34 (39.1%)	60 (41.1%)
Gastrointestinal disorders	12 (20.3%)	11 (12.6%)	23 (15.8%)
Investigations	5 (8.5%)	8 (9.2%)	13 (8.9%)
General disorders and administration site conditions	7 (11.9%)	5 (5.7%)	12 (8.2%)
Nervous system disorders	2 (3.4%)	8 (9.2%)	10 (6.8%)
Infections and infestations	2 (3.4%)	6 (6.9%)	8 (5.5%)
Vascular disorders	3 (5.1%)	5 (5.7%)	8 (5.5%)
Skin and subcutaneous tissue disorders	3 (5.1%)	4 (4.6%)	7 (4.8%)
Psychiatric disorders	3 (5.1%)	3 (3.4%)	6 (4.1%)
Respiratory, thoracic and mediastinal disorders	1 (1.7%)	4 (4.6%)	5 (3.4%)
Hepatobiliary disorders	0	4 (4.6%)	4 (2.7%)
Metabolism and nutrition disorders	2 (3.4%)	2 (2.3%)	4 (2.7%)
Cardiac disorders	2 (3.4%)	1 (1.1%)	3 (2.1%)
Eye disorders	1 (1.7%)	2 (2.3%)	3 (2.1%)
Musculoskeletal and connective tissue disorders	1 (1.7%)	2 (2.3%)	3 (2.1%)

RI patients mostly had higher rates of TEAEs vs. NRI patients. The most common were vomiting (24.7%) and nausea (23.3%) with diarrhoea in 18.5%. Overall, 49.3% experienced TEAEs of severe intensity and 28.8% had TEAEs with a maximum intensity of moderate. The most common drug-related TEAEs were nausea (7.5%) and vomiting (6.2%).

AEs of special interest

Acute Pancreatitis

One patient in study 9766-CL-0103 had pancreatitis/pancreatitis relapsing but had a history of pancreatitis. On day 1 lipase was >ULN and the patient experienced several episodes of pancreatitis during the course of the study, which were considered to be unrelated by the investigator but possibly related by the sponsor.

Psychiatric Events

In study 9766-CL-0104 psychiatric events of interest were reported in a similar proportion of isavuconazole and voriconazole patients (28.4% vs. 30.5%). The most frequent were insomnia (8.9% vs. 9.3%), anxiety (7.8% vs. 6.6%) and confusional state (6.2% vs. 7.7%). Hallucinations were reported by 2.3% vs. 4.2% and visual hallucinations by 1.2% vs. 4.2% while agitation was reported in 2 (0.8%) vs. 7 (2.7%). In study 9766-CL-0103 37 (25.3%) had psychiatric AESIs of interest, including 8.9% with insomnia, 6.8% with confusional state and 3.4% with somnolence.

Potential Ocular Toxicity

In study 9766-CL-0104 8.2% isavuconazole and 16.6% voriconazole patients had ocular AESIs, reflecting the rates of visual impairment (1.6% vs. 7.3%), vision blurred (1.6% vs. 2.3%), visual acuity reduced (0.4% vs. 2.3%), eye pain (0.4% vs. 1.5%) and cataract (0.4% vs. 1.2%). In study 9766-CL-0103, 8 (5.5%) had an ocular AESI, including 2 with unilateral blindness.

Potential Anaphylaxis and Severe Cutaneous Adverse Reactions (SCAR)

In study 9766-CL-0104 these TEAEs occurred in 1.9% per treatment group but there were no cases in study 9766-CL-0103, see following table:

Table 61 TE Anaphylaxis/SCAR AESIs in the Phase 3 Controlled Population, study 9766-CL-0104

MedDRA v12.1 Preferred Term	Isavuconazole (n = 257)	Voriconazole (n = 259)
Overall	5 (1.9%)	5 (1.9%)
Anaphylactic reaction	0	2 (0.8%)
Anaphylactic shock	1 (0.4%)	0
Circulatory collapse	1 (0.4%)	0
Dermatitis exfoliative	1 (0.4%)	1 (0.4%)
Erythema multiforme	2 (0.8%)	0
Shock	0	1 (0.4%)
Toxic skin eruption	0	1 (0.4%)

Since it was however not clear whether or how many individual TEAEs potentially representing hypersensitivity occurred concurrently in the same patients, the applicant was requested to gather all possible TEAEs representing hypersensitivity reactions, including non-serious rashes, and provide a review of concurrent occurrences and numbers of patients involved by treatment in study 9766-CL-0104. There were no imbalances in the incidence of TEAEs representing a potential hypersensitivity between isavuconazole and voriconazole.

Injection Site Reactions

In study 9766-CL-0104 infusion/injection site reactions were reported in 11/257 (4.3%) in the isavuconazole and 4/259 (1.5%) in the voriconazole group. The rate was similar (5%) for isavuconazole in study 9766-CL-0103.

Potential Infusion-Related Reactions

In study 9766-CL-0104 there was no difference between isavuconazole (70/257, 27.2%) and voriconazole (76/259, 29.3%) for TEAEs commonly associated with infusion-related reactions that occurred within 48 h of an IV dose. However, the Applicant was asked to present the data on infusion reactions in the isavuconazole groups in terms of what is known about the correct use of recommended filters in patients who did and did not have such events. It is concluded that the incidence of infusion-site reactions in patients administered isavuconazole with and without a protocol-specified filter is comparable and no relevant differences were identified between the groups. Dyspnoea occurred during IV infusion of isavuconazole and may be an element of an infusion reaction syndrome. An adequate warning has been included in the SmPC.

Torsades de pointes

In study 9766-CL-0104 5.8% isavuconazole and 7.3% voriconazole patients had a TEAE in the torsade de pointes SMQ. Most frequent were syncope (2.7% vs. 0.8%), loss of consciousness (1.2% vs. 0), ECG prolonged QT (0.8% vs. 3.1%) and cardiac arrest (0.4% vs. 2.3%), see following table:

Table 62 TE Torsade de Pointes AESIs in the Phase 3 Controlled Population

MedDRA v12.1 Preferred Term	Isavuconazole (n = 257)	Voriconazole (n = 259)
Overall	**15 (5.8%)**	**19 (7.3%)**
Cardiac arrest	1 (0.4%)	6 (2.3%)
Cardio-respiratory arrest	2 (0.8%)	2 (0.8%)
Electrocardiogram QT prolonged	2 (0.8%)	8 (3.1%)
Loss of consciousness	3 (1.2%)	0
Sudden cardiac death	0	1 (0.4%)
Syncope	7 (2.7%)	2 (0.8%)
Ventricular tachycardia	0	2 (0.8%)

In study 9766-CL-0103 there were 3 cases (2 cardiac arrest and 1 syncope), but none had *torsades de pointes* on an ECG.

Syncope and loss of consciousness

In study 9766-CL-0104 higher numbers in the isavuconazole group with syncope and with loss of consciousness were observed, although it was acknowledged that these numbers were overall small and the imbalances may have occurred by chance. The applicant was asked to provide details of when these events occurred in relation to dosing and whether all 3 with LOC were among the 7 with syncope. From the applicant's response it became clear that the 3 patients with loss of consciousness and were not among the 7 patients with syncope. These events seem not to be directly related to dosing. The applicant's conclusion, that syncope and loss of consciousness does not constitute a safety signal that would need to be addressed further in the SmPC and/or the Risk Management Plan, is endorsed by CHMP.

Serious adverse event/deaths/other significant events
Overall TEAE Leading to Death (Study 9766-CL-0104)

Fatal SAEs occurred in 24.1% isavuconazole and 27.8% voriconazole patients and those TEAEs leading to death that occurred in ≥ 2% were septic shock (3.1% vs. 1.5%), sepsis (2.7% vs. 1.9%), respiratory failure (2.3% vs. 2.3%), acute myeloid leukaemia (1.2% vs. 2.7%) and multi-organ failure (0.4% vs. 2.3%), see following table:

Table 63 Treatment Emergent Adverse Events Leading to Death in the Phase 3 Controlled Population (Study 97-CL-0104)

MedDRA v12.1 System Organ Class Preferred Term	Isavuconazole (n = 257)	Voriconazole (n = 259)
Overall	**62 (24.1%)**	**72 (27.8%)**
Blood and lymphatic system disorders	**2 (0.8%)**	**1 (0.4%)**
Haemorrhagic disorder	1 (0.4%)	0
Pancytopenia	0	1 (0.4%)
Thrombocytopenia	1 (0.4%)	0
Cardiac disorders	**4 (1.6%)**	**5 (1.9%)**
Acute myocardial infarction	0	1 (0.4%)
Cardiac arrest	1 (0.4%)	3 (1.2%)
Cardio-respiratory arrest	1 (0.4%)	1 (0.4%)
Congestive cardiomyopathy	1 (0.4%)	0
Pericarditis	1 (0.4%)	0
Gastrointestinal disorders	**0**	**1 (0.4%)**
Rectal haemorrhage	0	1 (0.4%)
General disorders and administration site conditions	**2 (0.8%)**	**8 (3.1%)**
Death	1 (0.4%)	1 (0.4%)
Multi-organ failure	1 (0.4%)	6 (2.3%)
Sudden cardiac death	0	1 (0.4%)
Hepatobiliary disorders	**1 (0.4%)**	**0**
Hepatitis acute	1 (0.4%)	0
Immune system disorders	**1 (0.4%)**	**0**
Acute graft versus host disease	1 (0.4%)	0
Infections and infestations	**28 (10.9%)**	**18 (6.9%)**
Acinetobacter bacteraemia	1 (0.4%)	0
Aspergillosis	3 (1.2%)	2 (0.8%)
Bronchopulmonary aspergillosis	1 (0.4%)	0
Endocarditis	1 (0.4%)	0
Fungal infection	3 (1.2%)	2 (0.8%)
Fusarium infection	1 (0.4%)	0
Infection	1 (0.4%)	0
Klebsiella sepsis	0	1 (0.4%)
Mucormycosis	1 (0.4%)	0
Pneumonia	1 (0.4%)	2 (0.8%)
Pseudomonal bacteraemia	0	1 (0.4%)
Pseudomonal sepsis	0	1 (0.4%)
Sepsis	7 (2.7%)	5 (1.9%)
Septic shock	8 (3.1%)	4 (1.5%)
Stenotrophomonas sepsis	0	1 (0.4%)
Metabolism and nutrition disorders	**0**	**2 (0.8%)**
Hypoglycaemia	0	1 (0.4%)
Metabolic acidosis	0	1 (0.4%)
Neoplasms benign, malignant and unspecified	**10 (3.9%)**	**21 (8.1%)**
Acute lymphocytic leukaemia recurrent	0	1 (0.4%)
Acute myeloid leukaemia	3 (1.2%)	7 (2.7%)
Acute myeloid leukaemia recurrent	0	4 (1.5%)
B-cell lymphoma	0	1 (0.4%)
Blast cell crisis	1 (0.4%)	1 (0.4%)
Burkitt's leukaemia	0	1 (0.4%)
Chronic lymphocytic leukaemia	0	2 (0.8%)
Table continued on next page		

MedDRA v12.1 System Organ Class Preferred Term	Isavuconazole (n = 257)	Voriconazole (n = 259)
Chronic lymphocytic leukaemia recurrent	1 (0.4%)	0
Lymphoma	0	1 (0.4%)
Malignant neoplasm progression	1 (0.4%)	1 (0.4%)
Multiple myeloma	2 (0.8%)	0
Myelodysplastic syndrome	1 (0.4%)	0
Myeloid leukaemia	1 (0.4%)	1 (0.4%)
Neoplasm progression	0	1 (0.4%)
Nervous system disorders	**3 (1.2%)**	**7 (2.7%)**
Cerebral haemorrhage	0	1 (0.4%)
Encephalitis	0	1 (0.4%)
Haemorrhage intracranial	2 (0.8%)	3 (1.2%)
Neurotoxicity	1 (0.4%)	0
Stupor	0	1 (0.4%)
Subarachnoid haemorrhage	0	1 (0.4%)
Renal and urinary disorders	**1 (0.4%)**	**0**
Renal failure	1 (0.4%)	0
Respiratory, thoracic and mediastinal disorders	**14 (5.4%)**	**12 (4.6%)**
Acute respiratory distress syndrome	0	1 (0.4%)
Acute respiratory failure	3 (1.2%)	1 (0.4%)
Haemoptysis	2 (0.8%)	1 (0.4%)
Pulmonary embolism	0	1 (0.4%)
Pulmonary haemorrhage	2 (0.8%)	1 (0.4%)
Pulmonary hypertension	0	1 (0.4%)
Respiratory distress	1 (0.4%)	0
Respiratory failure	6 (2.3%)	6 (2.3%)
Vascular disorders	**2 (0.8%)**	**1 (0.4%)**
Deep vein thrombosis	0	1 (0.4%)
Haemorrhage	1 (0.4%)	0
Hypovolaemic shock	1 (0.4%)	0

Sorting order: alphabetical by system organ class and preferred term

Seven isavuconazole patients and 6 voriconazole patients had fatal SAEs considered by the investigators to be drug-related. Those occurring in more than one patient were cardiac arrest (voriconazole: 2 patients) and fungal infection (isavuconazole: 2 patients), see following table:

Table 64 Study Drug-Related Treatment Emergent Adverse Events Leading to Death in the Phase 3 Controlled Population (9766-CL-0104)

MedDRA v12.1 System Organ Class Preferred Term	Isavuconazole (n = 257)	Voriconazole (n = 259)
Overall	**7 (2.7%)**	**6 (2.3%)**
Cardiac disorders	**1 (0.4%)**	**3 (1.2%)**
Cardiac arrest	0	2 (0.8%)
Cardio-respiratory arrest	0	1 (0.4%)
Congestive cardiomyopathy	1 (0.4%)	0
General disorders and administration site conditions	**0**	**1 (0.4%)**
Multi-organ failure	0	1 (0.4%)
Hepatobiliary disorders	**1 (0.4%)**	**0**
Hepatitis acute	1 (0.4%)	0
Infections and infestations	**3 (1.2%)**	**0**
Fungal infection	2 (0.8%)	0
Sepsis	1 (0.4%)	0
Nervous system disorders	**0**	**1 (0.4%)**
Subarachnoid haemorrhage	0	1 (0.4%)
Respiratory, thoracic and mediastinal disorders	**2 (0.8%)**	**1 (0.4%)**
Acute respiratory failure	1 (0.4%)	0
Respiratory distress	1 (0.4%)	0
Respiratory failure	0	1 (0.4%)

Although the overall proportion of TEAEs leading to death (isavuconazole 24.1%; voriconazole 27.8%) and of study drug related TEAE's leading to death (isavuconazole 2.7%; voriconazole 2.3%) was similar between treatment groups, there were differences in the SOCs "Infections and infestations" and "Neoplasms benign, malignant and unspecified".

More patients in the voriconazole treated group died due to the underlying (malignant) disease (isavuconazole: 10/257 (3.9%) vs voriconazole: 21/259 (8.1%), whereas more patients in the isavuconazole treated group died from infections and infestations (isavuconazole: 28/257 (10.9%) vs voriconazole: 18/259 (6.9%). Study drug-related TEAE leading to death encompassed 3 patients that died due to "(fungal) infections and infestations" and all were isavuconazole treated. This raises the posibility that isavuconazole patients might be "undertreated" and needed a increased dose of isavuconazole. However, the non-clinical data (single dose toxicity) suggests a steep dose response curve and increased dosages could possibly lead to a higher incidence of adverse events.

Study Drug Related Serious TEAEs (Study 9766-CL-0104)

Overall, a similar proportion of isavuconazole (28/257, 10.9%) and voriconazole (29/259, 11.2%) treated patients had study drug related serious TEAEs. Most of the study drug related serious TEAEs were single occurrences.

An important difference was observed between treatment groups for study drug-related serious TEAEs in the respiratory SOC (isavuconazole: 9/257, 3.5%; voriconazole: 2/259, 0.8%). The following study drug related serious TEAEs by preferred term were reported in the respiratory SOC: respiratory failure (isavuconazole 4 patients; voriconazole: 2 patients), dyspnea (isavuconazole 3 patients), acute respiratory failure (isavuconazole 2 patients), respiratory distress (isavuconazole 1 patient) and tachypnea (isavuconazole 1 patient).

Four subjects experienced serious adverse events in the phase 1 studies (0.4%, 4/1001), 1 subject received a single dose of isavuconazole and 3 subjects received multiple doses.

Phase 3 Uncontrolled population (study 9766-CL-0103)

There were 42 deaths (28.8%) through 28 days after the last dose of isavuconazole and 47 deaths in total (32.2%) with higher rates for RI vs. NRI subsets. Overall, 30.1% of patients experienced TEAEs leading to death (35.6% RI; 26.4% NRI). The most common TEAEs leading to death by PT that occurred in ≥ 2% were septic shock (3 RI and 0 NRI), malignant neoplasm progression (0 vs. 2) and pneumonia (0 vs. 2). One patient had a fatal SAE considered drug-related by the Investigator, which concerned possibly related severe septic shock 7 days after starting isavuconazole. The DRC assessed this patient as having no IFD.

The most common SAEs were infections and infestations (37.7%; 42.4% RI and 34.5% NRI). RI patients also had higher rates of cardiac SAEs (10.3% vs. 2.3%) and renal and urinary disorders (11.9% vs. 2.3%) (see following table). The most SAEs were renal failure acute (5.5%), pneumonia (4.8%), septic shock (4.1%), respiratory failure (3.4%) and abdominal pain. Overall, 8.9% had a drug-related SAE, of which few were experienced by more than one patient.

Table 65 Serious TEAEs by SOC (study 9766-CL-0103)

MedDRA v12.1 SOC	RI (n = 59)	NRI (n = 87)	Total (n = 146)
Overall	43 (72.9%)	46 (52.9%)	89 (61.0%)
Infections and infestations	25 (42.4%)	30 (34.5%)	55 (37.7%)
Respiratory, thoracic and mediastinal disorders	9 (15.3%)	11 (12.6%)	20 (13.7%)
Gastrointestinal disorders	8 (13.6%)	10 (11.5%)	18 (12.3%)
General disorders and administration site conditions	4 (6.8%)	5 (5.7%)	9 (6.2%)
Nervous system disorders	4 (6.8%)	5 (5.7%)	9 (6.2%)
Renal and urinary disorders	7 (11.9%)	2 (2.3%)	9 (6.2%)
Cardiac disorders	6 (10.2%)	2 (2.3%)	8 (5.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (3.4%)	6 (6.9%)	8 (5.5%)
Metabolism and nutrition disorders	3 (5.1%)	4 (4.6%)	7 (4.8%)
Blood and lymphatic system disorders	2 (3.4%)	3 (3.4%)	5 (3.4%)
Hepatobiliary disorders	3 (5.1%)	2 (2.3%)	5 (3.4%)
Immune system disorders	3 (5.1%)	2 (2.3%)	5 (3.4%)
Vascular disorders	4 (6.8%)	1 (1.1%)	5 (3.4%)
Musculoskeletal and connective tissue disorders	2 (3.4%)	2 (2.3%)	4 (2.7%)
Eye disorders	1 (1.7%)	1 (1.1%)	2 (1.4%)
Psychiatric disorders	2 (3.4%)	0	2 (1.4%)
Reproductive system and breast disorders	1 (1.7%)	0	1 (0.7%)

Laboratory findings

Chemistry

In study 9766-CL-0104 no clinically important mean changes from baseline to end of treatment were noted. The number (%) of patients with a shift from one category at baseline to another category for the highest or lowest post-baseline value was generally similar between treatment groups. Fewer isavuconazole patients had a decrease in calcium or an increase in AST, GGT or ALP, see following table:

In study 9766-CL-0103 the findings were similar to those described with isavuconazole above although there were some differences between the RI and NRI subgroups, as would be expected.

Table 66 Shifts in Chemistry Parameters from Baseline to Post-baseline (study 9766-CL-0104)

Parameter	Shift from baseline to post-baseline	Isavuconazole (n = 257)	Voriconazole (n = 259)
Sodium (µmol/L)	Increase	32/232 (13.8%)	39/234 (16.7%)
	Decrease	32/210 (15.2%)	21/209 (10.0%)
Potassium (µmol/L)	Increase	61/226 (27.0%)	65/232 (28.0%)
	Decrease	56/183 (30.6%)	53/176 (30.1%)
Chloride (µmol/L)	Increase	29/228 (12.7%)	30/226 (13.3%)
	Decrease	24/221 (10.9%)	23/224 (10.3%)
Calcium (µmol/L)	Increase	91/233 (39.1%)	94/236 (39.8%)
	Decrease	38/102 (37.3%)	48/95 (50.5%)
ALT (U/L)	Increase	64/174 (36.8%)	82/188 (43.6%)
	Decrease	12/239 (5.0%)	18/246 (7.3%)
AST (U/L)	Increase	79/202 (39.1%)	101/206 (49.0%)
	Decrease	16/219 (7.3%)	13/222 (5.9%)
Total Bilirubin	Increase	32/199 (16.1%)	37/208 (17.8%)
	Decrease	11/242 (4.5%)	12/243 (4.9%)
Direct Bilirubin (µmol/L)	Increase	32/172 (18.6%)	32/163 (19.6%)
	Decrease	13/230 (5.7%)	12/228 (5.3%)
GGT (U/L)	Increase	48/78 (61.5%)	66/93 (71.0%)
	Decrease	2/236 (0.8%)	0/243
Alkaline Phosphatase (U/L)	Increase	62/172 (36.0%)	79/167 (47.3%)
	Decrease	3/230 (1.3%)	2/231 (0.9%)
LDH (U/L)	Increase	70/161 (43.5%)	63/141 (44.7%)
	Decrease	7/219 (3.2%)	4/226 (1.8%)
Creatine kinase (U/L)	Increase	71/230 (30.9%)	76/232 (32.8%)
	Decrease	14/136 (10.3%)	11/146 (7.5%)
BUN (µmol/L)	Increase	64/216 (29.6%)	58/207 (28.0%)
	Decrease	3/234 (1.3%)	5/235 (2.1%)
Creatinine (µmol/L)	Increase	44/231 (19.0%)	43/228 (18.9%)
	Decrease	2/233 (0.9%)	3/238 (1.3%)
Amylase (U/L)	Increase	33/85 (38.8%)	31/90 (34.4%)
	Decrease	3/63 (4.8%)	5/65 (7.7%)
Triacylglycerol Lipase (U/L)	Increase	12/85 (14.1%)	13/94 (13.8%)
	Decrease	4/94 (4.3%)	1/101 (1.0%)
Albumin (g/L)	Increase	7/92 (7.6%)	4/99 (4.0%)
	Decrease	20/35 (57.1%)	15/28 (53.6%)
Urate (µmol/L)	Increase	106/233 (45.5%)	110/236 (46.6%)
	Decrease	6/97 (6.2%)	2/102 (2.0%)

In study 9766-CL-0104 fewer isavuconazole patients experienced increases in transaminases alone or concurrently with increases in total bilirubin. Also, fewer isavuconazole patients had increases > ULN at EOT. One isavuconazole vs. 7 voriconazole patients had ALT or AST > 3 x ULN and total bilirubin > 2 x ULN. No isavuconazole but 2 voriconazole patients had ALT or AST > 3 x ULN with ALP < 2 x ULN and total bilirubin > 2 x ULN at EOT.

For all post-baseline results 3 isavuconazole and 7 voriconazole patients had ALT or AST > 3 x ULN and ALP < 2 x ULN and total bilirubin > 2 x ULN, see following table:

Table 67 Potential Hepatotoxicity at any time post-baseline in study 9766-CL-0104

(ALT or AST) and Total Bilirubin†	(ALT or AST) > 3 x ULN and Total Bilirubin > 1.5 x ULN	12/251 (4.8%)	14/255 (5.5%)
	(ALT or AST) > 3 x ULN and Total Bilirubin > 2 x ULN	8/251 (3.2%)	10/255 (3.9%)
(ALT or AST) and ALP and Total Bilirubin†	(ALT or AST) > 3 x ULN and ALP < 2 x ULN and Total Bilirubin > 2 x ULN	3/251 (1.2%)	7/255 (2.7%)

Ten patients (3 isavuconazole) had concurrent increases in transaminases and total bilirubin post-baseline. There were 20 patients with AST or ALT > 10 x ULN of which 6/20 received isavuconazole as shown in the following table:

Table 68 AST or ALT > 10 X ULN post-baseline in study 9766-CL-0104

Patient/Treatment Duration (d)	Relationship Inv/ Sponsor	ALT (ULN) (U/L)	AST (ULN) (U/L)	Total bilirubin (ULN) (µmol/L)	Comment
Isavuconazole Treatment Group					
011820 / 62	NA / Possible	D1: 7 Post-BL: †	D1: 29 D57: 939 H(46)	D1: 8.6 D57: 20.5 H(17.1)	Concurrent potentially hepatotoxic agents. Resolved on isavuconazole.
070203 / 84	Unrelated / Unrelated	D1: 36 D75: 408 H(40)	D1: 19 D75: 213 H(40)	D1: 13.7 D75: 10.0	Chemotherapy started just before increase. Resolved on isavuconazole.
320452 / 35	NA / Unrelated	D1: 21 D36: 217 H(37)	D1: 25 D36: 472 H(36)	D1: 13.7 D36: 65.0 H(20.5)	Multi-organ failure secondary to IFD.
491005 / 84	NA / Unrelated	D1: 9 D2: 422 H(50)	D1: 5 L(10) D2: 804 H(50)	D1: 12.0 D2: 23.9 H(17.1)	Got another IMP as well as concurrent medications prior to day 2. Resolved on isavuconazole.
660604 / 2	NA / Unrelated	D1: 21 D2: 2002 H(40)	D1: 38 D2: 336 H(41)	D1: 15.4 D2: 37.3 H(20.5)	Concurrent fatal sepsis.
970912 / 4	Remote / Possible	D1: 29 D5: 349 H(39)	D1: 27 D5: 3294 H(40)	D1: 12.0 D5: NA	Acute hepatitis possibly secondary to fatal sepsis.

In study 9766-CL-0103 few patients had concomitant abnormalities as detailed in the following table. There were 8 patients with ALT > 5x but < 10xULN while 4 had AST >5xULN and 2 of these had > 10xULN.

Table 69 Potential Hepatotoxicity at Post-baseline

Analysis Visit Laboratory Test	Criteria	RI (n = 59)	NRI (n = 87)	Total (n = 146)
(ALT or AST) and T-Bili	(ALT or AST) > 3xULN and T-Bili > 1.5 x ULN	1/57 (1.8%)	2/85 (2.4%)	3/142 (2.1%)
	(ALT or AST) > 3x ULN and T-Bili > 2x ULN	1/57 (1.8%)	2/85 (2.4%)	3/142 (2.1%)
(ALT or AST) and ALP and T-Bili	(ALT or AST) > 3 x ULN and ALP < 2x ULN and T-Bili > 2x ULN	1/57 (1.8%)	1/85 (1.2%)	2/142 (1.4%)

In study 9766-CL-0104 similar proportions of isavuconazole and voriconazole patients had increases in serum creatinine at EOT and taking into account all post-baseline measurements, see following table:

Table Assessment of Potential Nephrotoxicity in study 9766-CL-0104

Analysis visit	Creatinine Increase Criteria	Isavuconazole (n =257)	Voriconazole (n =259)
End of Treatment	≥ 25%	77/242 (31.8%)	76/247 (30.8%)
	≥ 50%	42/242 (17.4%)	38/247 (15.4%)
	≥ 100%	8/242 (3.3%)	17/247 (6.9%)
Post-baseline	≥ 25%	118/242 (48.8%)	111/247 (44.9%)
	≥ 50%	69/242 (28.5%)	57/247 (23.1%)
	≥ 100%	23/242 (9.5%)	26/247 (10.5%)

In study 9766-CL-0103 the rates for each category of increase were similar to those for isavuconazole in study 9766-CL-0104 for each of EOT and all post-baseline data.

Haematology

In the CSRs for study 9766-CL-0104 and 9766-CL-0103 and in the summary of safety it was stated only that changes from baseline in mean haematology parameters did not reveal any remarkable trends in either treatment group and that the clinical relevance of observed changes is difficult to ascertain due to the common presence of underlying haematological malignancies and BMTs. However, the CSRs did contain full tabulations of the haematology data that were extremely lengthy and difficult to interpret. The applicant has provided new overview tables, as shown below:

Table 70 Study 9766-CL-0104: Mean change from baseline to EOT neutrophils, leukocytes, platelets and haemoglobin (safety population)

Laboratory parameter	Isavuconazole N=257			Voriconazole N=259		
	N	Mean change (SD)	Median change (min-max)	N	Mean change (SD)	Median change (min-max)
Neutrophils (10^9/L)	125	−0.22 (3.95)	−0.05 (−16 to 15)	126	0.17 (5.17)	0.10 (−17 to 29)
Leukocytes (10^9/L)	187	1.34 (9.71)	0.10 (−15 to 112)	190	1.32 (9.56)	0.55 (−86 to 42)
Platelets (10^9/L)	169	32.4 (105.1)	11.0 (−354 to 446)	170	50.1 (136.8)	14.5 (−430 to 939)
Haemoglobin (g/L)	191	8.3 (20.1)	6.0 (−47 to 82)	193	7.6 (17.9)	8.0 (−41 to 68)

Table 71 Study 9766-CL-0104: Categorical change from baseline to postbaseline for neutrophils, leukocytes, platelets and haemoglobin (safety population)

Laboratory parameter Category of change from baseline	Isavuconazole n/N (%)		Voriconazole n/N (%)		Total n/N (%)	
Neutrophils (10^9/L)						
Maximum increase from baseline						
≥0.5 to <1	6/128	(4.7)	8/129	(6.1)	14/257	(5.4)
≥1 to <2	15/128	(11.7)	21/129	(16.3)	36/257	(14.0)
≥2 to <3	10/128	(7.8)	14/129	(10.9)	24/257	(9.3)
≥3 to <5	20/128	(15.6)	23/129	(17.8)	43/257	(16.7)
≥5 to <10	17/128	(13.3)	9/129	(7.0)	26/257	(10.1)
≥10	5/128	(3.9)	10/129	(7.8)	15/257	(5.8)
Maximum decrease from baseline						
≥0.5 to <1	12/128	(9.4)	3/129	(2.3)	15/257	(5.8)
≥1 to <2	14/128	(10.9)	22/129	(17.1)	36/257	(14.0)
≥2 to <3	6/128	(4.7)	6/129	(4.7)	12/257	(4.7)
≥3 to <5	11/128	(8.6)	9/129	(7.0)	20/257	(7.8)
≥5 to <10	14/128	(10.9)	9/129	(7.0)	23/257	(8.9)
≥10	2/128	(1.6)	4/129	(3.1)	6/257	(2.3)
Leukocytes (10^9/L)						
Maximum increase from baseline						
≥0.5 to <1	10/190	(5.3)	7/193	(3.6)	17/383	(4.4)
≥1 to <2	12/190	(6.3)	20/193	(10.4)	32/383	(8.4)
≥2 to <3	12/190	(6.3)	18/193	(9.3)	30/383	(7.8)
≥3 to <5	29/190	(15.3)	37/193	(19.2)	66/383	(17.2)
≥5 to <10	40/190	(21.1)	28/193	(14.5)	68/383	(17.8)
≥10	19/190	(10.0)	30/193	(15.5)	49/383	(12.8)
Maximum decrease from baseline						
≥0.5 to <1	11/190	(5.8)	10/193	(5.2)	21/383	(5.5)
≥1 to <2	18/190	(9.5)	19/193	(9.8)	37/383	(9.7)
≥2 to <3	10/190	(5.3)	10/193	(5.2)	20/383	(5.2)
≥3 to <5	13/190	(6.8)	11/193	(5.7)	24/383	(6.3)
≥5 to <10	14/190	(7.4)	11/193	(5.7)	25/383	(6.5)
≥10	5/190	(2.6)	8/193	(4.1)	13/383	(3.4)
Platelets (10^9/L)						
Maximum increase from baseline						
≥25 to <50	20/172	(11.6)	23/173	(13.3)	43/345	(12.5)
≥50 to <100	30/172	(17.4)	22/173	(12.7)	52/345	(15.1)
≥100 to <200	30/172	(17.4)	33/173	(19.1)	63/345	(18.3)
≥200 to <300	11/172	(6.4)	17/173	(9.8)	28/345	(8.1)
≥300 to <500	9/172	(5.2)	9/173	(5.2)	18/345	(5.2)
≥500	2/172	(1.2)	10/173	(5.8)	12/345	(3.5)
Maximum decrease from baseline						
≥25 to <50	26/172	(15.1)	21/173	(12.1)	47/345	(13.6)
≥50 to <100	13/172	(7.6)	11/173	(6.4)	24/345	(7.0)
≥100 to <200	8/172	(4.7)	7/173	(4.0)	15/345	(4.3)
≥200 to <300	3/172	(1.7)	3/173	(1.7)	6/345	(1.7)
≥300 to <500	1/172	(0.6)	1/173	(0.6)	2/345	(0.6)
≥500	0/172		0/173		0/345	
Hemoglobin (g/L)						
Maximum increase from baseline						
≥10 to <20	49/194	(25.3)	48/196	(24.5)	97/390	(24.9)
≥20 to <30	29/194	(14.9)	40/196	(20.4)	69/390	(17.7)
≥30 to <40	25/194	(12.9)	20/196	(10.2)	45/390	(11.5)
≥40 to <50	13/194	(6.7)	15/196	(7.7)	28/390	(7.2)
≥50	10/194	(5.2)	8/196	(4.1)	18/390	(4.6)
Maximum decrease from baseline						
≥10 to <20	41/194	(21.1)	29/196	(14.8)	70/390	(17.9)
≥20 to <30	19/194	(9.8)	17/196	(8.7)	36/390	(9.2)
≥30 to <40	6/194	(3.1)	4/196	(2.0)	10/390	(2.6)
≥40 to <50	1/194	(0.9)	1/196	(0.5)	2/390	(0.5)
≥50	1/194	(0.9)	1/196	(0.5)	2/390	(0.5)

The results from these tables do not indicate any relevant differences between the two treatment groups.

ECGs

In study 9766-CL-0104 the mean changes from baseline for heart rate, PR, RR, QRS, QT and QTcB were small and similar between treatment groups. At EOT the mean change from baseline in QTcF was -6.7 ms in the isavuconazole group and 2.4 ms in the voriconazole group. The analysis of categorised QTcF values at EOT showed that fewer isavuconazole patients had QTcF values > 450 ms (7/250, 2.8% vs. 17/252, 6.7% for voriconazole) and more isavuconazole patients had values <360 ms (10.8% vs. 7.5%). No patients had QTcF > 500 ms and only 1 isavuconazole patients had a value <300 ms. Categorised changes from baseline in QTcF based on extreme values showed that fewer isavuconazole patients had increases from baseline in QTcF > 30 ms and > 60 ms at EOT or post-baseline.

Safety in special populations

Elderly people

The incidence of TEAEs for elderly people (stratified for age) is presented in the following table:

Table 72 Study 9766-CL-0104/9766-CL-0103: Overview of treatment-emergent adverse events in various adverse events categories (Safety population)

	Study 97766-CL-003 Isavuconazole N=146				Study 97766-CL-004 Isavuconazole N=257				Study 97766-CL-004 Voriconazole N=259			
Age (years)	< 65	65–74	75–84	≥ 85	< 65	65–74	75–84	≥ 85	< 65	65–74	75–84	≥ 85
Subgroup	N=116 n (%)	N=20 n (%)	N=9 n (%)	N=1 n (%)	N=194 n (%)	N=52 n (%)	N=11 n (%)	N=0 n (%)	N=197 n (%)	N=49 n (%)	N=12 n (%)	N=1 n (%)
Total	109 (94)	20 (100)	9 (100)	1 (100)	185 (95.4)	51 (98.1)	11 (100)	–	193 (98.0)	49 (100)	12 (100)	1 (100)
Fatal	27 (23.3)	12 (60.0)	5 (55.6)	–	45 (23.2)	13 (25.0)	4 (36.4)	–	53 (26.9)	13 (26.5)	5 (41.7)	1 (100)
Serious	66 (56.9)	15 (75.0)	7 (77.8)	1 (100)	95 (49.0)	31 (59.6)	7 (63.6)	–	111 (56.3)	28 (57.1)	7 (58.3)	1 (100)
Withdrawal	15 (12.9)	3 (15.0)	1 (11.1)	–	29 (14.9)	7 (13.5)	1 (9.1)	–	42 (21.3)	14 (28.6)	3 (25.0)	–
CNS (confusion/extrapyramidal)[1]	13 (11.2)	7 (35.0)	4 (44.4)	–	24 (12.4)	6 (11.5)	4 (36.4)	–	33 (16.8)	15 (30.6)	3 (25.0)	1 (100)
TEAE related to falling[2]	12 (10.3)	2 (10.0)	3 (33.3)	–	32 (16.5)	9 (17.3)	3 (27.3)	–	36 (18.3)	18 (36.7)	3 (25.0)	–
CV events[3]	2 (1.7)	–	–	–	1 (0.5)	2 (3.8)	–	–	5 (2.5)	2 (4.1)	–	–
CBV events[4]	–	2 (10.0)	1 (11.1)	–	3 (1.5)	2 (3.8)	–	–	4 (2.0)	2 (4.1)	–	–
Infections	64 (55.2)	14 (70.0)	5 (55.6)	–	111 (57.2)	34 (65.4)	9 (81.8)	–	125 (63.5)	25 (51.0)	9 (75.0)	–

[1] Extrapyramidal syndrome (SMQ broad), malaise, feeling abnormal, altered state of consciousness, stupor, daydreaming, confusional state, disorientation, hallucination, hallucination (visual).
[2] Vertigo, cataract, visual acuity reduced, altered visual depth perception, vision blurred, diplopia, visual impairment, gait disturbance, ataxia, fall, dizziness, syncope, presyncope.
[3] Coronary artery disease, cardiac failure, cardiac failure acute, cardiogenic shock, acute myocardial infarction, angina pectoris, sudden cardiac death.
[4] Cerebrovascular disorders (SMQ) broad.
CBV=cerebrovascular; CV=cardiovascular.

There appears to be no increased risk of developing specific age-related side effects.

General conclusions with regard to special populations

- In study 0104 the AE profile did not change substantially across age groups ≤65 vs. >65 years although the latter accounted for only one-fifth of the study population. For individual SOCs there was no consistent pattern by age and in some cases rates by age group went in the opposite direction for isavuconazole vs. voriconazole. On the basis of the available safety data no dose adjustment of isavuconazole is considered necessary in elderly patients (≥ 65 years of age). There were too few aged ≥75 years (10 isavuconazole and 7 voriconazole) for comment.
- For most SOCs there was no substantial difference between genders. There were a few SOCs in which rates were higher in women (e.g. hepatobiliary disorders in the isavuconazole group).
- In study 0104 the treatment differences observed for the overall analysis of TEAEs were consistent with those of the white and Asian subgroups.
- BMI category (< 25 [the majority], 26 - < 30 and ≥ 30 kg/m^2) did not have a major or at least no consistent impact on the safety profiles although few were ≥ 30 kg/m^2.
- For those with allogeneic HSCT/BMT status, uncontrolled malignancy or haematological malignancy the same overall pattern of treatment differences was observed although the rates varied by patient subset.
- In study 0104 the overall incidence of TEAEs was similar regardless of treatment duration and no difference was observed between treatment groups. The incidence TEAEs in the blood, gastrointestinal, immune, musculoskeletal, nervous system and skin disorders SOCs was higher in both treatment groups for patients who received > 42 to < 84 days. Numbers who received >84 days were small (24 isavuconazole and 20 voriconazole), which limits the comparisons made.
- Use of isavuconazole in pregnancy and lactation is to be avoided.
- Isavuconazole is not removed by hemodialysis. Treatment of isavuconazole overdose should be supportive.

Discontinuation due to adverse events

Phase 3 Controlled population (study 9766-CL-0104)

Fewer isavuconazole patients permanently discontinued study drug due to TEAEs. In particular, isavuconazole treated patients had fewer TEAEs causing discontinuation in the hepatobiliary and psychiatric disorders SOCs (see following table). Drug-related TEAEs leading to permanent discontinuation of study drug occurred in 21/257 (8.2%) in the isavuconazole vs 35/259 (13.5%) in the voriconazole group. The most common of these TEAEs were rash (0 vs. 3) and visual hallucination (0 vs. 3).

Table 73 TEAEs leading to discontinuation of study drug in study 9766-CL-0104

MedDRA v12.1 System Organ Class	Isavuconazole (n = 257)	Voriconazole (n = 259)
Overall	**37 (14.4%)**	**59 (22.8%)**
Infections and infestations	11 (4.3%)	15 (5.8%)
Respiratory, thoracic and mediastinal disorders	6 (2.3%)	5 (1.9%)
Nervous system disorders	5 (1.9%)	4 (1.5%)
Cardiac Disorders	4 (1.6%)	3 (1.2%)
Investigations	4 (1.6%)	6 (2.3%)
Renal and urinary disorders	3 (1.2%)	3 (1.2%)
Gastrointestinal disorders	2 (0.8%)	3 (1.2%)
Psychiatric Disorders	2 (0.8%)	6 (2.3%)
Skin and Subcutaneous Tissue Disorders	2 (0.8%)	5 (1.9%)
Blood and Lymphatic System Disorders	1 (0.4%)	3 (1.2%)
Eye Disorders	1 (0.4%)	1 (0.4%)
General disorders/administration site conditions	1 (0.4%)	1 (0.4%)
Hepatobiliary disorders	1 (0.4%)	6 (2.3%)
Musculoskeletal and connective tissue disorders	1 (0.4%)	0
Injury, Poisoning and Procedural Complications	1 (0.4%)	0
Vascular disorders	1 (0.4%)	0
Immune system disorders	0	1 (0.4%)
Metabolism and nutrition disorders	0	1 (0.4%)
Neoplasms benign, malignant and unspecified	0	7 (2.7%)

Phase 3 Uncontrolled population (study 9766-CL-0103)
Overall 13.0% of patients experienced at least one TEAE leading to permanent discontinuation of study drug (18.6% RI and 9.2% NRI) but no individual TEAE occurred in > 2 patients. Overall, 4.8% had a drug-related TEAE leading to permanent discontinuation of study drug but all individual TEAEs occurred in ≤ 2 patients, see following table:

Table 74 Study Drug Related TEAEs Leading to Permanent Discontinuation of Study Drug by SOC (study 9766-CL-0103)

MedDRA v12.1 SOC	RI (n = 59)	NRI (n = 87)	Total (n = 146)
Overall	5 (8.5%)	2 (2.3%)	7 (4.8%)
Infections and infestations	1 (1.7%)	1 (1.1%)	2 (1.4%)
Investigations	2 (3.4%)	0	2 (1.4%)
Gastrointestinal disorders	1 (1.7%)	0	1 (0.7%)
Hepatobiliary disorders	0	1 (1.1%)	1 (0.7%)
Psychiatric disorders	1 (1.7%)	0	1 (0.7%)
Renal and urinary disorders	1 (1.7%)	0	1 (0.7%)

2.6.1. Discussion on clinical safety

Overall, the observed safety profile of isavuconazole was in accordance with that expected for an azole antifungal medicinal product.

For the final dosing regimen used, the comparative safety data available from study 9766-CL-0104 indicated that the safety profile of isavuconazole compared favourably with that of voriconazole. In most SOCs isavuconazole had numerically lower rates of TEAEs, the differences observed for the SOCs eye disorders and hepatobiliary disorders being statistically significant. This difference was however difficult to interpret since the safety database of isavuconazole was rather limited and since the safety profile heavily relied on the results of the controlled study 9766-CL-0104.

There was no excess of deaths and fatal SAEs in the isavuconazole group and there were no apparent safety aspects for which isavuconazole was worse than voriconazole, except for the fact that a significant higher proportion of isavuconazole-treated patients than voriconazole-treated patients experienced study drug related TEAEs within the respiratory SOC (6.2% vs. 1.9%), reflecting the corresponding observed rates of dyspnoea (8, 3.1% vs. 2, 0.8%) and other imbalances in respiratory SAEs. Based on the case descriptions no direct relationship between the isavuconazole intake and the incidence of serious TEAEs in the respiratory SOC was apparent. In 8 out of the 9 described cases, underlying disease appeared to have played an (important) role. In one patient, the serious TEAE "acute respiratory failure" was considered as "possibly related", since there was a temporal relationship between the administration of isavuconazole and the onset of the event, and no clear alternative aetiologies could be identified. Nevertehless, it was not possible to conclude that the administration of isavuconazole in itself might lead to dyspnoea.

The incidence of infusion-site reactions in patients administered isavuconazole with and without a protocol-specified filter was comparable and no relevant differences were identified between the groups. Dyspnoea occurred during IV infusion of isavuconazole and may be an element of an infusion reaction syndrome. An adequate warning has been included in the SmPC.

No imbalance in the incidence of TEAEs representing potential hypersensitivities was observed between isavuconazole and voriconazole.

Loss of consciousness and syncope seem not to be directly related to dosing and these events do not constitute safety signals that would need to be addressed further in the SmPC and/or the Risk Management Plan.

No increased risk of developing specific age-related side effects was noted.

In the uncontrolled study 9766-CL-0103 the difference in AE rates between those with and without renal impairment is expected. Comparing rates between isavuconazole groups in the two pivotal studies was however considered not informative due to the differences in the study populations.

Isavuconazole was generally associated with fewer marked laboratory abnormalities than voriconazole but it is important to note that it does appear to share the toxicity profile of other triazoles, including DILI. Substantial proportions of healthy subjects showed increases in serum creatinine in phase 1 studies (258/1001 subjects had a ≥ 25% increase from baseline in serum creatinine and 15/1001 had a ≥ 50% increase) although in the phase 3 study 9766-CL-0104, rates for isavuconazole were comparable with those for voriconazole.

Overview tables on haematology also did not indicate any relevant differences between the two treatment groups.

2.6.1. Conclusions on the clinical safety

CHMP agreed that the safety profile of isavuconazole, as observed when using the posology recommended in the Cresemba SmPC is generally considered reassuring.

2.7. Risk Management Plan

The CHMP received the following PRAC opinion on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 5.0 is acceptable.

The CHMP endorsed this report without changes.

The CHMP endorsed the Risk Management Plan version 5.0 with the following content:

Summary of safety concerns

Important identified risks	Hepatic function abnormal or hepatitis Infusion-related reactions Severe cutaneous adverse reactions Arrhythmia due to QT shortening
Important potential risks	Teratogenicity Effect on children exposed to isavuconazole via breast milk Development of resistant strains Off-label use
Missing information	Use in patients < 18 years-old Use in patients with severe hepatic impairment Efficacy in invasive aspergillosis in Asian patients Clinical efficacy and safety of isavuconazole treatment in patients with *Mucorales* species

Table of planned additional pharmacovigilance studies / activities in the pharmacovigilance plan

Study (type and study number)	**Objectives**	**Efficacy uncertainties addressed**	**Status**	**Date for submission of interim or final reports**
Registry	To collect efficacy and safety data on the treatment of patients infected with Mucorales species	The clinical data for isavuconazole in the treatment of mucormycosis are based on one non-controlled clinical study in 37 patients. For individual *Mucorales* species, the clinical efficacy data are very limited, often to one or two patients. Susceptibility data were available in only a small subset of cases. The registry will collect further information, including patient history, underlying disease, speciation and MICs of pathogens causing mucormycosis, and outcome data.	Synopsis	Q2 2016 (Protocol submission)

Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hepatic function abnormal or hepatitis	SmPC Section 4.4 *Special warnings and precautions for use* includes: Elevated liver transaminases Elevated liver transaminases have been reported in clinical studies. The elevations in liver transaminases rarely required drug discontinuation. Consider monitoring hepatic enzymes, as clinically indicated. SmPC Section 4.8 *Undesirable effects* includes: Elevated liver chemistry tests are included as a common ADR for CRESEMBA. Laboratory effects In a double-blind, randomized, active-controlled clinical study of 516 patients with invasive fungal disease caused by *Aspergillus* species or other filamentous fungi, elevated liver transaminases (alanine aminotransferase or aspartate aminotransferase) > 3 × Upper Limit of Normal (ULN) were reported at the end of study treatment in 4.4% of patients who received CRESEMBA. Marked elevations of liver transaminases > 10 × ULN developed in 1.2% of patients on isavuconazole.	None
Infusion-related reactions	SmPC for isavuconazole 200 mg powder for concentrate for solution for infusion Section 6.6 *Special precautions for disposal and other handling (i.v. formulation*) includes: Dilution and administration After reconstitution, the entire content of the reconstituted concentrate should be removed from the vial and added to an infusion bag containing at least 250 mL of either sodium chloride 9 mg/ml (0.9%) solution for injection or 50 mg/ml (5%) dextrose solution. The infusion solution contains approximately 1.5 mg/ml isavuconium sulfate (corresponding to approximately 0.8 mg isavuconazole per mL). After the reconstituted concentrate is further diluted, the diluted solution may show fine white-to-translucent particulates of isavuconazole that do not sediment (but will be removed by in-line filtration). The diluted solution should be mixed gently, or the bag should be rolled to minimise the formation of particulates. Unnecessary vibration or vigorous shaking of the solution should be avoided. The solution for infusion must be administered via an infusion set with an in-line filter (pore size 0.2 μm to 1.2 μm) made of polyether sulfone (PES). CRESEMBA should not be infused into the same line or cannula concomitantly with other intraveneous products.	None

Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Section 4.2 *Posology and method of administration* of the SmPC for isavuconazole 200 mg powder for concentrate for solution for infusion includes: Method of administration *Precautions to be taken before handling or administering the medicinal product* CRESEMBA must be reconstituted and then further diluted to a concentration corresponding to approximately 0.8 mg/mL isavuconazole prior to administration by intravenous infusion over a minimum of 1 hour to reduce the risk for infusion-related reactions. The infusion must be administered via an infusion set with an in-line filter with a microporous membrane made of polyethersulfone (PES) and with a pore size of 0.2 µm to 1.2 µm. CRESEMBA must only be given as an intravenous infusion. Section 4.4 *Special warnings and precautions for use* includes: Infusion-related reactions (not relevant for capsules) During intravenous administration of isavuconazole, infusion-related reactions including hypotension, dyspnea, dizziness, paraesthesia, nausea, and headache were reported. The infusion should be stopped if these reactions occur.	
	Section 4.8 *Undesirable effects* Hypotension, dyspnoea, dizziness, pareasthesia, nausea, and headache are included as ADR for CRESEMBA	
Arrhythmia due to QT shortening	SmPC Section 4.3 *Contraindications* includes the following contraindication: CRESEMBA is contraindicated in patients with familial short QT syndrome. SmPC Section 4.4 *Special warnings and precautions for use* includes the following under Cardiovascular: *QT shortening* In a QT study in healthy human subjects, isavuconazole shortened the QTc interval in a concentration-related manner. For the 200 mg dosing regimen, the least squares mean (LSM) difference from placebo was 13.1 ms at 2 hours post dose [90% CI: 17.1, 9.1 ms]. Increasing the dose to 600 mg resulted in an LSM difference from placebo of 24.6 ms at 2 hours post dose [90% CI: 28.7, 20.4 ms]. Caution is warranted when prescribing CRESEMBAto patients taking other medicinal products known to decrease the QT interval, such as Rufinamide. SmPC Section 4.8 Undesirable effects includes: Electrocardiogram QT shortened is included as an uncommon ADR for CRESEMBA.	

Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Severe cutaneous adverse reactions	Section 4.4 *Special warnings and precautions for use* <u>Severe cutaneous adverse reactions</u> Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, have been reported during treatment with azole antifungal agents. If a patient develops a severe cutaneous adverse reaction, CRESEMBA should be discontinued. Section 4.8 *Undesirable effects* Drug eruption is included as an uncommon ADR and rash is included as a common ADRs for CRESEMBA.	None
Teratogenicity	SmPC Section 4.6 *Fertility, pregnancy and lactation* includes: <u>Pregnancy</u> There are no or limited amount of data from the use of isavuconazole in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. CRESEMBA must not be used during pregnancy except in patients with severe or potentially life-threatening fungal infections in whom isavuconazole may be used if the anticipated benefits outweigh the possible risks to the foetus. CRESEMBA is not recommended for women of childbearing potential who are not using contraception. SmPC Section 5.3 *Pre-clinical safety data* includes: In rats and rabbits, isavuconazole at systemic exposures below the therapeutic level were associated with dose-related increases in the incidence of skeletal anomalies (rudimentary supernumerary ribs) in offspring. In rats, a dose-related increase in the incidence of zygomatic arch fusion was also noted in offspring. Administration of isavuconazole to rats at a dose of 90 mg/kg/day (2.3-fold the human maintenance dose [200 mg] based on mg/m^2/day) during pregnancy through the weaning period showed an increased perinatal mortality of the pups. *In utero* exposure to the active moiety, isavuconazole, had no effect on the fertility of the surviving pups.	None
Effect on children exposed to isavuconazole via breast milk	SmPC Section 4.6 *Fertility, pregnancy and lactation* includes: <u>Breast-feeding</u> Available pharmacodynamic/toxicological data in animals have shown excretion of isavuconazole/metabolites in milk. A risk to newborns and infants cannot be excluded. Breast-feeding should be discontinued during treatment with CRESEMBA. SmPC Section 5.3 *Pre-clinical safety data* includes: Intravenous administration of ^{14}C-labelled isavuconazonium sulfate to lactating rats resulted in the recovery of radiolabel in the milk.	None

Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Development of resistance strains	SmPC: Section 4.2 *Posology and method of administration* includes: Maintenance dose *Duration of treatment* 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. SmPC Section 5.1 *Pharmacodynamic properties* includes: Mechanism(s) of resistance Reduced susceptibility to triazole antifungal agents has been associated with mutations in the fungal *cyp*51A and *cyp*51B genes coding for the target protein lanosterol 14-alpha-demethylase involved in ergosterol biosynthesis. Fungal strains with reduced in vitro susceptibility for isavuconazole have been reported, and cross-resistance with voriconazole and other triazole antifungal agents cannot be excluded. Breakpoints Interpretive criteria for isavuconazole for *Aspergillus* species are applicable to tests performed by the European Committee on Antimicrobial Susceptibility Testing [EUCAST, 2014] (Definitive Document E.DEF 9.2). EUCAST MIC breakpoints are defined for the following species (susceptible S; resistant R): ▪ *Aspergillus fumigatus*: S ≤ 1 mg/L, R > 1 mg/L ▪ *Aspergillus nidulans*: S ≤ 0.25 mg/L, R > 0.25 mg/L ▪ *Aspergillus terreus*: S ≤ 1 mg/L, R > 1 mg/L There are currently insufficient data to set clinical breakpoints for other *Aspergillus* species.	None
Off-label use	Section 4.1 *Therapeutic indications* states that: CRESEMBA is indicated in adults for the treatment of invasive aspergillosis mucormycosis in patients for whom amphotericin B is inappropriate (see sections 4.4 and 5.1) Section 4.2 *Posology and method of administration* includes: *Paediatric population* The safety and efficacy of CRESEMBA in children aged below 18 years has not yet been established. No data are available.	None
Use in patients < 18 years-old	SmPC Section 4.1 *Therapeutic indications* states that: CRESEMBA is indicated in adults for the treatment of invasive aspergillosis mucormycosis in patients for whom amphotericin B is inappropriate (see sections 4.4 and 5.1)	None

Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	SmPC Section 4.2 *Posology and method of administration* includes: *Paediatric population* The safety and efficacy of CRESEMBA in children aged below 18 years has not yet been established. No data are available. SmPC Section 5.1 *Pharmacodynamic properties* includes: <u>Paediatric population</u> The European Medicines Agency has deferred the obligation to submit the results of studies with CRESEMBA in one or more subsets of the paediatric population in the treatment of invasive aspergillosis and the treatment of mucormycosis.	

Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in patients with severe hepatic impairment	SmPC Section 4.2 *Posology and method of administration* includes: *Hepatic impairment* No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Classes A and B). SmPC Section 4.4 *Special warnings and precautions for use* will include: *Severe hepatic impairment* CRESEMBA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Use in these patients is not recommended unless the potential benefit is considered to outweigh the risks. These patients should be carefully monitored for potential drug toxicity. SmPC Section 5.2 *Pharmacokinetic properties* will include: *Hepatic impairment* After a single 100 mg dose of isavuconazole was administered to 32 patients with mild (Child-Pugh Class A) hepatic insufficiency and 32 patients with moderate (Child-Pugh Class B) hepatic insufficiency (16 intravenous and 16 oral patients per Child-Pugh Class), the least square mean systemic exposure (AUC) increased 64% in the Child Pugh Class A group and 84% in the Child-Pugh Class B group relative to 32 age and weight matched healthy subjects with normal hepatic function. Mean plasma concentrations (C_{max}) were 2% lower in the Child-Pugh Class A group and 30% lower in the Child-Pugh Class B group. The population pharmacokinetic evaluation of isavuconazole in healthy subjects and patients with mild and moderate hepatic dysfunction demonstrated that the mild and moderate hepatic impairment populations had 40% and 48% lower isavuconazole clearance (CL) values, respectively, compared to the healthy population. No dose adjustment is required in patients with mild to moderate hepatic impairment. CRESEMBA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Use in these patients is not recommended unless the potential benefit is considered to outweighs the risks. These patients should be carefully monitored for potential drug toxicity.	None
Efficacy in invasive aspergillosis in Asian patients	None proposed. The applicant intends to collect additional information through routine pharmacovigilance measures in order to determine whether risk minimization measures are required.	None

Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Clinical efficacy and safety of isavuconazole treatment in patients infected with *Mucorales* species	SmPC Section 4.4 *Special warnings and precations for use* includes: Limitations of the clinical data The clinical data for isavuconazole in the treatment of mucormycosis are limited to one prospective non-controlled clinical study in 37 patients with proven or probable mucormycosis who received isavuconazole for primary treatment, or because other antifungal treatments (predominantly amphotericin B) were inappropriate. For individual *Mucorales species*, the clinical efficacy data are very limited, often to one or two patients (see section 5.1). Susceptibility data were available in only a small subset of cases. These data indicate that concentrations of isavuconazole required for inhibition in vitro are very variable between genera/species within the order of *Mucorales*, and generally higher than concentrations required to inhibit Aspergillus species. It should be noted that there was no dose-finding study in mucormycosis, and patients were administered the same dose of isavuconazole as was used for the treatment of invasive aspergillosis. SmPC Section 5.1 *Pharmacodynamic properties* includes: Treatment of mucormycosis In an open-label non-controlled study, 37 patients with proven or probable mucormycosis received isavuconazole at the same dose regimen as that used to treat invasive aspergillosis. Median treatment duration was 84 days for the overall mucormycosis patient population, and 102 days for the 21 patients not previously treated for mucormycosis. For patients with probable or proven mucormycosis as defined by the independent Data Review Committee (DRC), all-cause mortality at Day 84 was 43.2% (16/37) for the overall patient population, 42.9% (9/21) for mucormycosis patients receiving isavuconazole as primary treatment, and 43.8% (7/16) for mucormycosis patients receiving isavuconazole who were refractory to, or intolerant of, prior antifungal therapy (mainly amphotericin B-based treatments). The DRC-assessed overall success rate at EOT was 11/35 (31.4%), with 5 patients considered completely cured and 6 patients partially cured. A stable response was observed in an additional 10/35 patients (28.6%). In 9 patients with mucormycosis due to Rhizopus spp., 4 patients showed a favourable response to isavuconazole. In 5 patients with mucormycosis due to Rhizomucor spp., no favourable responses were observed. The clinical experience in other species is very limited (Lichtheimia spp. n=2, Cunninghamella spp. n=1, Actinomucor elegans n=1).	None

ADR: adverse drug reaction; CI: confidence interval; CL: clearance; LSM: least squares mean; EUCAST: European Committee for Antimicrobial Susceptibility Testing; QTc: QT interval corrected for heart rate; SmPC: Summary of Product Characteristics; ULN: upper limit of normal.

2.8. Pharmacovigilance

Pharmacovigilance system

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

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet for hard capsules submitted by the applicant show that the package leaflet 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.*

A justification for not performing a full user consultation with target patient groups on the package leaflet for the powder for concentrate for solution for infusion has been submitted by the applicant and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Cresemba 100 mg hard capsules. The bridging report submitted by the applicant has been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Cresemba (isavuconazole) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

This application is primarily based on the results from two pivotal clinical trials, study 9766-CL-0104 relevant for the aspergillosis indication and study 9766-CL-0103, relevant for the mucormycosis indication.

Invasive aspergillosis

Non-inferiority of isavuconazole relative to voriconazole (which was considered an appropriate comparator by CHMP) was shown for the primary efficacy endpoint "crude rate of all-cause mortality through day 42 (in ITT)" in study 9766-CL-0104. Mortality in the isavuconazole treated patients was 18.6% (48/258 patients)

compared to 20.2% (52/258) of voriconazole treated patients. This treatment difference of -1.0% (95% CI: [-7.759, 5.683]) in favour of isavuconazole was well within the predefined non-inferiority margin of 10%. The results for the key secondary efficacy endpoint "DRC-assessed overall response at EOT (in mITT)" were very similar for the isavuconazole (51/143 patients, 35%) and voriconazole-treated patients (46/129 patients, 36,4%), resulting in a treatment difference of 1.6 (95%CI: [-9.336, 12.572]). This endpoint was considered more relevant by CHMP than all-cause mortality, as mortality could have resulted from causes unrelated to IFD in these severe ill patients and because mortality associated with IFD was difficult to discriminate in these complex cases. Analyses of mortality rates and DRC-assessed clinical and mycological success were generally consistent. In addition, in the myITT patients with aspergillosis that was not diagnosed based solely on GM, the success rates at EOT were very similar.

Mucormycosis

Study 9766-CL-0103 was an open-label single arm study with the primary objective to describe the efficacy of isavuconazole in the treatment of 37 patients with IFD caused by rare moulds, yeasts or dimorphic fungi (mITT population) and 24 patients with invasive aspergillosis and renal impairment (20 patients, 4 patients had normal renal function). At EOT the "DRC-assessed overall response rate" was 11/35 (31.4%) for Mucorales, with 5/35 (14.3%) of patients assessed to be a "complete success" and 6/35 (17.1%) assessed to be a "partial success". Two patients were still actively participating in the study and were not included in this analysis at the EOT. All-cause mortality was 37.8% (14/37) at day 42 and 43.2% (16/37) at day 84. The mortality rate with the use of isavuconazole was comparable to that reported in literature for the current standard of care, liposomal amphotericin B. Moreover, from the additional analyses presented by the applicant, it appeared that the overall success rates in study 9766-CL-0103 were also consistent with the clinical response rates (complete cure, partial cure, stable response or failure) observed in external control studies performed with amphotericin-B. The CHMP agreed that all the above, along with the additional data provided by the Applicant during the procedure on the compassionate use give support the indication "treatment of adult patients with mucormycosis for whom amphotericin B is inappropriate". CHMP also noted the adequate tolerability profile of isavuconazole, enabling long term treatment.

Intravenous and oral formulation of isavuconazole

Isavuconazole (available as IV and oral dosage forms) offers an added treatment option for renally impaired patients with invasive aspergillosis and mucormycosis. The advantage of the isavuconazole i.v. formulation is that it can be used in renally impaired patients, whereas voriconazole i.v. (the current standard of care in invasive aspergillosis) has to be avoided in moderate to severe renally impaired patients (creatinine clearance < 50 ml/min), because of the accumulation of its intravenous vehicle sulfobutylether-beta-cyclodextrin (SBECD).

Uncertainty in the knowledge about the beneficial effects.

Aspergillosis

CHMP noted that no definite conclusions could be made with regard to the dose–effect relation for isavuconazole, as no formal dose-finding studies were conducted. In addition, the majority of the myITT patients had a diagnosis based on the galactomannan test (GM) only. Therefore outcomes by MIC were available for a relatively small number of patients, and in these a threshold for response based on MIC could not be observed. Due to the fact that the PK sampling was also considered not adequate to support good quality analyses of the exposure-response relationship that take into account individual patient AUC/MIC ratios (i.e. PopPK-predicted AUC from individual sparse PK data and the MIC documented for that patient's

pathogen) it was not possible to conclude on the highest MICs that may be treatable with the recommended dose regimen of isavuconazole.

Asian patients had a numerically lower success rate in the isavuconazole group (25.9%, 7/27) than in the voriconazole treatment group (48.6%, 17/35). From the additional responses provided by the applicant during the procedure, it was concluded that the observed differences in response rates between Asian and non-Asian patients could not be explained by drug exposure. It was noted that out of six Asian patients with MIC values available, all MICs were below 2 µg/mL. CHMP agreed therefore that it was unlikely that resistance to isavuconazole would explain the data observed for the overall response at EOT. Moreover, the differences in favour of voriconazole were not consistent across the Asian countries; they were apparent in Thailand and South Korea, but not in China and India. Therefore CHMP agreed that no definitive conclusions could be drawn on this point. A potential ethnicity effect cannot be excluded at present and it is included as missing information in the RMP.

Mucormycosis

For Mucorales, no relation between the MIC and the probability of clinical response could be observed. The selected dose and dose regimen were not sufficiently substantiated, complicating the interpretation of the clinical efficacy data in study 9766-CL-0103. Further uncertainties encountered by CHMP in the interpretation of the observed results concern the absence of a formal dose selection study, no preclinical data supporting a PK/PD relationship, and the absence of a clear relationship between MICs and clinical responses.

The clinical data are confined to only a narrow range of organisms that belong to the order of Mucorales. Where MICs are available, these suggest that the dose may be insufficient. *In vitro* data indicated poor activity against several Mucorales specie. In addition, for patients with positive cultures and with MIC data available, the vast majority of the observed MICs were at least 8 µg/mL, whereas the expected mean trough value was only approximately 4 mg/L. The generally higher MIC may reflect the somewhat lower susceptibility of Mucorales to isavuconazole. The data suggest that some of the genera/species within the order Mucorales may be inherently not susceptible to isavuconazole.

CHMP noted that the applicant had based the external control data on the "standard care" liposomal amphotericin B by providing a literature review and a Fungiscope matched-control analysis. The mortality rate associated with the use of isavuconazole seemed compable to that reported for standard care liposomal amphotericin B in the treatment of mucormycosis; however CHMP acknowledged the limitations of this analysis, that was based on historical controls from the literature.

The data to put the DRC-assessed overall response at EOT (considered the most relevant endpoint) into context are even more sparse. It was noted that most pivotal studies performed with amphotericin B were old and did not comply with the recommendations published by EORTC/MSG -only the studies by Shoham (2010), Xhaard (2012) and Lanternier (2012) were considered appropriate for an external comparison of the overall response rates with those obtained from study 9766-CL-0103.

The complex patient population and the absence of a justification for the dose selection made the interpretation of the clinical data very difficult. The low number of patients enrolled (explained by the difficulty of enrolling patients in a study for this rare disease), the open-label single-arm design of the study, the heterogeneity of the included patient group in terms of the observed baseline characteristics, the interaction with other interventions (surgery, correction of predisposing conditions), and the lack of a direct comparison with other antifungals made the evaluation of the attributable efficacy of isavuconazole in mucormycosis very difficult.

Resistance development of Aspergillus

CHMP also noted that the applicant's conclusion that there was no signal of resistance development during treatment was based on only 2 patients, whereas substantial treatment failures occurred in overall population enrolled, and that no data at baseline and/or follow up MICs were available. CHMP could not conclude on the data from the 2 patients with regard to the potential of resistance development and supported that this issue is addressed in the Rosk Management Plan.

Intravenous formulation of isavuconazole

In the phase 3 studies in-line filters were to be used, but some sites used the wrong pore size and some patients received the unfiltered drug. However, during the assessment, based on the data provided by the applicant, CHMP concluded that these did not have an impact on the observed clinical efficacy of Cresemba.

Risks

Unfavourable effects

The most common treatment-related adverse reactions were nausea (26.1%), vomiting (24.8%), diarrhoea (21.8%), headache (17.1%), elevated liver chemistry tests (16.9%), hypokalaemia (15.6%), abdominal pain (15.1%), dyspnoea (14.9%), oedema peripheral (14.4%) and constipation (12.9%). The adverse reactions which most often led to permanent discontinuation of isavuconazole treatment during clinical studies were confusional state (0.7%), acute renal failure (0.7%), increased blood bilirubin (0.5%), convulsion (0.5%), dyspnoea (0.5%), epilepsy (0.5%), respiratory failure (0.5%) and vomiting (0.5%).

Isavuconazole is a substrate of CYP3A4 and contraindications are included in the SmPC for the concomitant use with the strong CYP3A4 inhibitor ketoconazole and with strong and moderate CYP3A4 inducers. In addition, due to the fact that isavuconazole induces UGT and CYP2D6, decreased plasma levels of UGT substrates and CYP2B6 substrates are expected, which may affect the efficacy of medicinal products which are UGT/CYP2B6 substrates. CHMP therefore agreed to include an adequate wording in the Cresemba SmPC, describing these interactions.

Overall, the observed safety profile of isavuconazole is similar to the safety profile that would be expected for an azole antifungal medicinal product and generally compared favourably with that of voriconazole. Nevertheless, some potential ADRs were of a severe nature and CHMP agreed that these needed to be reflected in the Cresemba SmPC.

In most other SOCs isavuconazole had a numerically lower rate of TEAEs, the differences observed for the SOCs eye disorders and hepatobiliary disorders being statistically significant lower than in the voriconazole arm. A significant higher proportion of isavuconazole-treated patients when compared with voriconazole-treated patients experienced study drug related TEAEs within the respiratory SOC.

Identified risks for isavuconazole are elevated liver transaminases and infusion related reactions.

Elevated liver transaminases have been reported with the use of isavuconazole in clinical studies, although not requiring study drug discontinuation. Hepatotoxicity is also known to occur with other triazoles. A warning in on the use of Cresemba in patients with mild-to-moderate hepatic impairment was included in the SmPC.

Infusion-related reactions have been reported with isavuconazole. During intravenous infusion of isavuconazole, hypotension, dyspnea, chills, dizziness, paresthesia, hypoesthesia, nausea, and headache were reported. The Cresemba SmPC includes a recommendation for an infusion of a minimum of one hour, and a relevant wording in section 4.4.

Uncertainty in the knowledge about the unfavourable effects

Although in most SOCs isavuconazole had a numerically lower rate of TEAEs, CHMP agreed that this aspect was difficult to interpret since the safety database of isavuconazole was rather limited (403 patients) and mainly relied on the results of the controlled study 9766-CL-0104 (257 patients). It was therefore acknowledged by CHMP that only uncommon or more frequent events could be described by the current generated information. Although the isavuconazole safety profile appeared to have been the expected one, the risk of the most important expected issues, such as hepatotoxicity, and the risk of unexpected rare issues, such as carcinogenicity, could not be fully elucidated based on the generated preclinical and clinical datasets.

Intravenous formulation of isavuconazole

In the phase 3 studies in-line filters were to be used but some sites used the wrong pore size and some patients received unfiltered drug. From the two analyses performed, for both studies separately, no occurrence of an embolic or thrombotic-type AE was observed.

Benefit-risk balance

Importance of favourable and unfavourable effects

Despite the current available antifungal therapies (AFTs) for invasive aspergillosis and mucormycosis, both diseases are life-threatening and still associated with high mortality rates. There is an urgent unmet medical need for new effective antifungal drugs for the treatment of the invasive fungal diseases.

Aspergillosis

Isavuconazole is a new triazole antifungal agent that showed non-inferiority relative to voriconazole, the current standard of care for the treatment of aspergillosis in adults. From the data submitted by the applicant, CHMP could not conclude whether isavuconazole had an added clinical benefit over other tri-azoles in the treatment of aspergilosis. It was however noted that study drug-related TEAEs leading to permanent discontinuation of study drug were less frequent in the isavuconazole group (8.2%) compared with the voriconazole group (13.5%). This apparent safety advantage of isavuconazole may constitute a benefit for isavuconazole in the treatment of aspergillosis.

Mucormycosis

Mucormycosis is a very difficult to treat disease, especially when located at certain body sites. The current standard of care for mucormycosis is liposomal amphotericin B.

The open-label study 9766-CL-0103, together with the external control data on the current standard of care liposomal amphotericin B and with the data obtained from the compassionate use cases support the indication "treatment of mucormycosis in adult patients for whom amphotericin B is inappropriate". Isavuconazole is well tolerated, enabling long term treatment in renal impaired patients.

Discussion on the benefit-risk balance

Aspergillosis

Like for other azoles, the dose-response relationship for isavuconazole is complex and ambiguous. However, CHMP agreed that the efficacy results of the performed active-controlled pivotal trial were reassuring in this respect. Study 9766-CL-0104 has shown non-inferiority of isavuconazole relative to voriconazole (which is

the standard of care for the treatment of aspergillosis) regarding all-cause mortality. The results of all additional efficacy analyses of the pivotal trial, including the key secondary endpoint DRC-assessed overall response, were generally in line with the main findings. The safety profile of isavuconazole appears to be similar that of voriconazole. CHMP noted also that in most SOCs, isavuconazole had a numerically lower rate of TEAEs. CHMP acknowledged the differences observed for the SOCs "eye disorders" and "hepatobiliary disorders" which were lower than with voriconazole were statistically significant, but agreed that this should be carefully interpreted, considering the limited safety database of isavuconazole.

Mucormycosis

CHMP agreed that from the public health perspective, new effective medicines for the treatment of mucormycosis are needed. The open-label study 9766-CL-0103, together with the external control data (mortality rates and clinical response rates) based on the current standard of care (liposomal amphotericin B) and on compassionate use cases are supportive for the indication "treatment of adult patients with mucormycosis for whom amphotericin B is inappropriate".

The current standard of care for mucormycosis is (liposomal) amphotericin B. (Liposomal) amphotericin B is the only medicinal product that is authorized for the primary treatment of mucormycosis in the EU.

L-amB has the broadest spectrum of antifungal activity against the species of the Mucorales order and its clinical efficacy in mucormycosis is by far the best documented; this medicine has therefore a first line indication for the treatment of mucormycosis. Nevertheless, in those case where the disease is refractory to L-AmB, as well as in the case of intolerance to L-amB after previous therapy with this medicine (amphotericin-B has known adverse renal effects, especially in the case of long-term treatment), isavuconazole has been shown to have beneficial effects in patients infected by at least some of the Mucorales species (f.e. Rhizopus spp, Actinomucor elegans, Lichtheimia corymbifera). Isavuconazole is well tolerated, enabling long term treatment in renally impaired patients and provides an alternative option for mucormycosis patients with renal impairment and to patients not responding to treatment with Amphotericin-B. Isavuconazole is available as an IV and an oral formulation which are easily switchable when clinically indicated.

Both indications

The benefit shown together with the favourable safety profile of isavuconazole in both indications outweighs the existing uncertainties, especially in the treatment of mucormycosis. Isavuconazole is well tolerated, enabling long term treatment in renal impaired patients.

CHMP therefore considered that the benefit-risk balance for Cresemba in the treatment of invasive aspergillosis in adults and in the treatment of mucormycosis in adult patients for whom amphotericin B is inappropriate is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Cresemba in the treatment of invasive aspergillosis in adults and of mucormycosis in adult patients for whom amphotericin B is inappropriate (see SmPC sections 4.4 and 5.1) is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product on 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The 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.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that isavuconazole (as isavuconazonium sulfate) is qualified as a new active substance.