Advisory Committee Briefing Document

Isavuconazonium

Invasive Aspergillosis and Invasive Mucormycosis

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Astellas

Including, but not limited to, Astellas Pharma Global Development, Inc.,
Astellas Pharma Europe B.V. and Astellas Pharma Inc.

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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List of Abbreviations

ABPA	Allergic bronchopulmonary aspergillosis
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AML	Acute myelogenous/myeloid leukemia
ANC	Absolute neutrophil count
APGD	Astellas Pharma Global Development
AST	Aspartate transaminase
BA	Bioavailability
BAL	Bronchoalveolar lavage
BAL19714	Drug substance impurity
BAL4815	Active moiety of isavuconazonium, isavuconazole
BAL8728	Inactive cleavage product of isavuconazonium
BCRP	Breast cancer resistance protein
BW	Body weight
CI	Confidence interval
CL	Clearance
CLCr	Creatinine clearance
CL_R	Renal clearance
CLSI	Clinical and Laboratory Standards Institute
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
COPD	Chronic Obstructive Pulmonary Disease
CTA	Clinical Trial Authorization
CYP	Cytochrome P450 enzymes
D5W	5 % glucose infusion solution
ddQTcF	Time-matched baseline-adjusted QTcF from placebo
DKA	Diabetic ketoacidosis
DRC	Data Review Committee
ECG	Electrocardiogram
ECIL 3	3rd European Conference on Infections in Leukemia
eGFR	Estimated glomerular filtration rate
EORTC/MSG	European Organization for the Research and Treatment of Cancer/Mycoses Study Group
EOT	End of treatment
ESCMID/ECMM	European Society of Clinical Microbiology and Infectious Diseases/European Confederation of Medical Mycology
ESRD	End stage renal disease
FDA	Food and Drug Administration
FE	Food effect
FLU	Fluconazole
GAIN	Generating Antibiotics Incentives Now
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLP	Good Laboratory Practice
GLSM	Geometric least squares mean
hCG	Human chorionic gonadotropin
hERG	Human ether-á-go-go-related
HIV	Human immunodeficiency virus

HR	Heart rate
HSCT	Hematopoietic stem cell transplantation
HIPAA	Health Insurance Portability and Accountability Act
IA	Invasive Aspergillosis
ICH	International Conference on Harmonisation
IDSA	Infectious Diseases Society of America
IDSMB	Independent Data Safety Monitoring Board
IFD	Invasive Fungal Disease
IM	Invasive Mucormycosis
IND	Investigational New Drug
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
LD_{50}	50% lethal dose
LPV/RTV	Lopinavir/ritonavir
LRTD	Lower respiratory tract disease
MAA	Marketing Authorisation Application (Europe)
MAD	Multiple-ascending dose
MATE	Multidrug and toxin extrusion
MB	Mass balance
MDR1	Multidrug resistance gene 1
MedDRA	Medical Dictionary for Regulatory Activities
MFCs	Minimal Fungicidal Concentration
MIC	Minimum inhibitory concentration
mITT	Modified intent-to-treat
mITT-Mucorales	Modified intent-to-treat with Mucorales infections
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid
myITT	Mycological intent-to-treat
NCS	Not clinically significant
NDA	New Drug Application
NIH	National Institutes of Health
NIM	Non-inferiority margin
NIS	Nationwide Inpatient Sample
NOS	Not otherwise specified
OAT1/OAT2	Organic anion transporters
OATP1B1/OATP1B3	Organic anion-transporting polypeptides
OCT1/OCT2	Organic cation transporters
OOPD	Office of Orphan Products Development
OSHA	Occupational Safety and Health Administration
P-gp	P-glycoprotein
PD	Pharmacodynamic
PK	Pharmacokinetic
PPS	Per protocol set
PT	Preferred term (MedDRA)
QIDP	Qualified Infectious Disease Product
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate by Fridericia's formula
RI	Renally impaired
SAD	Single-ascending dose
SAP	Statistical Analysis Plan

SMQ	Standard MedDRA Query
SOC	System Organ Class (MedDRA)
SOT	Solid organ transplant
Spp.	Species
SQTS	Short QT Syndrome
TEAE(s)	Treatment-emergent adverse event(s)
TRANSNET	Transplant-Associated Infection Surveillance Network
UC	Untreated controls
UGT	Uridine diphosphate-glucuronosyltransferase
ULN	Upper limit of normal
USP	United States Pharmacopeia
WBC	White blood cell

1 EXECUTIVE SUMMARY

1.1 Introduction

Astellas Pharma Global Development, Inc. (APGD), on behalf of Astellas Pharma US, submitted a New Drug Application (NDA) to the US Food and Drug Administration (FDA) on July 8, 2014 seeking approval for isavuconazonium in the following indications:

- patients 18 years of age and older in the treatment of invasive aspergillosis (IA)
- patients 18 years of age and older in the treatment of invasive mucormycosis (IM)

Isavuconazonium is a prodrug containing the active moiety, isavuconazole. Isavuconazonium is available as a sterile lyophilized powder for IV infusion and as a capsule for oral administration. Dosages are expressed in mg equivalents of the active drug isavuconazole. In this document, the study drug is referred to as isavuconazole unless further specificity is required.

The primary support for the indications (IA and IM) is based on the results of two phase 3 studies: a randomized, double-blind, active-control (i.e., voriconazole) study of adult patients with IA (Study 0104) and an open-label noncomparative study of isavuconazole in adult patients with IA and renal impairment or in patients with invasive fungal disease (IFD) caused by other rare fungi including IM (Study 0103).

This briefing document provides an overview of the isavuconazole development program and substantial evidence in support of the marketing authorization of isavuconazole for the treatment of both IA and IM.

1.2 Unmet Need

Invasive Aspergillosis

IA is a life-threatening angio-invasive infection that is seen predominantly in severely immunocompromised patients; i.e., patients with prolonged neutropenia related to antineoplastic chemotherapy and/or hematopoietic stem cell transplantation (HSCT), patients receiving immunosuppressants following solid organ transplants (SOT) and patients given high doses of corticosteroids.[2,3,4,5,6,7] Based on hospital discharge data, a US incidence rate of 36 per million cases of IA per year or approximately 12,000 cases per year is estimated.[9]

The most common site of IA infection is the lung, but hematogenous spread can lead to dissemination to other organs (e.g., sinus, cerebral).[2] The clinical presentation of IA can be nonspecific with symptoms such as fever, cough, sputum production, pleuritic pain, hemoptysis and dyspnea. Despite the availability of serologic testing, the diagnosis of IA can be difficult and may not be made prior to death. Thus, clinicians need to have a high index of suspicion and even treat patients with possible, meaning suspected, disease.[10,11]

Even when diagnosed and treated, IA is known to have high mortality rates (~30%).[12]

IA is commonly treated with systemic antifungal therapies, such as polyenes, mould active triazoles and echinocandins. The current treatment guidelines, issued in 2008 by Infectious

Diseases Society of America (IDSA), recommend voriconazole as first-line therapy.[6] Voriconazole administration is associated with toxicities that may be dose limiting, such as visual disturbances, photosensitivity, skin reactions, hallucinations, serious hepatic reactions and QT prolongation. Further, the IV formulation of voriconazole contains cyclodextrin, which limits its use in patients with moderate to severe renal dysfunction.[13]

For patients who are intolerant of or whose IFD continues to progress on voriconazole, there is little consensus as to the next course of action. The addition of another agent or switch to a different drug class for salvage therapy may be considered, with lipid-associated formulations of amphotericin B, caspofungin or posaconazole as potential agents, either as monotherapy or in combination.

Invasive Mucormycosis

IM is a devastating fungal infection caused by the filamentous fungi of the Mucorales order of the subphylum Mucoromycotina.[14,15]

Many of the conditions predisposing patients to IM are similar to IA and include hematological malignancy with or without stem cell transplantation and prolonged neutropenia. Other groups of patients at risk are those with poorly controlled diabetes mellitus with or without diabetic ketoacidosis, dialysis patients with iron overload as well as in patients with trauma or burns.[16]

The presentation of pulmonary IM often resembles that of IA or other invasive fungal infections. Other clinical forms include: rhinocerebral, gastrointestinal (GI), cutaneous and disseminated disease.[14] Given the lack of a serologic biomarker, diagnosis of IM usually requires culture or histology from involved tissue.[17,18]

Data on incidence rates for mucormycosis is very limited. In 2005, a review of the English-language literature since 1885 only identified 929 cases of mucormycosis.[19] While the incidence has been reported to be increasing, it remains much less common and less well-studied than IA. The best estimates of incidence come from analyses of specific at-risk populations. The Transplant-Associated Infection Surveillance Network (TRANSNET), a multicenter network of 23 academic tertiary care medical centers in the US, performed prospective surveillance for invasive fungal infections from 2001 through 2006. They detected Mucorales in 105 patients, 77 in HSCT recipients and 28 in SOT recipients. The overall 12-month cumulative incidence for mucormycosis was 0.29% in HSCT recipients and 0.07% in SOT recipients.[20] Rees and colleagues reported on a population-based active laboratory surveillance for mucormycosis from 1992 through 1993 that found approximately 500 cases per year in the US.[21]

The therapeutic approach to IM is multimodal and includes treatment of the underlying condition, surgical debridement and antifungal therapy. Given the rarity of IM, treatment guidelines are based primarily on case series and expert opinion as no well-controlled comparative antifungal treatment studies have been published.

Amphotericin B deoxycholate is the only antifungal approved for treatment of IM; however, the most recent guidelines (2013) issued by the 3rd European Conference on Infections in Leukemia (ECIL 3) and the European Society of Clinical Microbiology and Infectious Diseases/European Confederation of Medical Mycology (ESCMID/ECMM) recommend the use of lipid formulations of amphotericin B as first-line therapy.[17,18] Currently, there are no guidelines issued in the US for the treatment of IM.

Regardless of formulation, amphotericin B treatment has been associated with the development of severe renal toxicity, which has been associated with prolonged hospital stay and is a predictor of mortality.[22,23] For patients who progress or are intolerant of amphotericin therapy, there are limited therapeutic options. Although not approved, posaconazole is recommended by the ECIL3 and ESCMID/ECMM guidelines as salvage therapy.[17,24]

Despite aggressive surgical and antifungal treatments, IM is associated with high mortality. Published mortality rates vary widely depending on the underlying disease and extent of infection. Mortality rates were 66%, 44% and 96% in patients with hematologic malignancy, diabetes and disseminated disease, respectively.[19] In patients with IM (1991 through 2011) who had mixed underlying conditions (e.g., hematological malignancies, SOT, diabetes, etc.) and received amphotericin-based treatment, publications cited mortality rates that ranged from 35% to 61% [see Section 8.4.6].

Summary

In summary, IA and IM are rare infections primarily occurring in severely immunocompromised patients. The difficulty in diagnosis and high mortality necessitates that the treating physicians have a high index of suspicion and institute therapy early when IFD is suspected. Unfortunately, there are a limited number of therapeutic options and the preferred agents have significant limitations. For IA, voriconazole is the preferred agent, but requires cyclodextrin in its IV formulation, has significant pharmacokinetic variability and a side effect profile that necessitates drug discontinuation in some patients. For IM, amphotericin B is the only approved therapy. It is available only in an IV formulation and has significant renal toxicity that limits its use over the required treatment duration.

There is a significant need for alternative antifungal therapies that address some of the limitations of voriconazole in IA and amphotericin B in IM. Given the difficulty in diagnosis and similarity with which IA and IM may present, having an antifungal that is effective for both indications would be particularly useful to physicians treating these seriously ill patients.

1.3 FDA Designations – QIDP and Orphan

The FDA has granted Qualified Infectious Disease Product (QIDP) status for isavuconazole (in accordance with the Generating Antibiotics Incentives Now [GAIN] Act) for IA (Nov 2013) and IM (Feb 2014) indications. The GAIN Act was passed in 2012 in response to the increasing incidence of resistant and emerging organisms to stimulate the development of new anti-infectives. The GAIN Act provides additional exclusivity for certain antibacterial and antifungal drugs intended to treat serious or life-threatening infections. Under the GAIN

Act, an application for a qualified infectious disease product is eligible for both Priority Review and Fast Track designation programs for expediting drug development.

The Orphan Drug Designation program provides orphan status to drugs intended for treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the US. The FDA Office of Orphan Products Development (OOPD) granted isavuconazole Orphan Drug Designation for the treatment of IA (May 2013) and for the treatment of zygomycosis (now referred to as mucormycosis) (Oct 2013).

1.4 Product Description

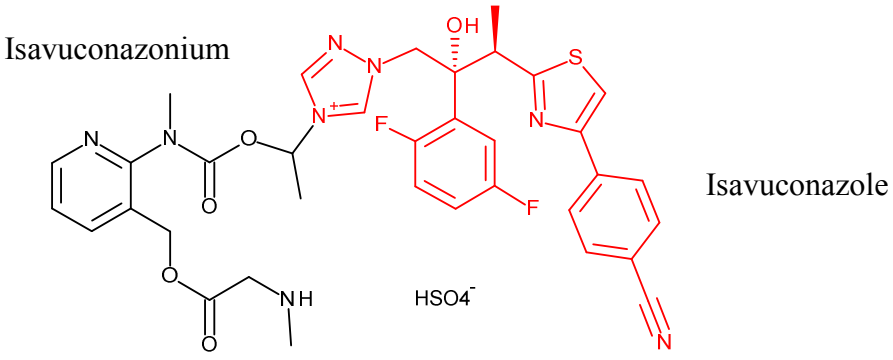
Isavuconazonium is a novel, water-soluble prodrug of the triazole isavuconazole, which is a broad spectrum antifungal agent developed for the treatment of adults with IA and IM. Following IV administration, isavuconazonium is rapidly converted by plasma esterases to the active moiety isavuconazole. After oral administration, isavuconazonium predominantly undergoes chemical hydrolysis in the GI lumen. No significant concentrations of the prodrug, isavuconazonium, were detectable in plasma after oral administration.

Isavuconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P450 (CYP) dependent enzyme lanosterol 14α-demethylase, which is responsible for the conversion of lanosterol to ergosterol in the fungal cell membrane. 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 IV formulation is a powder for concentrate for solution for infusion containing 372.6 mg isavuconazonium corresponding to 200 mg isavuconazole. The oral formulation is a hard capsule containing 186.3 mg isavuconazonium corresponding to 100 mg isavuconazole.

A graphical presentation of the chemical structure of the prodrug (entire structure), active drug (red) and inactive cleavage product (black) is shown in [Figure 1].

Figure 1 Chemical Structure of the Prodrug and Active Drug



1.5 Development Program

1.5.1 Nonclinical Development Program

A total of 177 nonclinical studies were conducted as part of the isavuconazonium development program: 76 pharmacology, 3 safety pharmacology, 34 pharmacokinetic and 64 toxicology studies.

1.5.1.1 Microbiology

Isavuconazole has demonstrated in vitro activity against *Aspergillus* species (spp.), species of Mucorales, *Candida* spp., *Cryptococcus* spp., and other rare fungi, illustrating a broad spectrum of activity. Isavuconazole has in vitro activity and demonstrated successful clinical outcomes in patients infected with strains of the following organisms in clinical trials: *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus sydowi*, *Rhizopus oryzae*, *Lichtheimia (Absidia) corymbifera*, *Fusarium solani*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Cryptococcus gattii* and *Paracoccidioides brasiliensis*.

In vivo efficacy was demonstrated in animal models of invasive pulmonary and disseminated aspergillosis, pulmonary mucormycosis and disseminated candidiasis. Isavuconazole showed potent concentration-dependent activity with significantly decreased fungal burden in tissues such as the lungs, kidneys and brain and enhanced survival.

AUC/minimum inhibitory concentration (MIC) correlated best with therapeutic efficacy in pharmacodynamic models. Pharmacodynamic targets from these models were used to estimate necessary humans target exposures in target attainment analyses.

1.5.1.2 Nonclinical Toxicology

Nonclinical safety of isavuconazole was evaluated in single dose toxicity studies in rats and cynomolgus monkeys; repeated dose toxicity studies in rats (up to 26 weeks) and cynomolgus monkeys (up to 39 weeks); in vitro and in vivo genotoxicity studies; reproductive and developmental toxicity studies in rats and rabbits; local irritation studies in rabbits; and other toxicity studies (eye irritation, phototoxicity and hemolysis).

The toxicological assessment showed that isavuconazonium had similar toxicities across species and the findings were consistent with that of an azole antifungal agent. Neither the prodrug (isavuconazonium) nor the active moiety (isavuconazole) showed genotoxic potential. The teratogenic potential of isavuconazole was noted in rats and rabbits and is also consistent with that previously noted for the azole class of antifungal agents.

Isavuconazole showed no discernible phototoxicity potential in vitro.

1.5.2 Clinical Development Program

The global clinical development program consisted of 44 studies and included 2166 subjects of whom 1692 subjects received isavuconazole. Two phase 2 and two phase 3 studies characterized the efficacy and/or safety of isavuconazole in patients. The two phase 2 studies (studies 0101 and 0102) evaluated isavuconazole in patients with esophageal candidiasis and as prophylaxis in neutropenic patients with acute myeloid/myelogenous leukemia (AML).

These phase 2 studies are not considered directly supportive of the efficacy of the proposed indications since they evaluated isavuconazole in different patient populations and clinical settings. Primary efficacy and safety data come from the two phase 3 studies (0104 [IA] and 0103 [IM]).

The efficacy for the indication of IA is primarily supported by data from a randomized (1:1), double-blind, multicenter, non-inferiority, comparative group study (Study 0104), which evaluated the efficacy and safety of isavuconazole compared to voriconazole for the treatment of IA and other filamentous fungi. Study 0104 included 516 adult patients with suspected IFD caused by *Aspergillus* species or other filamentous fungi. A blinded, independent Data Review Committee (DRC) assessed patients' IFD diagnosis and overall response. Study 0104 is a large comparative study conducted for the treatment of patients with IA and is an adequate, well-controlled trial that provides substantial evidence to support the claim of effectiveness.

The indication of IM is supported by data from an open-label, multicenter, single arm, phase 3 study (Study 0103), which evaluated isavuconazole for the treatment of IA in patients with renal impairment or in patients with IFD caused by rare moulds, yeasts or dimorphic fungi regardless of renal function. A total of 149 patients were enrolled in the study. An independent DRC assessed 37 patients to have had proven or probable IFD attributed to an organism of the Mucorales order, 21 of whom received isavuconazole as primary therapy. To support data interpretation, a matched control analysis was conducted for patients who received isavuconazole therapy relative to patients who received amphotericin-based therapy as primary therapy from the Fungiscope database, a contemporary international registry of rare fungal infections.

The FDA specified that for rare fungal pathogens, such as Mucorales, efficacy could be demonstrated in a minimum of 20 well-documented cases. While such data could not be utilized alone to support an approval, it could be assessed within the context of appropriate animal model testing, a larger NDA submission supporting efficacy in a more common invasive fungal infection and in information on the natural history of mucormycosis, including comparative mortality in untreated patients and patients treated with other mould-active agents.

Frequent regulatory interactions with the FDA Division of Anti-infective Products (and the former Division of Special Pathogens and Transplant Products) were held during the isavuconazole development program to ensure transparency and obtain FDA concurrence with the development program. The Division agreed that the phase 3 study designs could support the filing of an NDA for the treatment of IA and IM.

The demographics and underlying diseases of patients in the phase 3 studies are representative of the target indication populations and of sufficient magnitude and extent of exposure to allow a reasonable assessment of the safety and efficacy of the compound in the intended clinical indications. The safety evaluation performed in the clinical studies conducted as part of the isavuconazole clinical development program were consistent with

International Conference on Harmonization (ICH) E1A and allow for sufficient characterization and quantification of the safety profile of isavuconazole.

1.5.2.1 Overview of Clinical Pharmacology

Clinical Pharmacology

Forty phase 1 studies with 1322 subjects provided a thorough characterization of the clinical pharmacology of isavuconazole and included 2 bioavailability (BA) studies, 1 food effect (FE) study, 8 single- and multiple-ascending dose (SAD and MAD) pharmacokinetic studies in healthy subjects and special populations, 2 mass balance (MB) studies, 2 pharmacodynamic thorough QTc (QT interval corrected for heart rate) studies and 25 drug-drug interaction studies. A brief summary of the pharmacology of isavuconazole is provided herein.

The pharmacokinetics of isavuconazole are linear and dose-proportional following both oral and IV administration. Isavuconazole has a long half-life (~130 hours) enabling once daily maintenance dosing. Further, with rapid absorption, oral bioavailability of 98%, bioequivalence of AUC and an absence of a food or gastric pH effect, isavuconazole can be administered via both routes of administration under fed or fasting conditions or with medications that alter gastric pH with no need for dose adjustment.

The IV formulation of the highly soluble prodrug, isavuconazonium, does not include cyclodextrin. Upon administration, the prodrug is readily hydrolyzed in plasma by esterases ($t_{1/2}$ of 2 minutes) to isavuconazole, which is then slowly metabolized in the liver via CYP3A4 followed by the formation of glucuronides by uridine diphosphate-glucuronosyltransferase (UGT). In both healthy subjects and subjects with renal impairment, < 1% of unchanged isavuconazole was found to be eliminated by the kidney. In a special population study, the pharmacokinetics of isavuconazole were not affected by the level of estimated glomerular filtration rate (eGFR); therefore, there is no need for an isavuconazole dose adjustment in subjects with renal impairment or end stage renal disease (ESRD).

Isavuconazole has moderate interindividual pharmacokinetic variability, potentially limiting the risk of subtherapeutic or supratherapeutic exposure.

A summary of the involvement of key CYP enzymes in the metabolism of azole antifungal agents and the effect of azole antifungal agents on concomitant medications, respectively, is provided in [Table 1] and in the bullets below.

Table 1 Effect of Isavuconazole and Voriconazole on Substrates of CYP Enzymes

CYP	Substrate	Isavuconazole	Voriconazole[13,25,26]
3A4	Midazolam	↑ 2.05-fold	↑ 10.3-fold
	Sirolimus	↑ 1.84-fold	↑ 11.0-fold
1A2	Caffeine	NCS	NCS
2C8	Repaglinide	NCS	NCS
2C9	Warfarin	NCS	↑ 2-fold (PT)
2C19	Omeprazole	NCS	↑ 4-fold
2B6	Bupropion	↓ 42%	↑ 1.3-fold
2D6	Dextromethorphan	NCS	NCS

CYP: cytochrome P 450 enzymes; NCS: not clinically significant; PT: prothrombin time.

- Isavuconazole is a sensitive substrate of CYP3A (5-fold increase in isavuconazole AUC with concomitant ketoconazole), a mild-to-moderate inhibitor of CYP3A4 and a mild inducer of CYP2B6 [Table 1].
- Isavuconazole does not inhibit or induce CYP1A2, CYP2C9 or CYP2C19 and does not inhibit CYP2A6 and CYP2D6.
- Isavuconazole is a mild inhibitor of P-glycoprotein (P-gp), human organic cation transporters (OCT1/OCT2) and human multidrug and toxin extrusion (MATE1).
- Isavuconazole has no inhibitory effects on sensitive substrates of breast cancer resistance protein (BCRP), human organic anion transporters (OAT1/OAT2), organic anion-transporting polypeptide (OATP1B1/OATP1B3) or MATE2-K, but does have mild indirect inhibitory effects on substrates of UGT.
- Isavuconazole proposed labeling will recommend the following:
    - Contraindication of concomitantly administered strong inducers or strong inhibitors of CYP3A.
    - Therapeutic drug monitoring of cyclosporine, sirolimus and tacrolimus concentrations, if coadministered.
    - Monitoring digoxin levels when coadministered with isavuconazole.
    - Monitoring for mycophenolic acid (MPA)-related toxicity when isavuconazole is coadministered with mycophenolate mofetil (MMF).
- In addition, the proposed isavuconazole label will include the following:
    - Note that decreased systemic exposure to CYP2B6 substrates (bupropion) occurs when coadministered with isavuconazole.

Historically, antifungal agents in the azole class are known to prolong the QT interval. Isavuconazole caused QTcF (QT interval corrected for heart rate by Fridericia's formula) interval shortening in a thorough QT study. The largest shortening occurred at 2 hours (-13 msec [90% Confidence Interval (CI): -17.07%, -9.13%]) for the proposed maintenance dose (200 mg qd). The clinical importance of drug-induced QTc shortening is unknown.

1.5.2.2 Overview of Efficacy

Primary evidence for the efficacy of isavuconazole in the treatment of patients with IA comes from a randomized (1:1), double-blind, multicenter, non-inferiority and comparative group study (0104); whereas, the primary evidence for efficacy in the treatment of patients with IM

comes from an open-label, multicenter, single arm, phase 3 study (0103). Both studies were conducted globally. These studies included patients that are representative of the target patient population.

Invasive Aspergillosis (IA)

In Study 0104, male and female patients, ≥ 18 years of age with proven, probable and possible IFD defined according to criteria consistent with those established by the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) were eligible for enrollment.[27] Of the 527 patients in Study 0104, 516 patients were randomized to isavuconazole (258) or voriconazole (258), received at least one dose of study drug and were included in the intent-to-treat (ITT) analysis population. A blinded, independent DRC assessed patients' IFD diagnosis and overall response.

The modified ITT (mITT) analysis population (patients in the ITT who had a proven or probable IFD as determined by the DRC) consisted of 272 patients (143 isavuconazole and 129 voriconazole).

In Study 0104, isavuconazole demonstrated effectiveness for the treatment of patients with IA:

- The primary objective of the study was met as isavuconazole was non-inferior to voriconazole for all-cause mortality through day 42 in the ITT analysis population [see Table 12].
    - All-cause mortality through day 42 was 18.6% and 20.2% in the isavuconazole and voriconazole treatment groups, respectively, with an adjusted treatment difference (isavuconazole–voriconazole) of -1.0.
    - The upper bound of the 95% CI (-7.759, 5.683) for the adjusted treatment difference was lower than the prespecified non-inferiority margin (NIM) of 10%.
- Comparable results were seen for all-cause mortality across sensitivity analyses [Table 13, Figure 20 and Figure 21], populations and time points [Figure 17 and Figure 19] and subgroups [Figure 18] in IA, further supporting the effectiveness of isavuconazole.
- The results from analysis of the key secondary endpoint of success for DRC-assessed overall response in the mITT analysis population support the efficacy of isavuconazole [see Table 15].
    - Success rates for DRC-assessed overall response at end of treatment (EOT) were similar between isavuconazole and voriconazole treated patients (35.0% and 36.4%, respectively) with an adjusted treatment difference (voriconazole–isavuconazole) of 1.6.
    - The upper bound of the 95% CIs (-9.336, 12.572) for the adjusted treatment difference was below the 15% interpretive margin agreed upon with the FDA.
- DRC-assessed overall responses across the various prespecified analytical populations were similar to those observed for the mITT analysis population [see Figure 22].

In summary, the results of Study 0104 demonstrated that isavuconazole is as effective as voriconazole, the current gold standard, for the treatment of IA.

Invasive Mucormycosis (IM)

Study 0103 included male and female patients ≥ 18 years of age with proven, probable or possible IA with renal impairment or patients with proven or culture positive IFD caused by rare moulds, yeasts or dimorphic fungi (excluding *Aspergillus fumigatus* and *Candida* spp.).

An independent DRC assessed 37 patients to have proven or probable IFD attributed to an organism of the Mucorales order, 21 of whom received isavuconazole as primary therapy. A matched control analysis was conducted to support data interpretation for the patients who received isavuconazole for primary therapy relative to the patients who received amphotericin-based therapy.

Isavuconazole demonstrated effectiveness for the treatment of patients with IM:

- All-cause mortality through day 42 was 37.8% in the mITT-Mucorales population.
- The success rate for DRC-assessed overall response at the EOT was 31.4% in the mITT-Mucorales population.
- Isavuconazole demonstrated activity for the treatment of IM:
    - In the matched-case control analysis, crude mortality through day 42 in patients receiving isavuconazole as primary therapy in Study 0103 was 33.3% relative to 39.4% in patients receiving amphotericin-based treatment as primary therapy from matched controls from the Fungiscope Registry database [see Table 36].
    - The overall mortality rate (37.8%) for isavuconazole treated patients was similar to the mortality rate for amphotericin treated patients reported in the literature (37.8%) [Table 37 and Table 38]. Isavuconazole was also shown to have a clear treatment effect for all-cause mortality relative to untreated literature controls, which have a mortality rate approaching 100% [Figure 28].
- The activity of isavuconazole was demonstrated to be superior to that of placebo and similar to that of liposomal amphotericin in animal models of mucormycosis [see Figure 6, Figure 7 and Figure 8].

In summary, the results of Study 0103 show that isavuconazole demonstrated effectiveness for the treatment of IM when taken in context with the following: the large randomized, active-controlled study showing efficacy in IA; effectiveness in animal models of mucormycosis; in comparison with amphotericin treated matched controls; and relative to literature controls in amphotericin treated and untreated patients. Isavuconazole also offers an oral option for the treatment of this disease.

1.5.2.3 Overview of Safety

The clinical safety of isavuconazole was evaluated in subjects enrolled in 40 phase 1 studies and in patients enrolled in 4 phase 2 and phase 3 studies. A total of 547 patients were

included in the safety evaluation in the phase 2 and 3 studies, 144 patients in the phase 2 studies and 403 patients in the phase 3 studies.

The safety presentation provides an overview of safety results from the clinical development program for isavuconazole with a focus on Study 0104 and comparative safety with voriconazole in the Safety Population.

In the overall study, the mean age of patients was 51 years and the majority of patients were White (78.1%), ≤ 65 years of age (77.9%) and male (59.7%). The population of patients enrolled in Study 0104 is representative of the patient population likely to receive antifungal treatment for proven, probable or possible IFD. The high morbidity of this population was shown by the high prevalence of hematologic malignancy (83.9%), with many patients in an immunocompromised state because of neutropenia (65.5%; defined as absolute neutrophil count [ANC] < 0.5 x 10^9/L), T-cell immunosuppressant use (42.6%) and corticosteroid use (16.9%). In addition, the patient's immunocompromised state was likely exacerbated by the high rate of active malignancy (69.8%), which may also require chemotherapy. These characteristics are present in a similar proportion of patients in both treatment groups as shown for the ITT Population in [Section 7.3].

The median duration of IV dosing was 5 days in both treatment groups. The total (IV and oral) duration of study drug administration in the ITT Population was similar between treatment groups and is presented in [Section 7.3.3].

In active-controlled Study 0104, overall safety results were generally comparable between treatment groups. Differences were noted between the respective isavuconazole and voriconazole treatment groups especially for study drug-related adverse events (42.4% and 59.8%).

When treatment-emergent adverse events (TEAEs) regardless of causality were analyzed by system organ class (SOC), a lower proportion of patients in the respective isavuconazole treatment group compared to the voriconazole treatment group had TEAEs in the Skin and Subcutaneous Tissue Disorders (33.5% vs 42.5%), Eye Disorders (15.2% vs 26.6%) and Hepatobiliary Disorders (8.9% vs 16.2%) SOCs. These differences were driven by events of rash, erythema and drug eruption; visual impairment, photophobia and reduced visual acuity; and hyperbilirubinemia, abnormal hepatic function, jaundice and cholestasis.

More than half of the patients experienced at least one serious TEAE (isavuconazole 52.1%, voriconazole 57.5%). The overall proportion of patients with serious TEAEs was similar between treatment groups.

No new safety issues were identified in Study 0103 compared to the safety profile observed in Study 0104.

In summary, isavuconazole was safe and well tolerated in the treatment of patients with IA and other filamentous fungi.

1.6 Benefit-Risk

Alternative therapies are needed for the treatment of IA and IM. Mortality remains high in both of these rare infections. Patients whose IA progresses or who are intolerant of voriconazole have few viable options and there are no approved primary treatments for IM other than amphotericin B deoxycholate, which is poorly tolerated over the necessary treatment course of IM.

Results from studies of the oral and IV formulations of isavuconazole are summarized below:

- The IV formulation of the prodrug, isavuconazonium, does not include cyclodextrin. Further, < 1% of unchanged isavuconazole is cleared by the kidney, allowing IV administration of isavuconazole in patients with renal impairment and ESRD.
- Isavuconazole has dose-proportional, predictable (linear) pharmacokinetics.
- Isavuconazole has moderate interindividual pharmacokinetic variability, potentially limiting the risk of subtherapeutic or supratherapeutic exposure.
- Isavuconazole has a long half-life enabling once daily maintenance dosing. Further, with rapid absorption, oral bioavailability of 98%, bioequivalence of AUC and an absence of a food or gastric pH effect, isavuconazole can be administered via both routes of administration under fed or fasting conditions.
- A more manageable drug-drug interaction profile was observed with isavuconazole than with other mould-active azoles.

Isavuconazole demonstrated efficacy in the studies of IA and IM:

- Isavuconazole demonstrated non-inferior efficacy compared to voriconazole for the primary endpoint of all-cause mortality through day 42 in IA.
- Comparable results between treatment groups were seen for all-cause mortality across sensitivity analyses, populations, time points and subgroups, demonstrating the robustness of the results of isavuconazole in IA.
- The results from analysis of the key secondary endpoint of success for DRC-assessed overall response in the mITT analysis population also support the efficacy of isavuconazole in IA.
- For IM, the results of Study 0103 showed that isavuconazole demonstrated effectiveness for the treatment of IM with similar mortality outcomes relative to amphotericin-treated matched and literature controls, with a large treatment effect relative to untreated literature controls. In animal models of mucormycosis, superior efficacy to placebo and similar efficacy to liposomal amphotericin was demonstrated.

Isavuconazole safety profile:

- Isavuconazole demonstrated a favorable safety profile compared to voriconazole:
    - Fewer isavuconazole than voriconazole treated patients experienced TEAEs considered by the investigator to be related to study drug.
    - Fewer isavuconazole treated patients experienced adverse events in the skin, eye and hepatobiliary disorders SOCs than voriconazole treated patients.

Historically, antifungal agents in the azole class are known to prolong QT interval; in contrast, isavuconazole induces QTc shortening as characterized in a thorough QTc study. The clinical importance of drug-induced QTc shortening is unknown. The proposed label indicates the degree of QTc shortening induced by isavuconazole and includes a contraindication for Short QT syndrome (SQTS) and a warning regarding the potential for QTc shortening and risk if used with other medications known to shorten QT. Describing drug-related QTc shortening in the label should avoid treatment of subjects with rare SQTS. There is a precedent for this approach in the rufinamide FDA approved label.[28]

In summary, results from the development program showed that isavuconazole has a favorable benefit-risk profile and offers a needed alternative for the treatment of life-threatening IA and IM fungal infections.

2 BACKGROUND/OVERVIEW OF ISAVUCONAZOLE

2.1 Brief Therapeutic Background

2.1.1 Invasive Aspergillosis (IA)

IA is a life-threatening angio-invasive infection that is seen predominantly in severely immunocompromised patients. Patients at greatest risk for IFD are those with prolonged neutropenia related to antineoplastic chemotherapy and/or HSCT, those receiving immunosuppressants following SOT and those given high doses of corticosteroids.[,5,7,8]

A number of retrospective analyses of large databases from US hospital discharge and death records showed an estimated 10,190 aspergillosis-related hospitalizations annually in the US resulting in 1,970 deaths in 1996. These cases represented 38 hospitalizations per million.[29]

Hospital discharge data for patients with a primary or secondary diagnosis of aspergillosis were extracted from the 2003 Nationwide Inpatient Sample (NIS) and the fiscal year 2003 Medicare Provider Analysis and Review file. The NIS contains a total of over 38 million projected hospital discharges. From these, 10,400 aspergillosis cases were identified resulting in a US incidence rate of 36 per million per year![9]

Based on the above, we estimate that there are approximately 12,000 cases of IA in the US per year.

The clinical presentation of IA can be nonspecific with symptoms such as fever, cough, sputum production, pleuritic pain, hemoptysis and dyspnea. Even with available serologic testing for galactomannan, diagnosis can be difficult.

One of the largest reports of autopsy data from more than 1000 patients with hematological malignancies treated at MD Anderson Cancer Center revealed that 31% of patients had IFD at autopsy![10]Importantly, 75% of these infections were not diagnosed prior to death. Even in the era of galactomannan testing, diagnosis remains difficult. In 2008, Sinkó and colleagues[11] reported on a consecutive series of 38 allogeneic stem cell recipients who died; all had autopsies performed, 10 patients were found to have died with IFD. Despite the regular use of galactomannan testing, a diagnosis of proven or probable IFD prior to death could only be

established in 4 of 10 autopsy verified cases. In the remaining 6 patients, invasive mycoses were missed premortem and were revealed only by postmortem histology. Three of these patients did in fact have IA. Two patients were diagnosed with pulmonary mucormycosis and one with disseminated candidiasis.

Thus, patients continue to die of IFD that may not be diagnosed until after death, despite aggressive diagnostic testing. So, clinicians need to have a high index of suspicion and treat patients with possible, meaning suspected, disease. Treatment is, therefore, initiated with systemic antifungal agents when IFD is suspected and continued until an alternative etiology is identified.

IA is commonly treated with systemic antifungal agents, such as polyenes, mould active triazoles and echinocandins. Amphotericin B was the first-line of therapy for IA for many years but its use was associated with significant toxicity and a lack of efficacy in high-risk patients.[30,31] While lipid-associated formulations of amphotericin B were developed to circumvent the nephrotoxic potential of amphotericin B, renal- as well as infusion-related toxicities continue to be treatment limiting with no improvement in outcomes.[32]

There are several antifungal agents approved by the FDA for the treatment of IA including amphotericin products, itraconazole, voriconazole and caspofungin; however, the current treatment guidelines, issued in 2008 by the IDSA, recommend voriconazole as first-line therapy.[6] The basis for this is a study that demonstrated reduced mortality and improved outcomes in patients receiving voriconazole compared to amphotericin B for primary therapy of IA. A mortality rate of 30% was reported for voriconazole treated patients in the first 12 weeks of treatment.[12]

Despite the introduction of voriconazole, IA still remains a difficult to treat and life-threatening disease. While voriconazole demonstrates good activity against *Aspergillus* strains, its safety profile limits its use in a number of patient populations. Voriconazole administration is associated with visual disturbances, with blurred vision, photosensitivity and altered color perception being the most commonly noted.[32,33] Additional known side effects of voriconazole include skin reactions, hallucinations, serious hepatic reactions and QT prolongation.[13] Further, the use of cyclodextrin in the voriconazole solution for IV administration limits the use of the IV formulation in patients with moderate to severe renal dysfunction.[13]

For patients who are intolerant of or progress on voriconazole, there is little consensus as to the next course of action. The addition of another agent or switch to a different drug class for salvage therapy may be considered, such as lipid-associated formulations of amphotericin B, caspofungin or posaconazole, either as monotherapy or in combination. The clinical benefit of combination therapies against IA remains unclear. A large randomized, double-blind study comparing the combination of voriconazole plus anidulafungin versus voriconazole alone for the treatment of IA was inconclusive for the general population.[34] Currently, routine administration of combination antifungal treatment regimens in first-line therapy for IA is not recommended, but may be considered in salvage situations.[6]

2.1.2 Invasive Mucormycosis (IM)

IM is a devastating fungal infection caused by the filamentous fungi of the Mucorales order of the subphylum Mucoromycotina.[14,15] The majority of human IM infections are caused by fungi belonging to the genera of *Rhizopus, Mucor*, *Rhizomucor, Cunninghamella* and *Absidia*.[35,36]

Many of the conditions predisposing patients to IM are similar to IA and include hematological malignancy with or without stem cell transplantation and prolonged neutropenia. Other groups of patients at risk are those with poorly controlled diabetes mellitus with or without diabetic ketoacidosis, dialysis patients with iron overload as well as in patients with trauma or burns.[16]

The presentation of pulmonary IM often resembles that of IA or other invasive fungal infections. Other clinical forms include rhinocerebral, GI, cutaneous and disseminated disease.[14]

Due to the relative rarity of the disease, it is difficult to perform stringent epidemiological studies to estimate the exact incidence of IM. Data on incidence estimates for mucormycosis is very limited. In 2005, a review of the English-language literature from 1885 to 2003 only identified 929 cases of IM.[19] While the incidence has been reported to be increasing, it remains much less common and less well-studied than IA. The best estimates of incidence come from analyses of specific at-risk populations such as hematological patients or patients who have undergone transplantation. TRANSNET, a multicenter network of 23 academic tertiary care medical centers in the US, performed prospective surveillance for invasive fungal infections from 2001 through 2006. They detected Mucorales in 105 patients, 77 HSCT recipients and 28 SOT recipients. Follow-up data were available for 15,820 HSCT recipients from 22 sites. Overall 12-month cumulative incidence for mucormycosis in HSCT recipients was 0.29%. Follow-up data were available for 16,457 SOT recipients from 15 sites. In SOT recipients, the overall 12-month cumulative incidence of mucormycosis was 0.07%.[20] Rees and colleagues reported on a population-based active laboratory surveillance for mucormycosis from 1992 through 1993 that found approximately 500 cases per year in the US.[21]

The therapeutic approach to IM is multimodal and includes treatment of the underlying condition, surgical debridement and antifungal therapy. Surgical debridement in areas of tissue infarction and necrosis helps to reduce the mass of organisms, prevent extension of the infection and is strongly recommended in the most recent guidelines.[17] Although improving chances for survival, extensive surgical debridement often led to severe debilitating consequences such as blindness, facial disfiguration, amputations or pneumonectomy.[37,38,39]

Antifungal treatment guidelines are based primarily on case series and expert opinion. No randomized, well-controlled comparative antifungal treatment studies have been published. Although amphotericin B deoxycholate is the only antifungal approved for the treatment of IM, the most recent guidelines (2013) issued by the ECIL-3 and the ESCMID/ECMM recommend the use of lipid formulations of amphotericin B as first-line therapy, with

posaconazole and a combination of a polyene and an echinocandin recommended as options in salvage therapy.[17,24] Currently, there are no guidelines issued in the US for the treatment of IM.

Amphotericin B treatment has been associated with the development of severe renal toxicity, which has been associated with prolonged hospital stay and is a predictor of mortality.[22,23]

In a review of the literature, an overall mortality rate of 97% was seen in cases of mucormycosis that were not treated.[19] Despite aggressive surgical and antifungal treatments, IM is associated with high mortality. Published mortality rates vary widely depending on the underlying disease and extent of infection. Mortality rates were 66%, 44% and 96% in patients with hematologic malignancy, diabetes and disseminated disease, respectively.[19] In patients with IM (1991 through 2011) who had mixed underlying conditions (e.g., hematological malignancies, SOT, diabetes, etc.) and received amphotericin-based treatment, publications cited mortality rates that ranged from 35% to 61% [see Section 8.4.6].

2.1.3 Summary

IA and IM are rare infections primarily occurring in severely immunocompromised patients. The difficulty in diagnosis and high mortality necessitates that the treating physicians have a high index of suspicion and institute therapy early when an IFD is suspected. Unfortunately, there are a limited number of therapeutic options and the preferred agents have significant limitations. For IA, voriconazole is the preferred agent, but requires cyclodextrin in its IV formulation. Voriconazole has significant pharmacokinetic variability and a side effect profile that necessitates drug discontinuation in some patients. For IM, amphotericin B is the only approved therapy, and it is available only in an IV formulation and has significant renal toxicity that limits use over the required treatment duration. There is a significant need for alternative antifungal therapies that address some of the limitations of voriconazole in IA and amphotericin B in IM. Given the difficulty in diagnosis and similarity with which IA and IM may present, having an antifungal that is effective for both indications would be particularly useful to physicians treating these seriously ill patients.

2.2 Pharmacological Class

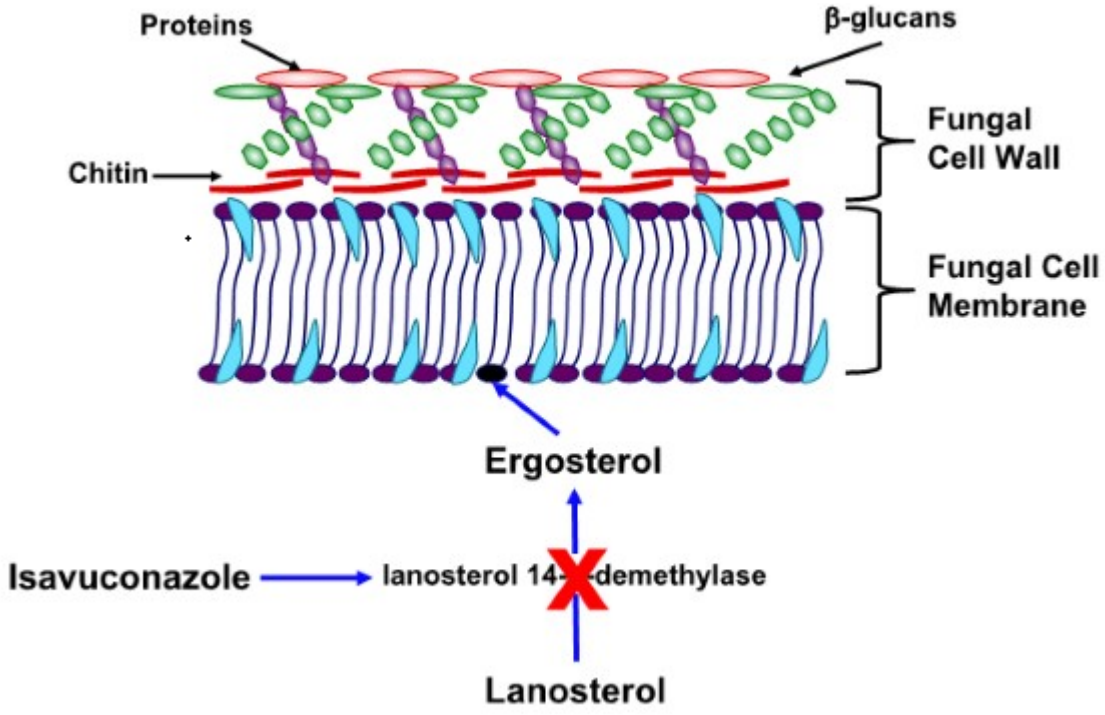
Isavuconazonium is a novel, water-soluble prodrug of the triazole isavuconazole, which is a broad spectrum antifungal agent.

Unlike the IV formulations of other mould-active azoles, isavuconazonium is administered as a water soluble prodrug that does not require the addition of cyclodextrin to enable solubility and, therefore, has a reduced risk of nephrotoxicity

2.3 Mechanism of Action

Isavuconazole inhibits lanosterol 14-alpha-demethylase, which is responsible for the synthesis of ergosterol, a key component of the fungal cell membrane. Inhibition of this CYP enzyme results in the accumulation of methylated sterol precursors and the depletion of ergosterol thereby weakening the structure as well as compromising the function of the fungal cell membrane [Figure 2].

Figure 2 Isavuconazole Mechanism of Action in Fungal Cells



3 REGULATORY AND DEVELOPMENT HISTORY

An overview of the timeline of the global development of isavuconazole is shown in [Figure 3].

In 2002, Basilea Pharmaceutica International, Ltd., Basel, Switzerland, submitted the Clinical Trial Authorization (CTA) and began the first phase 1 study of isavuconazole in healthy subjects. The Investigational New Drug (IND) application was submitted in 2005 and the phase 3 studies were initiated in 2007 and 2008. In 2009, enrollment was suspended to allow for the completion of in vivo genotoxicity studies of a newly identified impurity. The in vivo studies were successfully completed and supported the resumption of enrollment.

In February 2010, Astellas licensed the development and marketing rights for isavuconazole and assumed responsibility for the sponsorship of the clinical development program. Astellas re-initiated enrollment in the phase 3 studies in 2011.

Regulatory interactions with the Division of Anti-Infective Products (and the former Division of Special Pathogens and Transplant Products) were held at regular intervals during the development of isavuconazole. The interactions included discussions regarding the design and analyses for phase 3 Studies 0104 and 0103.

Specifically, the study design for Study 0104 was addressed and agreement with the FDA was reached on the study endpoints. In conjunction with FDA discussions, the primary endpoint of overall response in the initial 0104 protocol was changed to all-cause mortality. The primary reason for this modification was to support the justification of the NIM, which

requires documentation of a placebo response rate that is available in the literature for all-cause mortality, but not for overall response. The NIM for the all-cause mortality endpoint is 10%. This modification resulted in an increase in sample size, but no change in the overall conduct of the study. Overall response was retained as a key secondary endpoint.

The 0104 protocol design was also in accordance with the FDA draft guidance for industry: Non-inferiority clinical trials, 2010. Agreement on the Statistical Analysis Plan for Study 0104 was received from the Division in June 2013 and recommendations from the Division were incorporated prior to unblinding of the database, including agreement on a 15% interpretive margin for the key secondary endpoint.

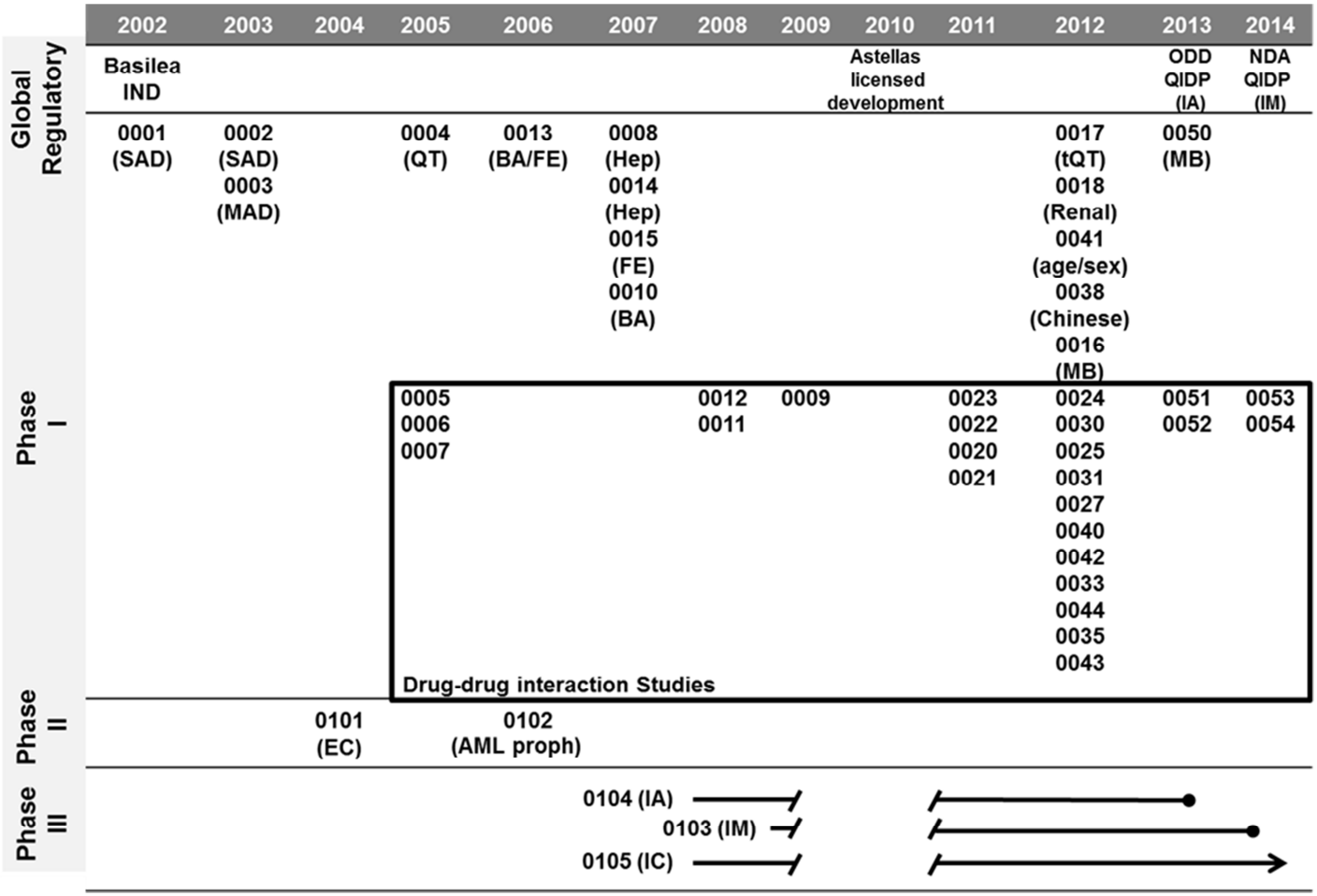
The FDA specified that for rare fungal pathogens, such as Mucorales, efficacy be demonstrated in a minimum of 20 well-documented cases where the study drug is used as initial therapy or in refractory disease in patients who received limited prior antifungal treatment. While such data could not be utilized alone to support an approval, it could be assessed within the context of a larger NDA submission supporting efficacy in a more common invasive fungal infection and including data from animal models (FDA communication received June 5, 2006). Therefore, to support the indication of treatment for IM, results from the open-label, single-arm Study 0103 are supported by the efficacy of isavuconazole in Study 0104 in the treatment of patients with IA, data from studies in animal models and information on the natural history of mucormycosis, including mortality rates in untreated and treated patients from the literature. In addition, a matched-case control analysis was conducted to provide further context relative to the interpretation of the results. The Division agreed that the phase 3 study designs would support the filing of an NDA for the treatment of IA and IM.

The FDA has granted QIDP status for isavuconazole (in accordance with the GAIN Act) for the IA (Nov 2013) and IM (Feb 2014) indications. The GAIN Act was passed in 2012 in response to the increasing incidence of resistant and emerging organisms to stimulate the development of new anti-infectives. The GAIN Act provides additional exclusivity for certain antibacterial and antifungal drugs intended to treat serious or life-threatening infections. Under the GAIN Act, an application for a QIDP is eligible for both Priority Review and Fast Track designation programs for expediting drug development.

The Orphan Drug Designation program provides orphan status to drugs intended for treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the US. The FDA OOPD granted isavuconazole Orphan Drug Designation for the treatment of IA (May 2013) and for the treatment of zygomycosis (now referred to as mucormycosis) (Oct 2013).

In parallel with US regulatory interactions, discussions with the European regulatory authorities were held. Shortly after Astellas submitted the NDA to the FDA, the European Marketing Authorisation Application (MAA) was filed by Basilea Pharmaceutica International, Ltd. for isavuconazole treatment of IA and IM.

Figure 3 Isavuconazole Clinical Development Program Timeline



Enrollment was put on hold from January 2009 to March 2011 to allow for the completion of genotoxicity studies of a newly identified impurity [Section 4.4.2].
Enrollment in Study 0105 is ongoing.
AML: acute myeloid/myelogenous leukemia; BA: bioavailability; EC: esophageal candidiasis; FE: food effect; hep: hepatitis; IA: invasive aspergillosis; IC: invasive candidiasis; IM: invasive mucormycosis; IND: Investigational New Drug; MB: mass balance; MAD: multiple-ascending dose; NDA: New Drug Application; ODD: Orphan Drug Designation; QIDP: Qualified Infectious Disease Product; SAD: single-ascending dose; tQT: thorough QT.

4 NONCLINICAL STUDIES

4.1 Summary of the Nonclinical Study Results

- Toxicities observed in the toxicological assessment of isavuconazonium were similar across species and were consistent with toxicities expected for azole antifungal agents.
- Neither the prodrug (isavuconazonium) nor the active moiety (isavuconazole) showed genotoxic potential.
- The teratogenic potential of isavuconazole was noted in rats and rabbits and is also consistent with that previously noted for azole antifungal agents.
- Isavuconazole showed no discernible phototoxicity in vitro suggesting little or no in vivo risk for phototoxicity.

4.2 Safety Pharmacology

The standard battery of safety pharmacology studies was performed and demonstrated the following:

Central Nervous System (CNS): Isavuconazonium had no effect on general behavior (modified Irwin method), spontaneous activity, drug or electrical convulsive activity, acetic acid pain response or body temperature. Isavuconazonium did prolong pentobarbital sleep duration in mice (30 mg/kg; human equivalent dose 0.39-fold the clinical maintenance dose of 200 mg/day isavuconazole); however, this is thought to be secondary to CYP inhibition. Support for this conclusion comes from the observation that other azole compounds that inhibit CYP enzymes are also reported to prolong pentobarbital sleep duration.[40]

Cardiovascular System: In vitro, isavuconazole inhibited the hCav1.2 calcium channel with an IC_{50} that was 38-fold higher than the non-protein bound clinical C_{max}. This effect probably contributes to the QTc interval shortening observed clinically. Isavuconazole also inhibited the human ether-á-go-go-related (hERG) potassium current with IC_{50} values that were 34- to 113-fold the clinical non-protein bound C_{max}. Despite the inhibitory effects on potassium and calcium channel conductance, no statistically significant effect on the QTc interval (shortening or prolongation) was reported for cynomolgus monkeys.

Intravenous administration of isavuconazonium to monkeys at human equivalent doses up to 2.2-fold the clinical maintenance dose resulted in transient and reversible decreases in systolic and diastolic blood pressure during the infusion period. An increase in heart rate was also noted at the highest dose tested.

Respiratory System: There was no effect on respiratory rate or blood pH.

Renal System: There was no effect on electrolyte and water excretion.

GI and Autonomic Nervous Systems: There was no effect on GI transport; however, in vitro, isavuconazonium accentuated acetylcholine induced contraction of the guinea pig ileum, but had no effect on histamine or barium chloride induced contraction.

4.3 Pharmacokinetics

After a single-dose IV bolus administration, isavuconazonium was rapidly converted to the active moiety, isavuconazole (BAL4815) and the inactive cleavage product (BAL8728). In rats and cynomolgus monkeys, the elimination half-life ($t_{1/2}$) of isavuconazole after IV dosing was 5.07 and 9.84 h, respectively. Plasma clearance of isavuconazole was low and its distribution was large in monkeys. After a single-dose oral administration, isavuconazonium was not detected in the plasma, suggesting a rapid conversion of isavuconazonium in the intestinal tract and/or by a high first-pass metabolism in the intestine and liver as well as plasma. The C_{max} of isavuconazole was observed at 2 to 3 hours after oral dosing. The relative oral bioavailability of isavuconazole was 61.9% in rats and 86.9% in monkeys, suggesting a good oral absorption. Additionally, the inactive cleavage product (BAL8728) was not detected in the plasma of monkeys and detectable levels of the inactive cleavage product were only reported in rats at limited (earliest) sampling time points. In cynomolgus monkeys, oral administration of isavuconazonium with food reduced AUC of isavuconazole by 19%, C_{max} by 51% and delayed t_{max} from 3.33 to 5.00 hours.

Repeated-dose oral and IV toxicokinetic studies in rats and cynomolgus monkeys demonstrated that the AUCs of isavuconazole were almost dose-proportional and there were no indications of drug accumulation.

4.4 Toxicology

Pivotal safety pharmacology studies and toxicology studies were performed in compliance with the standards for nonclinical studies on drug safety (Good Laboratory Practice: GLP), in accordance with the Guidance for Industry Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals ICH M3(R2), in accordance with the Guidance for Industry Safety Pharmacology Studies for Human Pharmaceuticals (ICH S7A) and in accordance with Guidelines for General Pharmacology Studies (Notification 4 of the Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, Japan).

4.4.1 Single and Repeat Dose Studies

Single Dose

Single dose oral and IV administration studies with isavuconazonium were conducted in rats and cynomolgus monkeys. The oral 50% lethal dose (LD_{50}) values in male and female rats were estimated at 1024 mg/kg and 708 mg/kg, respectively. In the cynomolgus monkey, a single oral dose of 2000 mg/kg resulted in the death of 1 of 2 male animals (LD_{50}).

After IV administration, the LD_{50} values in rat were estimated at 10.2 mg/kg in males and 9.8 mg/kg in females at an infusion rate of 1 mL/min and > 20 mg/kg in both sexes after IV administration at an infusion rate of 0.1 mL/min. A similar finding with toxicity depending

upon the speed of administration was observed in cynomolgus monkeys. A single IV bolus injection of isavuconazonium at a dose of 64 mg/kg was lethal to monkeys (2/2 animals), while a 2-hour IV infusion at a dose of 120 mg/kg resulted in a 50% mortality rate.

Repeat Dose

Liver: The increased liver weights and centrilobular hepatocyte hypertrophy was attributable to induction of CYP enzymes in the animals (CYP3A and CYP2B in female rats and CYP2B in male and female cynomolgus monkeys), which is considered adaptive and not injurious.[41] The finding was reversible at the end of the recovery period.

Thyroid: The increased thyroid weights and cellular hypertrophy (increased small follicles) in rats are considered secondary to hepatocellular enzyme induction and are consistent with an adaptive physiological response in rodents.[42] Findings were reversible at the end of the recovery period.

Adrenal: The increased adrenal weight, cortical vacuolation and thickening of zona fasciculata observed in cynomolgus monkeys are hypothesized to be the result of increased steroid synthesis secondary to increased glucocorticoid metabolism due to CYP2B induction mediated by isavuconazole.[43,44] Findings were reversible at the end of the recovery period.

Vascular irritation: In the repeated dose rat and monkey studies, injection site irritation was seen with high dose. In those studies, vascular irritation was attributable to methodological limitations including repeated percutaneous injections of a high concentration solution of isavuconazole (approximately 5-fold the clinical concentration). In a local irritation study, at clinically relevant concentrations (0.5 – 1 mg/mL), there was limited protein extravasation (as measured by trypan blue), no injection site edema and no erythema.

4.4.2 Genotoxicity

Neither the prodrug, isavuconazonium, nor the active moiety, isavuconazole, showed genotoxic potential. The inactive cleavage product (BAL8728) did not trigger a genotoxic alert in the DEREK system. DEREK positive starting materials, intermediates and drug substance impurities with genotoxic potential were, with the exception of the drug substance impurity (BAL19714) and the degradation product (2-butenal), reduced to levels below the threshold of concern. BAL19714 was unstable in plasma and showed no genotoxic potential in vivo at doses over 6000-fold higher than the dose administered with isavuconazonium. The 2-butenal administered at the proposed specification was below the permissible exposure limits established by the Occupational Safety and Health Administration (OSHA) and therefore was not considered to pose an appreciable clinical genotoxic risk.

4.4.3 Carcinogenicity

Carcinogenicity studies were not performed for isavuconazonium because treatment duration is not expected to exceed 6 months.

4.4.4 Reproductive and Developmental Toxicity

Early embryonic development: Isavuconazonium had no effect on early embryonic development.

Embryo-fetal development: In rats and rabbits, skeletal abnormalities and variations were observed. A visceral variation was also noted in rabbits. These findings are consistent with those previously reported for azole anti-fungal agents.[45,46,47] Based on the preclinical findings of skeletal anomalies in both rats and rabbits at systemic exposures below that of the human systemic exposures, it is concluded that isavuconazonium, as a member of the azole class of anti-fungal agents, has the potential to adversely affect human embryo-fetal development and should only be considered for use in pregnancy when the benefit to the mother outweighs the risk to the fetus.

Pre and postnatal development: After IV administration of [cyano-^{14}C] isavuconazonium and [pyridinylmethyl-^{14}C] isavuconazonium to lactating rats, isavuconazole-derived constituents were excreted into milk. Isavuconazonium (90 mg/kg/day) orally administered to rats during pregnancy and through nursing resulted in an increased perinatal (lactation day 0 to 4) mortality of the pups.

4.4.5 Other Toxicity Studies

The effect of ocular exposure was evaluated in rabbits where it was shown that minimal eye irritation occurred following instillation in the conjunctival sac at concentrations of 5 or 10 mg/mL. These concentrations are at least 667-fold higher than the human C_{max} at the maintenance dose of 200 mg/day isavuconazole and, as such, suggest that the systemic levels achieved following oral or IV administration of isavuconazonium should pose little risk of eye irritation. Further support for this conclusion comes from the rat and monkey repeated dose studies where ophthalmologic assessments showed no indication of ocular toxicity. The data support the conclusion that isavuconazonium poses little risk for eye irritation or injury in the clinical setting.

Isavuconazole will be available for both oral and IV administration. As such, in vitro hemolysis assessments are necessary; and in those studies, it was observed that hemolysis of human blood cells could be induced by isavuconazonium at concentrations of at least 1 mg/mL. Because these concentrations are at least 133-fold higher than the human C_{max} at the maintenance dose of 200 mg/day isavuconazole, it is unlikely that the in vivo plasma concentrations would result in a similar outcome. Therefore, it is concluded that the risk of hemolysis is minimal.

Isavuconazole was shown to absorb light in the ultraviolet wavelength range (250 to 320 nm). As such, an in vitro assessment of phototoxicity was performed. Isavuconazole showed no discernible phototoxicity in vitro suggesting little or no in vivo risk for phototoxicity.

4.4.6 Summary of Observed Toxicities in Nonclinical Studies

Toxicities observed in the toxicological assessment of isavuconazonium were generally similar across species and were consistent with toxicities expected for azole antifungal agents. The key findings and exposure levels are summarized in [Table 2].

Table 2 Key Findings and Exposure Levels of Isavuconazole

Key Findings		Rat		Rabbit		Monkey	
		LOAEL (mg/kg/ day)	**X-Fold Human AUC**	**LOAEL (mg/kg/ day)**	**X-Fold Human AUC**	**LOAEL (mg/kg/ day)**	**X-Fold Human AUC**
Liver	Increased weight	M: 30 F: 90	M: 0.1† F: 0.5‡	ND	ND	M: >40 F: 40	M: > 0.7†† F: 0.8‡‡
	Hepatocellular hypertrophy	M: 30 F: 90	M: 0.1† F: 0.5‡	ND	ND	NP	ND
Thyroid	Increased weight	M: 90 F: 90	M: 0.3¶ F: 0.5‡	ND	ND	NP	ND
	Follicular cell hypertrophy	M: 90 F: 90	M: 0.3¶ F: 0.5‡	ND	ND	NP	ND
Adrenal	Increased weight	NP	ND	ND	ND	M: >40 F: >40	M: >0.7†† F: >0.8‡‡
	Enlarged vacuolated cortical cells	NP	ND	ND	ND	M: 40 F: 40	M: 0.7†† F: 0.8‡‡
Embryo-fetal	Fetal skeletal findings	6	0.2¶¶	45	0.1§	ND	ND

Human AUC at the maintenance dose of 200 mg/day isavuconazole = 121402 ng·h/mL.

LOAEL: Lowest Observable Adverse Effect Level; ND: Not determined; NP: Not present

†AUC = 12600 ng·h/mL; ‡AUC = 59400 ng·h/mL; ¶AUC = 37100 ng·h/mL; §AUC = 9833 ng·h/mL; ††AUC = 87800 ng·h/mL; ‡‡AUC = 98100 ng·h/mL**;** ¶¶AUC = 4560 ng·h/mL.

Taken collectively, the data provided in the nonclinical assessment provide an understanding of the efficacy and safety profile of isavuconazonium and supports the proposed routes and dose of administration to adult patients with systemic fungal infections.

5 MICROBIOLOGY

5.1 Summary of Microbiology of Isavuconazole

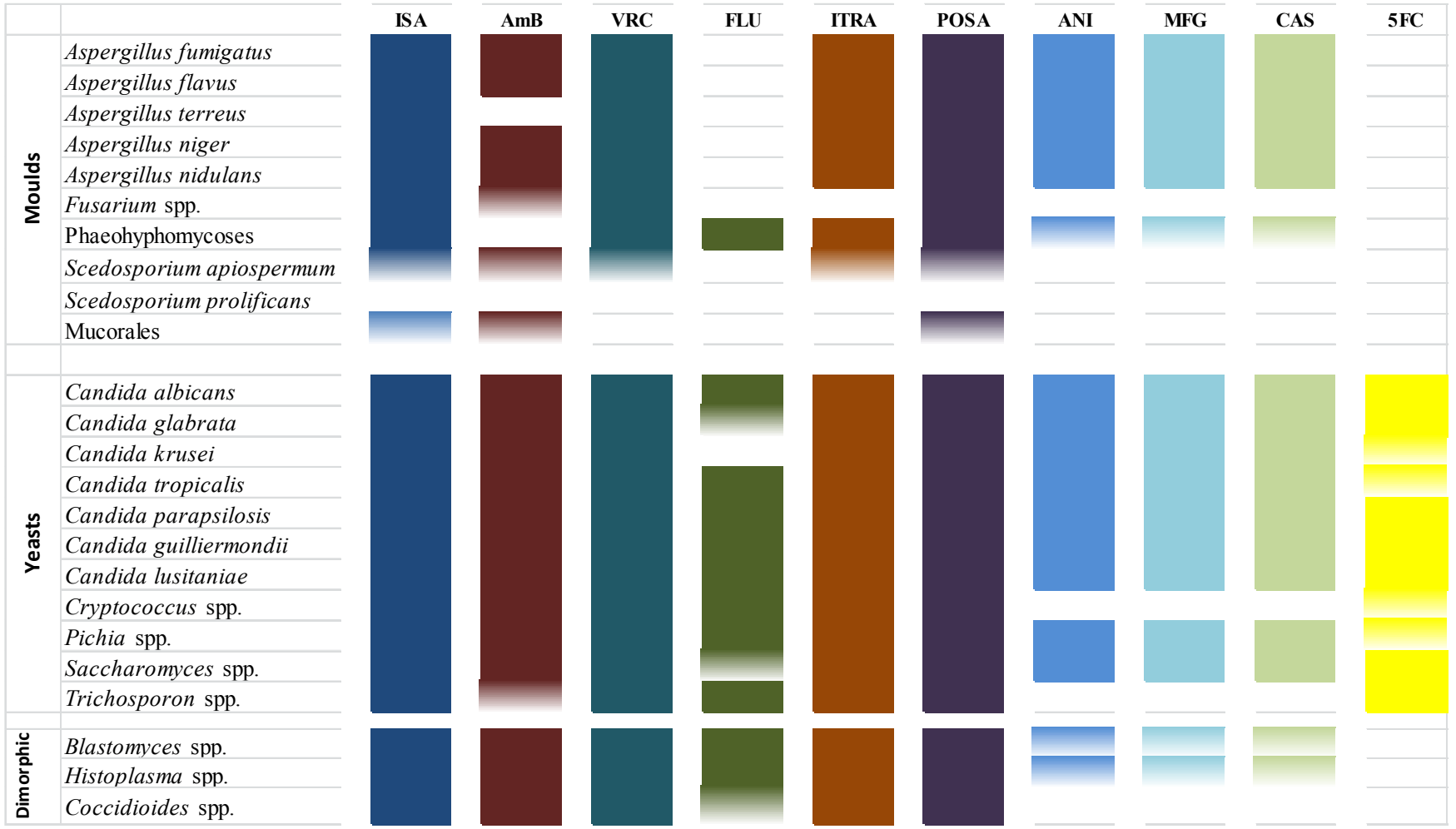
Isavuconazole has demonstrated activity against *Aspergillus* spp., several species of Mucorales, *Candida* spp. and other rare fungi, illustrating a broad spectrum of activity:

- Isavuconazole has potent activity against filamentous fungi including most strains of *Aspergillus* spp. with MIC_{90} ranging from 1 to 2 mg/L.
- Isavuconazole demonstrated in vitro activity against rare moulds such as Mucorales, including *Rhizomucor* spp., *Rhizopus* spp., *Absidia* spp., *Mucor* spp. and *Cunninghamella* spp.
- In vivo, isavuconazole reduced tissue fungal burden and increased the survival rate in animal models of *Aspergillus* spp. and *Rhizopus oryzae* fungal infections.
- Similar to other triazoles, the pharmacodynamic parameter AUC/MIC correlated best with treatment outcome for *Aspergillus* and *Candida* spp.
- Isavuconazole MICs for posaconazole- and itraconazole-resistant *Aspergillus fumigatus* strains with well-characterized CYP51A mutations were not impacted by mutations in the G54 region and had variable activity to strains with mutations at the M220 region, similar to voriconazole.
- Isavuconazole MICs for azole-resistant *Candida* spp. were not affected by multidrug resistance (MDR1) or fluconazole resistance (FLU1) transporters, unlike fluconazole and voriconazole.
- In vivo and in vitro dynamic models utilizing isolates with elevated MICs to azoles or well-characterized mutations in the target gene demonstrated that efficacy could be optimized by increasing isavuconazole exposure.

5.2 Microbiological Activity In Vitro

Isavuconazole demonstrates broad spectrum in vitro activity against a variety of important pathogenic fungi. An overview of the antifungal spectrum of activity of available antifungal drugs, including isavuconazole, against common moulds and yeasts is presented in [Figure 4].[48,49]

Figure 4 In Vitro Antifungal Spectrum of Activity of Antifungal Drugs against Common Moulds, Yeasts and Dimorphic Fungi



Completely filled cell = activity; shaded cell = variable activity; open cell = no activity.

5FC: 5-flucytosine; AmB: amphotericin B deoxycholate; ANI: anidulafungin; CAS: caspofungin; FLU: fluconazole; ISA: isavuconazole; ITRA: itraconazole; MFG: micafungin; POSA: posaconazole; VRC: voriconazole.

Isavuconazole has in vitro activity against most strains of the following organisms: *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus sydowi*, *Rhizopus oryzae*, *Lichtheimia (Absidia) corymbifera*, *Fusarium solani*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Cryptococcus gattii* and *Paracoccidioides brasiliensis*. Efficacy was demonstrated in patients from the phase 3 studies in which clinical isolates of these organisms were found to be the causative agent.

Isavuconazole demonstrated differential in vitro activity against *Aspergillus fumigatus* strains with well-characterized azole-resistant mechanisms that were dependent on the specific point mutation in the target enzyme. The activity tended to mirror the activity of voriconazole, but was different to that of posaconazole and itraconazole.

Isavuconazole also has in vitro activity against the clinically important rare moulds and yeasts. A summary of the MIC values for common *Aspergillus* spp. and Mucorales organisms are included in [Table 3]. The MIC_{90} values of isavuconazole against *Cryptococcus neoformans* and *Cryptococcus gattii* ranged from 0.0086 to 0.25 mg/L.

Table 3 Isavuconazole MIC Values for Common *Aspergillus* Species and Mucorales Organisms (CLSI)

Species	Isolates (n)	MIC Parameters (mg/L)			
		Min	Max	MIC_{50}	MIC_{90}
Aspergillus					
Aspergillus spp.	1,717	0.06	32	0.5	2
Aspergillus fumigatus	875	0.12	8	1	1
Aspergillus flavus	145	0.12	16	1	4
Aspergillus niger	101	0.12	32	1	2
Aspergillus terreus	432	0.06	32	0.25	1
Aspergillus nidulans	85	0.12	16	0.5	1
Mucorales					
Lichtheimia (Absidia) spp.	67	0.12	32	1	8
Cunninghamella spp.	13	0.25	32	4	32
Mucor spp.	68	0.12	32	4	16
Rhizomucor spp.	18	0.12	8	1	4
Rhizopus spp.	134	0.12	32	1	8

CLSI: Clinical and Laboratory Standards Institute; MIC: minimum inhibitory concentration.

Isavuconazole exhibits in vitro activity against *Candida* spp. including many fluconazole-resistant strains. Isavuconazole activity was unaffected by mutations in the MDR1 or FLU1 transporter genes in azole-resistant *Candida* spp. In addition, isavuconazole demonstrated MIC_{90} values of 1 μg/mL or less using Clinical and Laboratory Standards Institute (CLSI) methodology against the following species: *Candida albicans*, *Candida glabrata*, *Candida guilliermondii*, *Candida krusei*, *Candida lusitaniae*, *Candida parapsilosis* and *Candida tropicalis*.

5.3 MIC Distribution and Epidemiological Cut-off Values for *Aspergillus* Species

MIC frequency distributions and epidemiological cut-off values have been established for the major *Aspergillus* spp. for CLSI methodology.[50] Epidemiological cut-off values are defined

as the MIC value identifying the upper limit of the wild-type population. A microorganism is defined as wild-type for a species by the absence of acquired and mutational mechanisms of resistance to the agent. Epidemiological cut-off values are set by evaluating a large MIC dataset from multiple laboratories using a standard susceptibility test methodology and can assist in identifying isolates with raised MICs and/or a greater risk of the presence of a mechanism of resistance. The epidemiological cut-off values for isavuconazole against *Aspergillus* spp. are found in [Table 4].

Table 4 Epidemiological Cut-off Values for Isavuconazole (CLSI)

Organisms	Number of Isolates	ECV (CLSI methodology)† (mg/L)
Aspergillus fumigatus	855	1
Aspergillus flavus	444	1
Aspergillus niger	207	4
Aspergillus terreus	386	1

CLSI: Clinical and Laboratory Standards Institute; ECV: epidemiological cut-off value.

† Calculated ECVs comprising ≥ 95% and ≥ 97.5% of the statistically modeled MIC population.[50]

5.4 Microbiological Activity in Animal Models

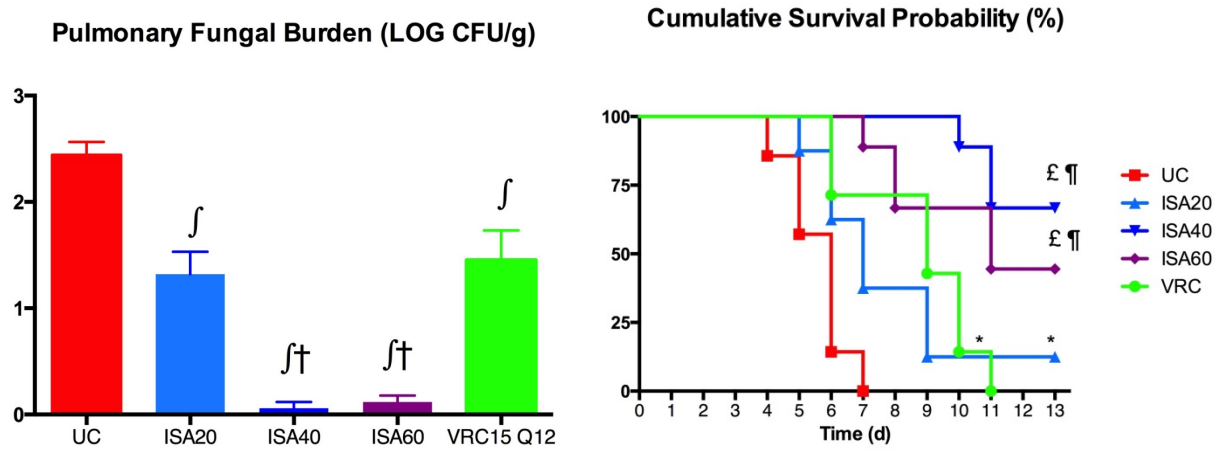
In vivo models of infection are a valuable tool to understand the antimicrobial activity of a compound in a controlled setting.[51] In infectious diseases, these models are highly predictive of clinical activity because the drug target is the organism and this activity can be easily measured in the experimental setting.

Aspergillosis

Isavuconazole has been tested in several models of systemic infection. Isavuconazole was active in immunocompromised and immunocompetent mice and immunocompromised rabbits with systemic and/or pulmonary infections due to *Aspergillus fumigatus* and in immunocompromised mice with systemic infections due to *Aspergillus flavus* (including isolates with known azole-resistance mechanisms). In each model, isavuconazole demonstrated potent in vivo activity through increasing survival and decreasing tissue fungal burden.

Isavuconazole showed consistent antifungal activity across multiple efficacy endpoints against invasive pulmonary aspergillosis in profoundly neutropenic rabbits. Results included significant reduction of residual fungal burden in the lungs, decreased pulmonary injury, prolonged survival, lowered galactomannan index in serum and bronchoalveolar lavage (BAL) fluid and lowered plasma (1-3)- β -D-glucan concentrations compared to untreated (UC) and active (voriconazole) controls. Graphical presentations of prolonged survival and reduction of pulmonary fungal burden by isavuconazole are provided in [Figure 5].

Figure 5 Isavuconazole Activity in a Rabbit Model of Pulmonary IA



Number of rabbits/group = 8.

CFU: colony forming units; IA: invasive aspergillosis; ISA: isavuconazole; UC: untreated controls; VRC: voriconazole.

∫ $P < 0.001$ for ISA-treatment groups and $P < 0.01$ for VRC-treatment group in comparison to that of UC.

† $P < 0.001$ in comparison to VRC.

¶ $P < 0.05$ in comparison to VRC.

£ $P < 0.001$ in comparison to UC.

* $P < 0.05$ in comparison to UC.

Mucormycosis

The efficacy of isavuconazole was also demonstrated in in vivo efficacy models of IM, which included 4 experimental mouse models of mucormycosis: diabetic ketoacidosis (DKA) and neutropenic models in mice with intratracheal mucormycosis infection and DKA and neutropenic models in mice with hematogenous disseminated mucormycosis (IV infection).

A sensitive strain of *Rhizopus oryzae* was used in mice made susceptible to infection by inducing DKA or neutropenia. Since most cases of mucormycosis infection are acquired through inhalation, the newly developed and validated intratracheal infection models in DKA and neutropenic mice were used as the primary models.[52] The intratracheal model was specifically developed via National Institutes of Health (NIH) funding (through a Task Order for development of Small Animal Models of Invasive Fungal Infections) to test drugs and immunotherapeutic interventions against mucormycosis.

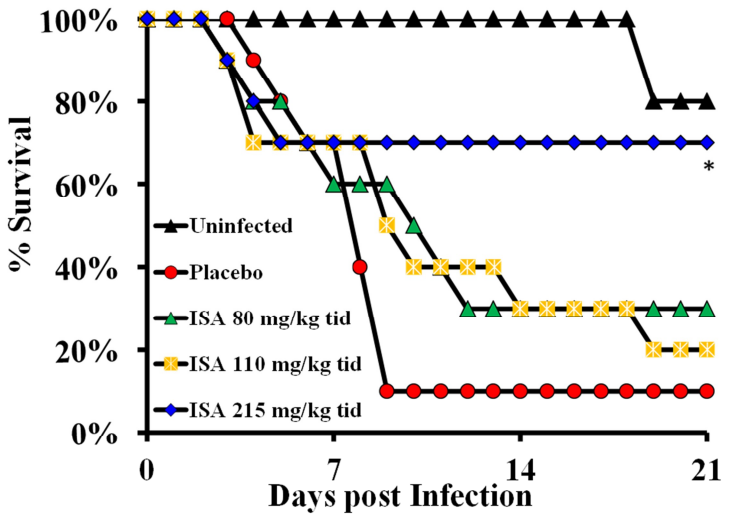
The goals of this study were to determine the in vivo efficacy of isavuconazole against experimental mucormycosis in mice and to compare isavuconazole efficacy with that of liposomal amphotericin B. First, a number of isolates of *Rhizopus oryzae* were tested in vitro for isavuconazole activity. In vitro MICs and minimal fungicidal concentrations (MFCs) ranged from 0.125 to 1 mg/L after 48 hours, showing that the isolates were susceptible to isavuconazole.

After immunosuppression, neutropenic or DKA mice were infected intratracheally with *R. oryzae* 99-880 and then treated with isavuconazonium prodrug (80, 110 and 215 mg/kg,

orally, 3 times daily) starting 8 hours after infection for a total of 5 days. Fungal burden was evaluated at the end of the dosing period and survival was evaluated through 21 days. Mice in the placebo group were infected intratracheally and treated with sterile water. There were 10 mice in each treatment group. In vivo efficacy was assessed by comparing the survival time of each group of mice.

Isavuconazonium 215 mg/kg given 3 times daily in neutropenic mice demonstrated enhanced efficacy compared to placebo (70% survival in the isavuconazonium treated mice versus 10% survival in the placebo treated mice after 21 days) [Figure 6].[53]

Figure 6 Survival Rates of Uninfected, Placebo-treated and Isavuconazonium-treated Neutropenic Mice in a Model of Mucormycosis Pneumonia



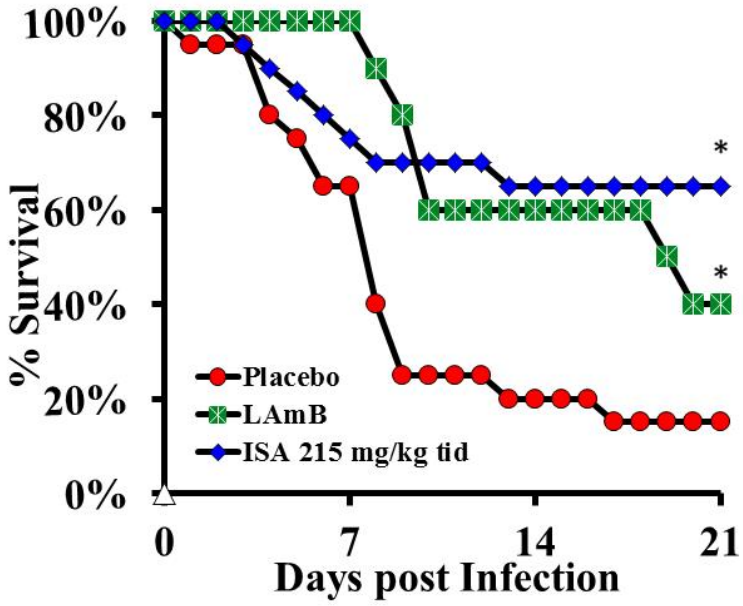
Number of mice/group = 10.

ISA: isavuconazonium.

* $P < 0.05$ compared to placebo-treated mice by Log Rank test.

The next experiment aimed to compare the in vivo efficacy of isavuconazole to high dose liposomal amphotericin B (the standard therapy in this model) in protecting mice from *R. oryzae* infection. Mice were rendered neutropenic and infected intratracheally, as described above, then treated with isavuconazonium prodrug (215 mg/kg, orally, 3 times daily) or with liposomal amphotericin B (15 mg/kg, once daily, intravenously). Mice in the placebo group were infected and administered a comparable volume of vehicle. Treatment started 8 hours post infection and continued for 5 days. Isavuconazole was as effective as liposomal amphotericin B in treating neutropenic mice with mucormycosis. After 21 days, the rates of survival for isavuconazonium-, liposomal amphotericin B- and placebo-treated mice were 65%, 40% and 15%, respectively [Figure 7].[53]

Figure 7 Effect of Treatment with Placebo, Isavuconazonium or Liposomal Amphotericin B on the Protection of Neutropenic Mice from Mucormycosis after Intratracheal *Rhizopus oryzae* Infection



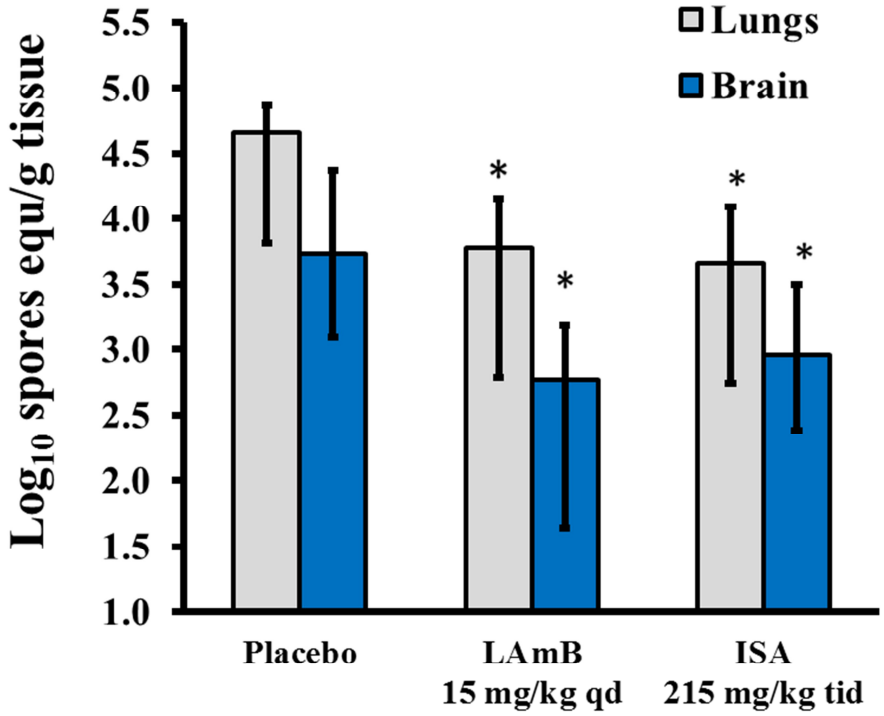
Number of mice = 20/group for placebo and ISA and 10/group for LAmB.

ISA: isavuconazonium; LAmB: liposomal amphotericin B.

* P = 0.025 or P = 0.004 for LAmB or isavuconazonium treated mice, respectively, compared to placebo treated mice by Log Rank test.

Since isavuconazole increased the survival rate of neutropenic mice infected with *R. oryzae*, the effects of isavuconazole and liposomal amphotericin B on fungal burden were also determined in the target organs (lungs and brain) of these mice. Fungal burden in lung and brain was decreased by approximately 1 log in mice receiving isavuconazole, compared with the mice receiving placebo. A similar decrease in lung and brain fungal burden was noted in the liposomal amphotericin B-treated animals [Figure 8].[53]

Figure 8 Effect of Treatment with Placebo, Isavuconazonium or Liposomal Amphotericin B on Lung and Brain Fungal Burden in Neutropenic Mice after Intratracheal *Rhizopus oryzae* Infection



Number of mice = 9/group.

ISA: isavuconazonium; LAmB: liposomal amphotericin B.

* $P < 0.05$ compared to placebo treated mice by Wilcoxon Rank Sum test.

DKA mice administered isavuconazonium prodrug at a dose of 110 mg/kg 3 times daily strongly trended to show enhanced survival compared to placebo-treated mice.

In the hematogenous models, isavuconazole did not demonstrate a survival benefit in hematogenously disseminated mucormycosis (IV infection) DKA or neutropenic models. The hematogenously disseminated model represents a more severe and advanced disease model. Similar trends in results between the intratracheal and hematogenous models were also seen when posaconazole was studied in this severe infection model.[54] In the hematogenous model, posaconazole failed to improve survival in mice; however, in the intratracheal model, efficacy was seen with posaconazole compared to control animals.

In summary, isavuconazole demonstrated in vitro antifungal activity against *R. oryzae* clinical isolates. In the mouse mucormycosis model, isavuconazole demonstrated efficacy in an experimental model of mucormycosis and was equivalent to the standard therapy of high dose liposomal amphotericin B in neutropenic mice.

Candidiasis

In in vivo models of disseminated candidiasis, isavuconazole decreased kidney fungal burden in neutropenic mice infected with *C. albicans, C. krusei* and *C. tropicalis*. In addition, isavuconazole lowered brain fungal burden in temporarily and persistently neutropenic mice infected with *C. krusei*. Isavuconazole also induced 100% survival in both temporarily and persistently neutropenic mice infected with *C. albicans*.

AUC/MIC correlated best with therapeutic efficacy in pharmacodynamic models. The *C. albicans* pharmacodynamic target was a total drug AUC/MIC of approximately 5053. A 10-fold lower pharmacodynamic target, approximately 312, was estimated for non-*albicans* species (*C. tropicalis* and *C. glabrata*), compared with *C. albicans*.

Isavuconazole showed potent concentration-dependent activity with prolonged survival and reduced fungal burden in animals infected with *Candida albicans*, *C. krusei*, *C. tropicalis* and *C. glabrata*.

5.5 Drug Resistance

Fungal isolates exhibiting reduced susceptibility to fluconazole, itraconazole, voriconazole or posaconazole may also show reduced susceptibility to isavuconazole, suggesting cross-resistance can occur among these azoles. The relevance of cross-resistance and clinical outcome has not been fully characterized; however, clinical cases where azole cross-resistance is demonstrated may require alternative antifungal therapy.

Isavuconazole MICs for certain posaconazole- and itraconazole-resistant *Aspergillus fumigatus* strains with well-characterized CYP51A mutations were not impacted by mutations in the G54 region and had variable activity to strains with mutations at the M220 region, similar to voriconazole. In vivo studies showed similar results indicating that some mutations can be overcome with increasing isavuconazole concentrations. Decreased susceptibility, as measured by MIC testing, developed in vitro after continuous exposure to isavuconazole over a range of concentrations. The occurrence of the laboratory generated resistance was rare and less frequent than other azoles tested (itraconazole and voriconazole). No resistance mechanisms were characterized for the isolates with elevated MICs to isavuconazole from in vitro studies. These organisms also exhibited elevated MICs to other azoles (itraconazole and voriconazole) in this study. In vivo, these isolates demonstrated similar virulence as the corresponding wild-type organisms. The relevance of these findings is unknown at this time.

6 BIOPHARMACEUTICS AND PHARMACOKINETICS OF ISAVUCONAZOLE

6.1 Summary of the Clinical Pharmacology of Isavuconazole

The results of 40 clinical pharmacology studies of isavuconazole demonstrated:

- Dose proportional increases in isavuconazole exposure
- Rapid absorption with high oral bioavailability (98%)
- No food or gastric pH effect
- Moderate interindividual pharmacokinetic variability
- Large volume of distribution (450L)
- Long terminal elimination half-life (~130 hours) enabling once daily maintenance dosing
- < 1% of unchanged drug excreted by the kidneys
- No dose adjustments are recommended in elderly or renally impaired subjects
- CYP3A4 metabolism
- Manageable drug-drug interaction profile:
    - Isavuconazole is a sensitive substrate of CYP3A (5-fold increase in isavuconazole AUC with concomitant ketoconazole), a mild-to-moderate inhibitor of CYP3A4 (2-fold increase in midazolam AUC) and a mild inducer of CYP2B6 (42% decrease in bupropion AUC).
    - Isavuconazole does not inhibit or induce CYP1A2, CYP2C9 or CYP2C19 and does not inhibit CYP2A6 or CYP2D6.
    - Isavuconazole is a mild inhibitor of P-gp, OCT1/OCT2 and MATE1.
    - Isavuconazole has no inhibitory effects on sensitive substrates of BCRP, OAT1/OAT2, OATP1B1/OATP1B3 or MATE2-K, but does have mild indirect inhibitory effects on substrates of UGT.

6.2 Biopharmaceutics

This section describes the biopharmaceutics of isavuconazole as characterized in 2 bioavailability studies and 1 food effect study. A tabular description of these studies is provided in [Appendix 1].

With an oral bioavailability of 98%, bioequivalence of AUC and absence of a food or gastric pH effect, isavuconazole can be administered via both routes of administration under fed or fasting conditions and in the presence of drugs that increase gastric pH with no need for dose adjustment.

6.2.1 Formulations

6.2.1.1 Oral Formulations

The proposed commercial formulation is the same as the formulation that has been used in phase 3 clinical studies except the capsule shells, which are different in color and imprint from those for commercial capsules. The proposed commercial scale manufacturing processes will be the same as those for the production of phase 3 clinical trial materials batches.

6.2.1.2 IV Formulations

The formulation of the freeze-dried powder for solution for infusion can be reconstituted with water for injection and, after dilution with isotonic saline, infused intravenously in patients. Since isavuconazonium is a moisture-sensitive drug substance, lyophilized products were developed and used for clinical studies. An IV formulation of the sulfate salt of isavuconazonium has been used. Mannitol was used as a bulking agent and sulfuric acid was used for pH adjustment. Two dose strengths were formulated: 186.3 mg isavuconazonium, corresponding to 100 mg isavuconazole per vial (used for phase 2 dose escalation study) and 372.6 mg isavuconazonium, corresponding to 200 mg isavuconazole per vial (used from phase 2 onwards). The ratio of mannitol to sulfate salt of isavuconazonium was the same for both strengths. The proposed commercial formulation is the same as the formulation that has been used in phase 3 clinical studies. The proposed commercial scale manufacturing processes will be the same as that for the production of phase 3 clinical trial batches.

Isavuconazonium for injection 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). Visible translucent to white particulate can be observed when the reconstituted solution is diluted into saline or D5W.

The precipitate was identified as isavuconazole, the active moiety of the prodrug, isavuconazonium. During manufacturing, hydrolysis of the prodrug to isavuconazole and the inactive cleavage product cannot be completely prevented, resulting in the presence of a small amount of isavuconazole in the lyophilized powder. This isavuconazole forms particulate due to the low solubility of isavuconazole in aqueous media. Robust manufacturing controls have been implemented to minimize the formation of isavuconazole, and levels cannot be further reduced.

The infusion solution is recommended to be administered through an in-line filter (0.2 to 1.2 μm pore size), placed between the infusion bag and patient access and is required to produce an infusion solution that is free of visible particulates and meets United States Pharmacopeia (USP) <788> requirements for subvisible particle counts.

Isavuconazole is expected to rapidly dissolve in human blood and plasma and, therefore, the observed particulate matter is not believed to carry any untoward risk.

6.2.2 Bioavailability

Isavuconazole bioavailability was 98% after oral administration of 745.2 mg isavuconazonium (corresponding to 400 mg isavuconazole). The 90% CIs for the oral-to-IV ratio for AUC_{inf} of isavuconazole were contained in the equivalence limits of 80% to 125%. Isavuconazole C_{max} was 22% lower after oral administration compared to IV administration. Differences in isavuconazole C_{max} following oral and IV administration of isavuconazonium are anticipated due to the different routes of administration and depend on the rate/duration of infusion.

6.2.3 Food Effect

Concurrent administration of isavuconazonium capsules with a high-fat breakfast had no clinically relevant effect on the pharmacokinetics of isavuconazole. After administration of a single dose of 400 mg with a high-fat breakfast, geometric least squares mean (GLSM) ratios for isavuconazole C_{max} and AUC_{inf} with and without food were 91.9% and 109.6%, respectively, with 90% CIs contained entirely within the default no effect boundaries of 80% to 125%. The 2-hour delay in t_{max} with food was not considered clinically relevant. Pivotal clinical efficacy and safety trials were conducted regardless of food intake. The proposed dosing recommendation for oral isavuconazonium in relation to food is that isavuconazonium can be taken with or without food.

6.2.4 Gastric pH

Coadministration of steady state esomeprazole (40 mg daily for 10 days) with steady state isavuconazole resulted in a 7.6% increase in AUC_{tau} and a 4.8% increase in the C_{max} of isavuconazole compared to isavuconazole alone. These findings indicate that concomitant medications that alter the gastric pH (i.e., proton-pump inhibitors, H2-receptor antagonists and antacids) do not significantly affect the pharmacokinetics of isavuconazole.

6.3 Pharmacokinetics/Pharmacodynamics

This section describes the pharmacokinetics of isavuconazole as characterized in 37 phase 1 studies: 8 single- and multiple-dose pharmacokinetic studies in healthy subjects and special populations, 2 mass balance studies, 2 pharmacodynamic (thorough QTc) studies and 25 drug-drug interaction studies. A tabular description of the clinical studies is provided in [Appendix 1].

6.3.1 Absorption and Exposure

Following IV administration, isavuconazonium is rapidly and quantitatively converted to the active moiety isavuconazole and its cleavage product (BAL8728) by enzymatic hydrolysis. After oral administration, isavuconazonium predominantly undergoes chemical hydrolysis in the GI lumen. No significant concentrations of the prodrug, isavuconazonium, or the inactive cleavage product (BAL8728) were detectable in plasma after oral administration.

After IV administration, the active moiety, isavuconazole, exposure increased approximately dose-proportionally with maximum plasma concentrations (C_{max}) reached at the end of infusion after single and multiple dosing.

After oral administration of single and multiple doses, isavuconazole generally reached C_{max} in 2 to 3 hours. For both routes of administration, isavuconazole concentrations were generally measurable in plasma for at least 480 hours postdose.

6.3.2 Distribution and Protein Binding

Isavuconazole is highly protein bound (> 99%), primarily to albumin and is extensively distributed throughout the body with a mean volume of distribution of approximately 450 L after administration in healthy subjects and patients.

6.3.3 Metabolism

In vitro studies demonstrated that isavuconazonium is rapidly hydrolyzed in blood to isavuconazole by esterases, predominately by butyrylcholinesterase, and that isavuconazole is a sensitive CYP3A substrate. Further, in vivo studies indicate that CYP3A4, CYP3A5 and subsequently UGTs are involved in the metabolism of isavuconazole.

Following single doses of [cyano-^{14}C] isavuconazonium and [pyridinylmethyl-^{14}C] isavuconazonium in humans, a number of minor metabolites were identified in addition to the active moiety, isavuconazole, and the inactive cleavage product (BAL8728). Except for the active moiety, no major individual metabolites (exposure > 10% of drug-related material in plasma according to the ICH M3 R2 guidance) were observed in plasma or feces following a single oral solution dose of ^{14}C-labeled isavuconazonium (target 200 mg isavuconazole). Plasma concentration-time profiles of radioactivity and isavuconazole declined in parallel, indicating that metabolites exhibit formation rate limited kinetics.

6.3.4 Elimination

Isavuconazonium is eliminated by chemical hydrolysis and/or plasma esterases to isavuconazole and the inactive cleavage product (BAL8728). The isavuconazonium half-life was not estimated in pharmacokinetics studies because isavuconazonium plasma concentrations were essentially undetectable after oral administration and typically only quantifiable during the infusion interval. Once the infusion was stopped, isavuconazonium plasma concentrations decreased rapidly and were generally undetectable within 30 minutes postinfusion. BAL8728 had a terminal half-life of approximately 1 hour after IV administration.

Isavuconazole plasma concentrations declined in a biphasic manner after both oral and IV administration. Additional peaks in plasma concentrations were often observed in the declining phase of individual isavuconazole plasma concentration-time profiles, with these secondary peaks usually occurring about 6 to 12 hours postdose and typically coinciding with a meal or snack. The population mean half-life of isavuconazole was approximately 130 hours for both routes of administration across a range of doses, suggesting that the elimination process of isavuconazole is not dependent on dose or administration route. Isavuconazole has a low clearance (CL) of approximately 2.4 L/h, which represents < 10% of liver plasma flow; therefore, the hepatic extraction ratio of isavuconazole must be low in agreement with the observed high oral bioavailability of isavuconazole.

6.3.5 Excretion

Following a single oral solution dose of [cyano-^{14}C]-labeled isavuconazonium (200 mg isavuconazole), a mean of 46.1% of the administered radioactive dose was recovered in feces and 45.5% was recovered in urine through the last collection interval. Most of the administered radioactivity was recovered in the first 312 hours postdose (81.6%). The overall mean recovery of radioactivity in urine and feces samples was 91.6% over the 600-hour study, with recovery in individual subjects ranging from 86.3% to 96.7%

Isavuconazole accounted for the majority of the radioactivity in feces (33% up to 144 hours postdose). The majority of the [cyano-^{14}C]-radioactivity recovered in urine was excreted as metabolites of isavuconazole, such as a thiazole ring cleaved product of isavuconazole, a carboxylic acid form of the destriazole metabolite, along with several glucuronides.

Renal excretion of isavuconazole itself was < 1% of the dose administered. The renal clearance (CL_R) of isavuconazole is low, with mean estimates ranging from 7.42 to 13.99 mL/h in healthy subjects. The mean estimate for unbound CL_R (95.6 - 115 mL/min) is similar to the glomerular filtration rate (GFR) (approximately 110 mL/min), indicating that tubular secretion does not contribute significantly to the renal clearance of isavuconazole.

The inactive cleavage product (BAL8728) is primarily eliminated by metabolism and renal excretion of the metabolites. Following IV administration of [pyridinylmethyl-^{14}C] isavuconazonium, 95% of the total radioactive dose was excreted in the urine; the major form of urine radioactivity was the oxidative carbamate cleavage metabolite M4 (56% of total dose). Renal elimination of intact BAL8728 was < 1% of the total dose administered.

6.3.6 Dose Proportionality

The dose proportionality of isavuconazole exposure after oral and IV administration of isavuconazonium was explored in several studies in both healthy subjects and patients. The data indicate that there are no relevant deviations from dose proportionality in isavuconazole plasma exposure for both routes of administration.

In the second thorough QTc study in healthy subjects, AUC_{tau} at 600 mg/day was 2.9-fold higher than at 200 mg/day. C_{max} at 600 mg/day was 2.7-fold higher than at 200 mg/day, and t_{max} was 1 hour later at the higher dose.

Approximately dose-proportional pharmacokinetics of isavuconazole were also observed in patients undergoing chemotherapy for AML, who received either a high dose regimen (800/400/400 mg day 1, 400 mg bid day 2 and 400 mg day 3 up to day 28; n=12) or a low dose regimen (400/200/200 mg day 1, 200 mg bid day 2 and 200 mg day 3 up to day 28; n=11) of IV isavuconazonium. The geometric mean ratio for dose-normalized AUC_{tau} and C_{max} on day 7 was 98% (90% CI: 78%, 122%) and 107% (90% CI: 82%, 139%), respectively.

6.3.7 Accumulation and Time-dependency

Assessment of isavuconazole predose trough concentrations indicates that near steady state conditions of isavuconazole are achieved within 14 days of once daily oral and IV dosing. This is consistent with an apparent terminal half-life of approximately 130 hours. Mean isavuconazole AUC increased approximately 4- to 5-fold at steady state after once daily administration relative to single-dose data after maintenance doses of 50 and 100 mg. Isavuconazole C_{max} was approximately 2- to 3-fold higher at steady state compared to after a single dose. The prodrug cleavage product (BAL8728) did not accumulate after once daily IV doses.

The time dependency of isavuconazole pharmacokinetic parameters (measured as the ratio of AUC_{tau} at steady state to AUC_{inf} after a single dose) has not been formally assessed in a dedicated study. Based on between-study comparisons of single-dose AUC_{inf} and multiple-dose AUC_{tau} of isavuconazole, there appeared to be no major changes in (apparent) clearance with time following once daily oral or IV dosing. Single-dose AUC_{inf} and multiple-dose AUC_{tau} of isavuconazole were comparable after 100 mg single and multiple doses for both routes of administration.

6.3.8 Intersubject Variability

The interindividual variability of isavuconazole AUC is moderate and similar between oral and IV dosing. In healthy subjects from 10 Phase 1 studies (20-24 subjects/study), who were dosed with the oral clinical dosing regimen (200 mg TID for 2 days followed by 200 mg QD), the interindividual geometric %CV ranged from 22% to 37%. Predicted AUCs from 232 Phase 3 patients obtained through population pharmacokinetic modeling had an interindividual geometric %CV of 46%.

6.3.9 Special Populations

Summaries of the pharmacokinetics of isavuconazole in special populations are provided for the following subgroups: age, sex, race, hepatic impairment and renal impairment.

No relevant differences were observed between the clearance of patients and healthy subjects.

6.3.9.1 Age and Sex

The C_{max} and AUC of isavuconazole following a single oral dose (200 mg) in elderly subjects (≥ 65 years) were similar to those in younger subjects (18 to 45 years) and in female and

male subjects. Elderly females exhibited the highest mean AUC_{inf} values compared with non-elderly female and elderly male subjects. The GLSM AUC_{inf} ratio was 164.21% (90% CI: 132.76, 203.10) for elderly female compared with non-elderly female subjects, and 137.18% (90% CI: 110.91, 169.68) for elderly female compared with elderly male subjects. No difference in mean AUC_{inf} was observed between elderly and non-elderly males. Based on the safety profile and pharmacokinetic/pharmacodynamic relationship for antifungal activity of isavuconazole, the differences were not considered clinically significant and no dose adjustments are required based on age or sex. The pharmacokinetics of isavuconazole in pediatric patients has not been evaluated.

Population pharmacokinetic modeling was able to adequately describe the isavuconazole plasma concentrations and was able to determine the effect of age and sex on the pharmacokinetics of isavuconazole. Results indicated that only elderly female subjects had higher exposure as compared to non-elderly subjects and elderly male subjects due to reduced clearance.

6.3.9.2 Race

The population pharmacokinetic analysis of Chinese and Western subjects from Europe who were predominantly Caucasian revealed that the nearly 50% higher exposure seen in Chinese subjects as compared to Western subjects was primarily due to a reduction in total systemic clearance. Body mass index and age did not play a significant role in the observed differences. Based on the safety profile and pharmacokinetic/pharmacodynamic relationship for the antifungal activity of isavuconazole, the differences are not considered as clinically significant; no dose adjustment is required.

Similar isavuconazole exposures were seen in Black/African American and White healthy subjects in pooled data from 10 phase 1 studies [Table 5].

Table 5 Pharmacokinetics of Isavuconazole in African Americans and Whites (Pooled Data from 10 Phase 1 Studies)

		Black/African American		White	Ratio	90% CI
	n	LS Mean†	n	LS Mean†	Black/White‡	of Ratio‡
AUC_{tau} (h•ng/mL)	76	90403	130	85011	106.34	(98.97, 114.27)
C_{max} (ng/mL)	78	5687.13	130	5470.32	103.96	(97.65, 110.69)

LS: least square.

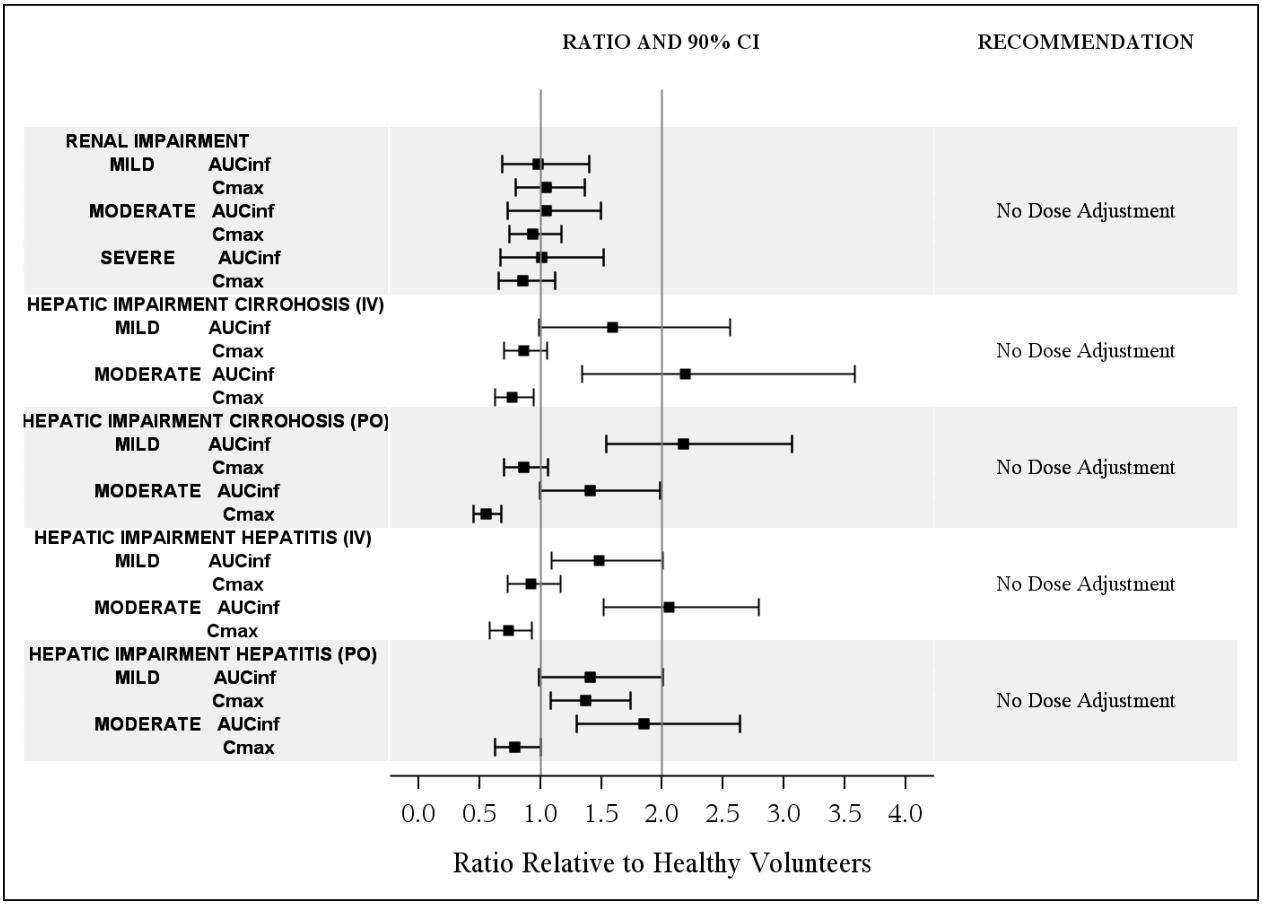
† Geometric mean based off of natural log-transformed data transformed back to raw units.

‡ Ratios and CIs are transformed back to raw units and expressed as a percent.

6.3.9.3 Hepatic and Renal Impairment

The effects of renal and hepatic impairment on the pharmacokinetics of isavuconazole are presented in [Figure 9].

Figure 9 Effect of Renal and Hepatic Impairment on the Pharmacokinetics of Isavuconazole



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 IV and 16 oral patients per Child-Pugh Class) due to alcoholic cirrhosis or hepatitis, the GLSM systemic exposure (AUC) increased 64% in the Child Pugh Class A group and 84% higher in the Child-Pugh Class B group relative to 32 age- and weight-matched healthy volunteers with normal hepatic function. GLSM 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 volunteers and patients with mild and moderate hepatic dysfunction demonstrated that the mild and moderate hepatic impairment population had 40% and 48% lower isavuconazole clearance values, respectively, compared to the healthy population. The risk of lack of efficacy with a lower dose was considered greater than the risk of adverse reactions with the standard dose. It is recommended that the standard isavuconazole loading dose and maintenance dose regimen be utilized in patients with mild to moderate hepatic disease. Isavuconazole has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

Renal Impairment

A population pharmacokinetic assessment of the pharmacokinetics of isavuconazole in healthy volunteers and patients with mild, moderate and severe renal dysfunction as well as patients with ESRD revealed there were no clinically relevant differences in the concentration-time profile with the degree of renal impairment.

From the noncompartmental analysis, the GLSM AUC ratios of isavuconazole in subjects with mild, moderate and severe renal impairment are similar to those of healthy control volunteers, indicative that the decrease in renal clearance in patients with mild, moderate and severe renal impairment had no significant impact on the overall clearance of isavuconazole as the isavuconazole is metabolized by CYP3A4 and < 1% of the administered isavuconazole dose is eliminated via the kidney. In the ESRD population, the pharmacokinetic parameters of isavuconazole were influenced by the experimental conditions of dosing that influence intravascular volume such as intercompartmental fluid shifts (hemodilution postdialysis and hemoconcentration during dialysis). When these intravascular shifts are taken into account, the pharmacokinetics of isavuconazole in ESRD subjects do not appear to be significantly altered. The highly protein bound (> 99%) isavuconazole is not readily dialyzable. Less than 1% of the administered isavuconazole dose was recovered in dialysate fluid. Dialysis is not expected to have any appreciable effects on the pharmacokinetics of isavuconazole.

No dose adjustment is required in the patients with mild, moderate or severe renal impairment or in subjects with ESRD. Isavuconazole is not readily dialyzable and extracorporeal therapy cannot be used to treat overdosage.

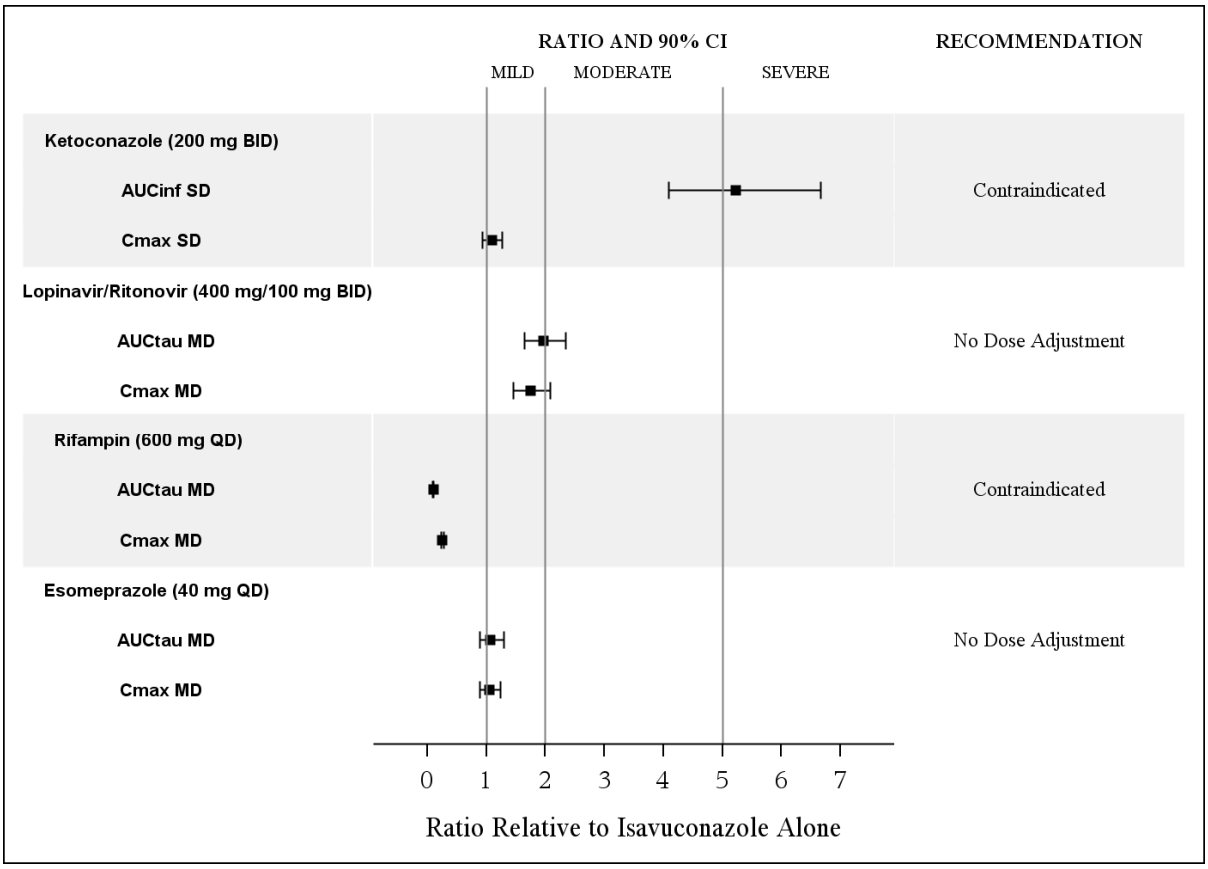
6.3.10 Drug-Drug Interactions

Isavuconazole is a sensitive-substrate of CYP3A (5-fold increase in isavuconazole AUC with concomitant ketoconazole). CYP3A inhibitors or inducers may alter the plasma concentrations of isavuconazole. Isavuconazole is a mild-to-moderate inhibitor of CYP3A (1.8-fold increase in sirolimus AUC and 2-fold increase in midazolam AUC) and a mild inducer of CYP2B6 (42% decrease in bupropion AUC*)*. Isavuconazole did not affect the pharmacokinetics of sensitive substrates of CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6. Isavuconazole is a mild inhibitor of P-gp, OCT1/OCT2 and MATE1. Isavuconazole had no inhibitory effects on sensitive substrates of BCRP, OAT1/OAT2, OATP1B1/OATP1B3 and MATE2-K, but did have mild indirect inhibitory effects on substrates of UGT.

The effects of other drugs (i.e., ketoconazole, lopinavir/ritonavir (LPV/RTV), rifampin and esomeprazole) on the pharmacokinetics of isavuconazole are shown in [Figure 10].

- No modification of the isavuconazole dose or the LPV/RTV dose is recommended when the drugs are coadministered.
- Coadministration is contraindicated for the following:
    - Strong CYP3A4 inhibitors such as ketoconazole
    - Strong CYP3A4 inducers such as rifampin, carbamazepine, St. John's wort or long-acting barbiturates.

Figure 10 Effects of Other Drugs on the Pharmacokinetics of Isavuconazole

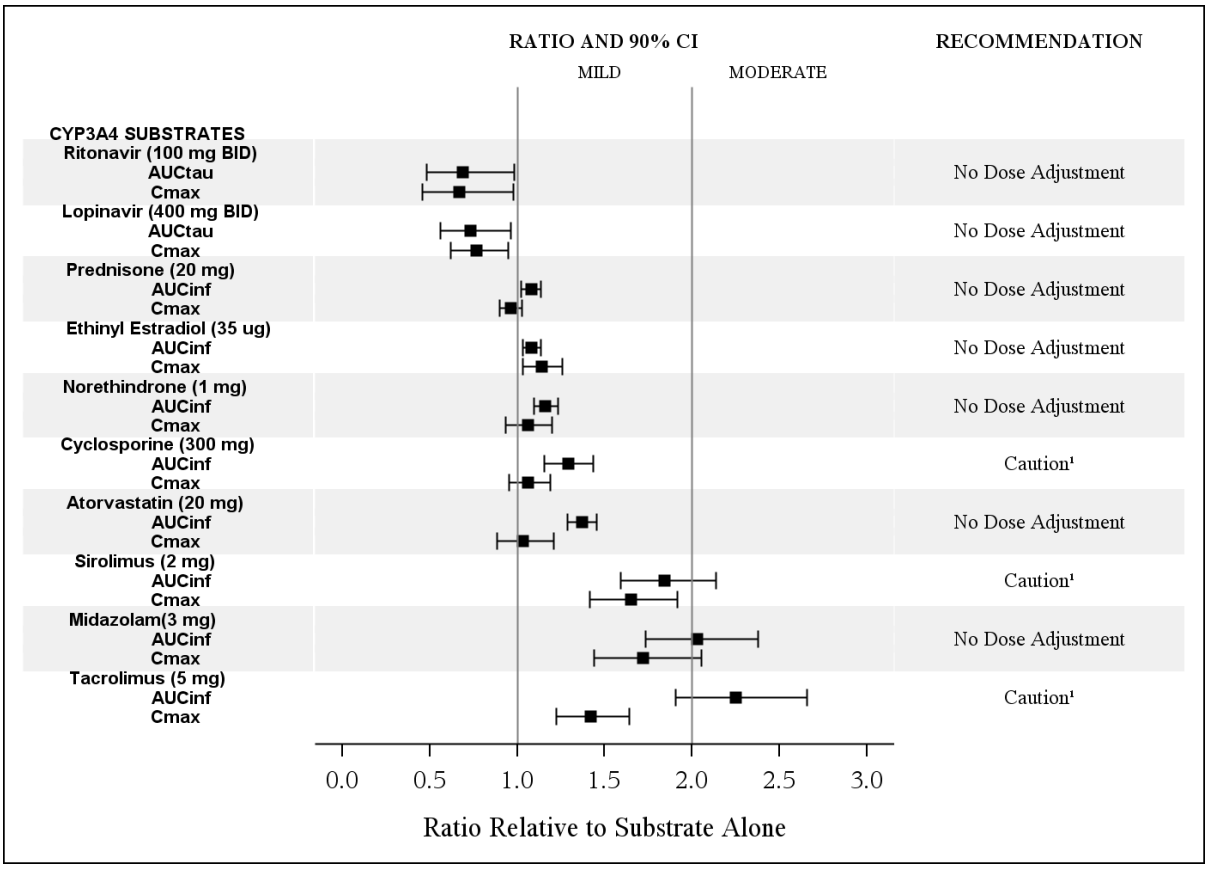


SD: single dose; MD: multiple dose.

The effects of isavuconazole on the CYP3A substrates ritonavir, lopinavir, prednisone, ethinyl estradiol, norethindrone, cyclosporine, atorvastatin, sirolimus, midazolam and tacrolimus are shown in [Figure 11].

- No dose adjustments are recommended for midazolam, prednisone, atorvastatin and oral contraceptives comprised of ethinyl estradiol and norethindrone when given concurrently with isavuconazole.
- Caution is advised if isavuconazole is coadministered with CYP3A substrates with narrow therapeutic indexes such as the immunosuppressants tacrolimus, sirolimus and cyclosporine and may require appropriate therapeutic drug monitoring and dose adjustment of these immunosuppressants.

Figure 11 Effect of Isavuconazole on Pharmacokinetics of CYP3A Substrates

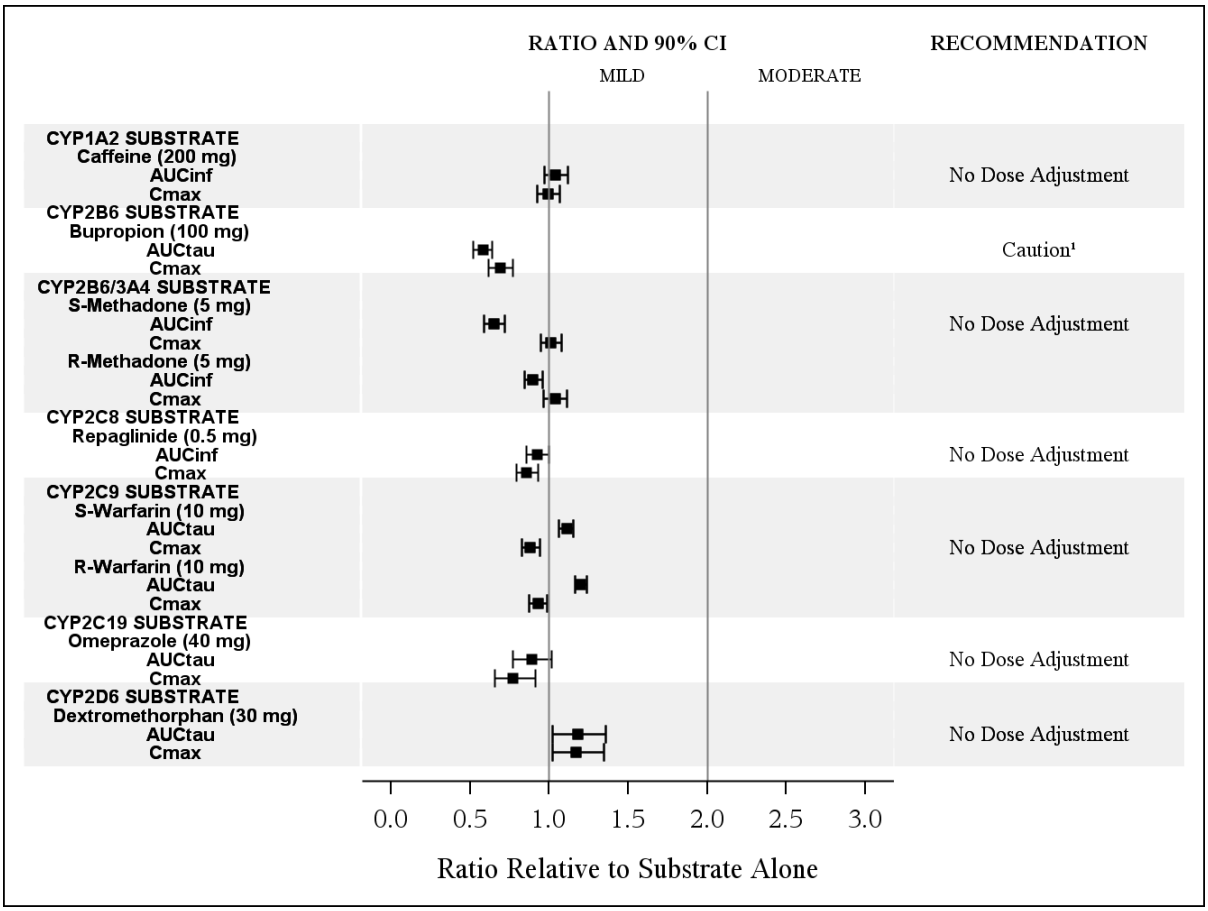


Caution[1]: Appropriate therapeutic drug monitoring and dose adjustment of tacrolimus, sirolimus and cyclosporine may be necessary when coadministered with isavuconazole.

The effects of isavuconazole on the pharmacokinetics of other CYP substrates such as caffeine, bupropion, methadone, repaglinide, warfarin, omeprazole and dextromethorphan are presented in [Figure 12].

- No dose adjustment is recommended with warfarin or other CYP2C9 substrates when coadministered with isavuconazole.
- No dose adjustment is recommended with methadone, a CYP2B6/3A4 substrate.
- No dose adjustment is recommended for CYP1A2 and CYP2C8 substrates such as caffeine or repaglinide when coadministered with isavuconazole.
- Isavuconazole does not inhibit CYP2C19. No dose adjustment is recommended with omeprazole or other CYP2C19 substrates when coadministered with isavuconazole.
- Isavuconazole does not inhibit CYP2D6. No dose adjustment is recommended with dextromethorphan or other CYP2D6 substrates when coadministered with isavuconazole.
- Isavuconazole decreased the systemic exposure of bupropion. Caution is advised if isavuconazole is coadministered with CYP2B6 substrates, especially narrow therapeutic index drugs such as efavirenz and cyclophosphamide. No dose adjustment is required for methadone.

Figure 12 Effect of Isavuconazole on Pharmacokinetics of Other CYP Substrates



Caution[1]: Isavuconazole decreased the systemic exposure of bupropion. Caution is advised if isavuconazonium is coadministered with CYP2B6 substrates, especially narrow therapeutic index drugs such as efavirenz and cyclophosphamide.

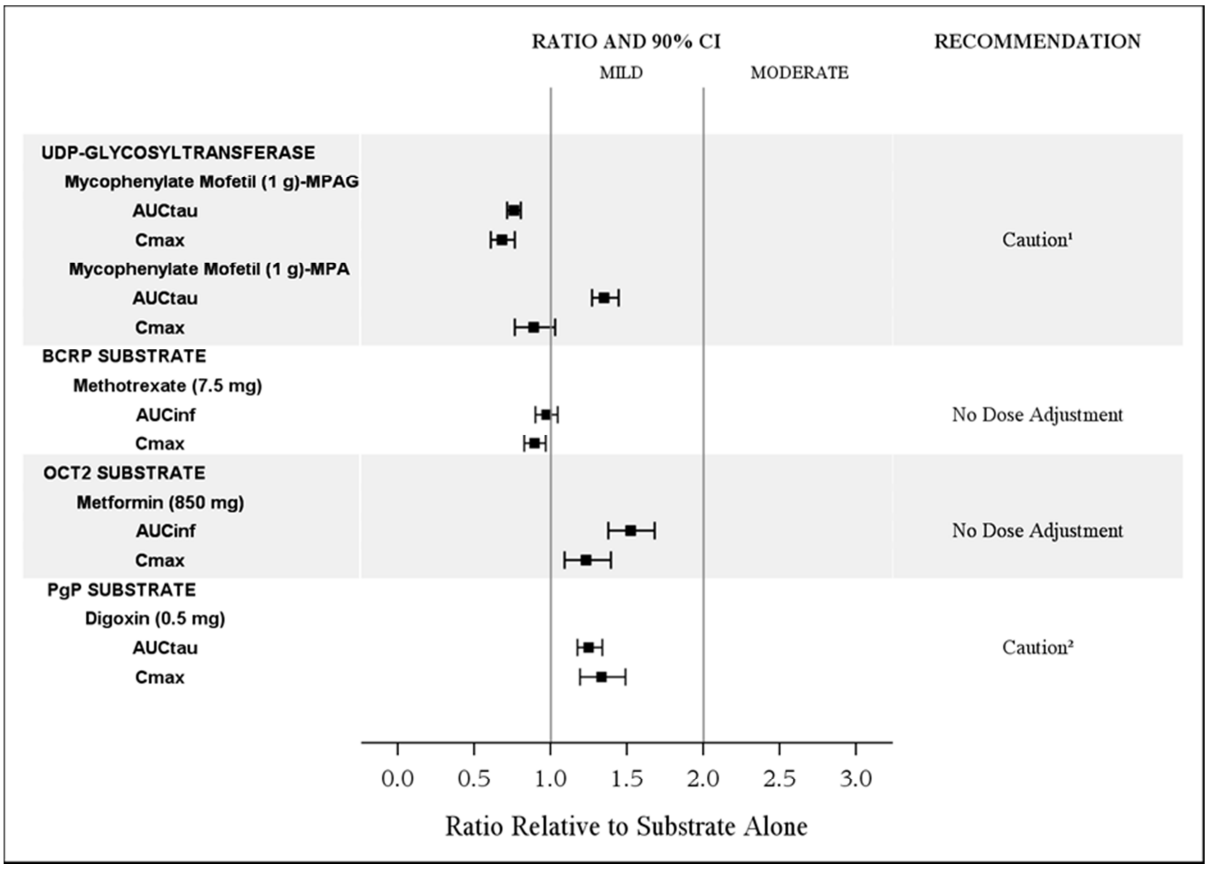
CYP: Cytochrome P450.

The effects of isavuconazole on the pharmacokinetics of UGT (MMF), BCRP and OAT1/OAT2 (methotrexate), OCT1/OCT2 and MATE1 (metformin) and P-gp transporter substrates (digoxin) are shown in [Figure 13].

- No dose adjustment is recommended for the OCT1/OCT2 substrate, metformin, when coadministered with isavuconazole.
- No dose adjustment is recommended for the BCRP substrate, methotrexate, when coadministered with isavuconazole.
- Coadministration with drugs with a narrow therapeutic window that are P-gp substrates (e.g., digoxin, colchicine and dabigatran etexilate) may require dose adjustment.
- Coadministration with MMF may require monitoring for MPA-related toxicities.
- In addition, although not shown in the figure below, the effects of isavuconazole on the pharmacokinetics of OATP1B1 and OATP1B3 were evaluated with atorvastatin (a substrate of OATP1B1/1B3) and CYP3A4, as well as with repaglinide (a substrate of

OATP1B1/1B3 in addition to CYP2C8). The results of these two DDI studies indicated that isavuconazole does not inhibit OATP1B1 or OATP1B3 substrates.

Figure 13 Effect of Isavuconazole on the Pharmacokinetics of UGTs and Transporters



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

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

BCRP: breast cancer resistance protein; MMF: mycophenolate mofetil; MPA: mycophenolic acid; MPAG: phenolic glucuronide of MPA; OCT2: organic cation transporter 2; P-gp: P-glycoprotein; UDP: uridine diphosphate; UGT: uridine diphosphate-glucuronosyltransferase.

6.3.11 Pharmacodynamic Studies: Thorough QT

A thorough QT study was performed to examine the effects of therapeutic (200 mg/day maintenance) and supratherapeutic (600 mg/day maintenance) doses on the QT interval. Unlike findings with other azoles, there was no evidence of QTc prolongation, but QT shortening was observed. For both 200 mg and 600 mg isavuconazole, a shortening of the QTcF interval was observed at all time points. The largest shortening occurred at 2 hours for both doses (isavuconazole 200 mg: -13.10 msec [90% CI: -17.07, -9.13]; isavuconazole 600 mg: -24.56 msec [90% CI: -28.71, -20.41]).

A detailed ion-channel in vitro study revealed that isavuconazole inhibited the L-type calcium channel (hCav1.2) with an IC_{50} of 6.57 µM (38-fold the human non-protein bound C_{max} at the clinical maintenance dose of 200 mg/day). This ion channel finding is consistent with the QTcF interval shortening reported in the clinical thorough QT study.

Pharmacokinetics-QT Analyses

The relationship between isavuconazole plasma concentrations and difference in time-matched baseline-adjusted QTcF from placebo (ddQTcF) was investigated [Table 6].

Table 6 Relationship Between Isavuconazole Plasma Concentrations and ddQTcF

Parameter Estimate (P-value)		Isavuconazole	
		200 mg	600 mg
Intercept	Slope	Predicted Mean ddQTcF (90% CI)†	Predicted Mean ddQTcF (90% CI)†
-6.09 (< 0.0001)	-1.03E-03 (< 0.0001)	-13.84 (-14.47, -13.21)	-26.80 (-27.89, -25.71)

All enrolled subjects who completed at least 1 time-matched ECG extraction on days -1 and 13 (ECG analysis set).

ddQTcF: time-matched isavuconazole-placebo difference in QTcF interval, baseline-adjusted;
ECG: electrocardiogram.

†The predicted mean ddQTcF and 90% CI at the mean C_{max} for each treatment.

There was a concentration-dependent shortening of ddQTcF with increasing isavuconazole plasma concentrations, with predicted mean ddQTcF at the mean C_{max} for the 200 and 600 mg isavuconazole treatment groups of -13.84 and -26.80, respectively. The clinical relevance of the observed dose-dependent shortening of cardiac repolarization cannot yet be determined.

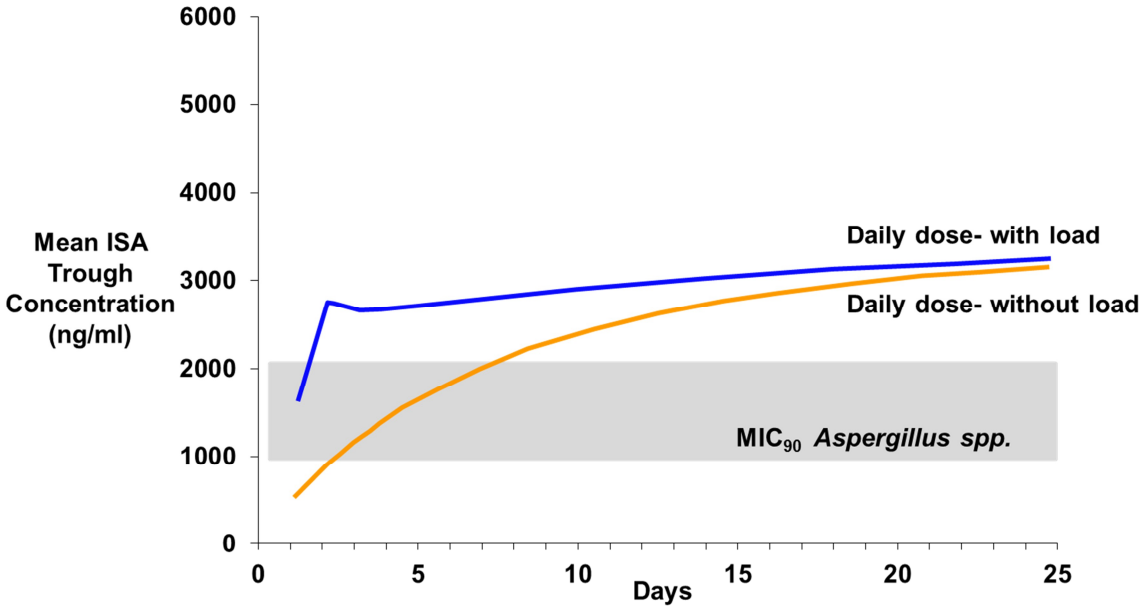
Historically, antifungal agents in the azole class are known to prolong the QT interval. Isavuconazole testing in healthy subjects revealed QTcF interval shortening. The clinical significance of drug-induced QTc shortening is unknown. The proposed labeling includes a contraindication for SQTS and a warning regarding the potential for QTc shortening and risk if used with other medications known to shorten QTc. Describing drug-related QTc shortening in the label should avoid treatment of subjects with rare SQTS. There is a precedent for this approach in the rufinamide FDA approved label.[28]

6.3.12 Dose Selection

IA and IM are life-threatening fungal infections necessitating rapid achievement of efficacious exposures.

The dose regimen for the phase 3 studies achieves rapid mean isavuconazole concentrations above the epidemiological cut-off values for *Aspergillus* spp. (i.e., > 1 mg/L). It was determined that a loading dose would be required to ensure rapid attainment of such target isavuconazole trough concentrations [Figure 14].

Figure 14 Achievement of Target Isavuconazole Trough Concentrations with and without a Loading Dose



ISA: isavuconazole; MIC_{90}: minimum inhibitory concentration that inhibits 90% of organisms.

Data from pharmacodynamic-pharmacokinetic experimental models demonstrated AUC/MIC is the pharmacodynamic index that drives efficacy.[55] The pharmacodynamic targets from these experiments were used in a probability of target attainment analysis to confirm the adequacy of the phase 3 dosing regimen to reach the pharmacodynamic target in patients. The probability to attain the pharmacodynamic target AUC/MIC (50 using CLSI methodology) was determined for a range of MIC values. Based on this analysis, greater than 90% of the simulated population achieved the pharmacodynamic target after administration of the clinical dosing regimen at MICs up to and including 1 mg/L. Importantly, this MIC value is at the upper limit of the wild-type population as defined by the epidemiological cut-off value for most *Aspergillus* spp. In addition, exposure-response analyses, which did not reveal any relationships to exposure and outcome, further support the clinical dosing regimen studied in Phase 3.

For IM, in vivo pharmacodynamics models are not available to guide target exposures and dose selection. Furthermore, MIC values have not been found to be helpful in guiding therapy in IM.[24] Thus, the same dose regimen selected for IA was utilized for treatment of IM in Study 0103. The results from Study0103 support the proposed isavuconazole dose regimen.

7 EFFICACY IN INVASIVE ASPERGILLOSIS

7.1 Summary of Efficacy Results in IA

Isavuconazole demonstrated effectiveness for the treatment of patients with IA:

- The primary efficacy objective of the study was met as isavuconazole was noninferior to voriconazole for all-cause mortality through day 42 in the ITT analysis population.
    - All-cause mortality through day 42 was 18.6% and 20.2% in the isavuconazole and voriconazole treatment groups, respectively, with an adjusted treatment difference (isavuconazole-voriconazole) of -1.0.
    - The upper bound of the 95% CI (-7.759, 5.683) for the adjusted treatment difference was lower than the prespecified NIM of 10%.
- Comparable results between treatment groups were seen for all-cause mortality across sensitivity analyses, populations, time points and subgroups, further supporting the effectiveness of isavuconazole in IA.
- The results from analysis of the key secondary endpoint of success for DRC-assessed overall response in the mITT analysis population support the efficacy of isavuconazole.
    - Success rates for DRC-assessed overall response at EOT were similar between isavuconazole and voriconazole treated patients (35.0% and 36.4%, respectively).
- DRC-assessed overall responses across the various prespecified analytical populations were similar to those observed for the mITT population.

7.2 Study 0104 Design

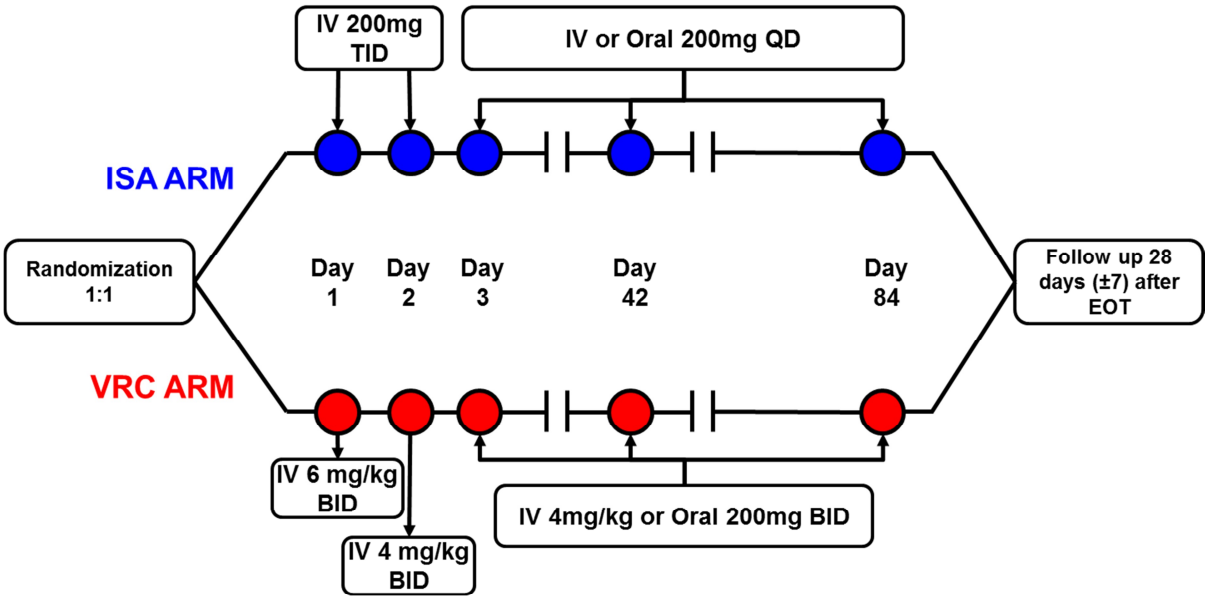
7.2.1 Overview of Study 0104 Design

Primary evidence of the efficacy and safety of isavuconazole comes from randomized, double-blind, non-inferiority, multicenter, active-controlled Study 0104. A total of 527 adult patients with suspected IFD caused by *Aspergillus* species or other filamentous fungi were randomized 1:1 via a central Interactive Voice Response System (IVRS) with stratification by geographical region, allogeneic HSCT status and uncontrolled/active malignancy status at baseline. Study 0104 was an adequate, well-controlled trial and provides substantial evidence to support the claim of effectiveness.

Study drug (isavuconazole) or active comparator (voriconazole) was administered as an IV loading dose followed by IV or oral maintenance dosing [Figure 15]. A switch from IV to

oral administration of study drug was to be made as early as possible from day 3 onward at the investigator's discretion. Patients were treated for 7 days following resolution of clinical signs and symptoms or until they had received treatment for a maximum period of up to 84 days, consistent with the design of the voriconazole registration program for IA.[12]

Figure 15 Overview of Study Design (0104)



EOT: end of treatment; ISA: isavuconazole; VRC: voriconazole

The Sponsor, clinical research organization staff, investigators, patient and study coordinator(s) were blinded to randomization of study drug. Only the authorized unblinded person(s), e.g., the pharmacist(s) or designee(s) at the study center, unblinded monitors or unblinded Sponsor team member(s) who were not directly involved in the patient management were aware of the randomized drug assignment. The pharmacist (or designee) prepared the study drug according to treatment allocation. The authorized unblinded pharmacist(s) prepared the study drug for IV administration in such a way that investigators and staff remained blinded to the study drug being administered. During the loading phase of the study, patients randomized to the voriconazole treatment arm received a placebo infusion in between the two active voriconazole infusions. If the patient continued to receive study treatment via IV infusion during the maintenance phase, patients randomized to the isavuconazole treatment arm received a placebo infusion 12 hours +/- 2 hours after receiving an isavuconazole infusion. The blind was preserved during oral administration by the use of placebo capsules (isavuconazole- or voriconazole-matched capsules) to mirror the treatment regimens.

7.2.2 Inclusion/Exclusion Criteria

Male and female patients, ≥ 18 years of age with proven, probable and possible IFD defined according to criteria consistent with those established by the EORTC/MSG[27] were eligible for enrollment in Study 0104.

Key exclusion criteria from Study 0104:

- Hepatic dysfunction, defined as:
    - Total bilirubin ≥ 3 x the upper limit of normal (ULN), alanine transaminase (ALT) or aspartate transaminase (AST) ≥ 5 x ULN or known cirrhosis or chronic hepatic failure
- Moderate to severe renal dysfunction defined as:
    - Calculated creatinine clearance < 50 mL/min at screening, currently on dialysis or likely to require dialysis during administration of study drug
- Chronic aspergillosis, aspergilloma or allergic aspergillosis
- > 4 cumulative days of systemic antifungal therapy (posaconazole, itraconazole and voriconazole) within 7 days prior to first dose
- Advanced human immunodeficiency virus (HIV: CD4 < 200 cells/mm^3) or acquired immunodeficiency syndrome (AIDS)-defining condition
- Unlikely to survive 30 days or on mechanical ventilation

A full list of inclusion/exclusion criteria per the 0104 protocol can be found in [Appendix 2].

Renally-impaired patients (estimated creatinine clearance < 50 mL/min) were excluded from the randomized active-controlled study (0104) based on labeling associated with the use of IV voriconazole.

7.2.3 Study Endpoints

7.2.3.1 Primary Endpoint

The primary endpoint in Study 0104 was all-cause mortality through day 42, which is an unambiguous endpoint for which a formal justification of a 10% NIM could be made in line with the FDA draft Guidance for Industry on Non-inferiority Clinical Trials, dated March 2010 [see Section 7.2.7.2]. The 10% NIM was agreed upon with the FDA. In particular, the treatment effect of voriconazole compared to placebo could be estimated. All-cause mortality through day 42 was evaluated for the ITT population as a primary analysis.

Day 42 was selected as the time point based on a report by Wingard and colleagues demonstrating that a vast majority of deaths within the first 6 weeks of initiating antifungal therapy were due to IA, and deaths occurring after 6 weeks were primarily due to causes related to the underlying disease.[56] The ITT population is the primary analysis population as it represents the patient population that would be candidates for systemic antifungal therapy in the clinical setting.

7.2.3.2 Secondary Endpoints

The key secondary endpoint was the success rate for DRC-assessed overall response at EOT, which provided further evidence to support the efficacy of the drug. The key secondary endpoint analysis was conducted in the mITT analysis population, which consisted of ITT patients who had proven or probable IFD as determined by the DRC. Overall response was assessed by the DRC based on the DRC charter and consistent with EORTC/MSG 2008

guidelines as shown in [Appendix 3].[57] For overall response, patients with complete or partial responses were considered a success and patients with stable or progression responses were considered a failure. Patients who died before or on day 42 were considered failures for the day 42 assessment even if the DRC considered them a success. Patients who died before or on day 84 were also considered failures for the day 84 assessment even if the DRC considered them a success.

Other secondary efficacy endpoints included crude rates of all-cause mortality through day 84, probability of survival estimates through day 84 by Kaplan-Meier method and DRC-assessed overall response at day 42 and at day 84. The components of overall response (clinical, mycological and radiological responses) were evaluated at EOT, day 42 and day 84.

7.2.4 Choice of Active Comparator

Voriconazole was chosen as the active comparator in Study 0104 as it is the first-line agent recommended by IDSA.[6]

The dose of voriconazole used in the study was consistent with current dosing recommendations in the prescribing information.[13]

7.2.5 Independent Data Safety Monitoring Board (IDSMB)

An Independent Data Safety Monitoring Board (IDSMB) monitored the data from Study 0104 on an ongoing basis to ensure the continuing safety of patients. The IDSMB could recommend stopping the study for safety reasons. The study was not stopped due to safety concerns and no alterations in study design or conduct were requested by the IDSMB.

7.2.6 Data Review Committee (DRC)

In Study 0104, patient data were reviewed and adjudicated by an independent, blinded DRC consisting of experts in fungal infections. The DRC was responsible for categorizing the baseline diagnosis of IFD, assessing overall response outcomes, confirming the infection causing pathogen and/or galactomannan criteria, confirming the location(s) of the invasive infection and evaluating attributable mortality based on the DRC Charter.

Review of patient data by the DRC was conducted using patient profiles. The information in the patient profiles did not include the assigned treatment group or the investigator assessments of baseline mycological criteria or the investigator assessments of clinical, mycological or radiological responses at the various time points.

A blinded, independent radiology expert was responsible for providing a written evaluation of each image and an assessment of radiological response, which was included in the patient profiles provided to the DRC.

The DRC Review Team for Study 0104 consisted of 4 teams of 3 members each (one of whom was designated as the Team Lead), who reviewed patient data. Consensus was required by all 3 members within a team for all data points. If consensus was not reached, the data were discussed at a consensus meeting that included all 3 members of the DRC Review

Team. If consensus was not reached by the DRC Review Team, the majority opinion prevailed and/or the opinion of the DRC Review Team Lead.

Baseline IFD and response to treatment was assessed based on the study protocol and DRC Charter, which were consistent with the EORTC/MSG 2008 consensus criteria.[27][57] Specific diagnostic criteria definitions used in Study 0104 are provided in [Appendix 3].

Baseline Diagnosis of IFD

The DRC categorized baseline diagnosis based on the 2008 EORTC/MSG guidelines,[27] as follows:

No-IFD: Patients were categorized in this group if the DRC determined there was insufficient evidence or documentation of IFD.

Possible IFD**:** Patients were categorized in this group if the DRC determined there was adequate evidence of IFD based on at-risk host factors (e.g., neutropenia, HSCT, immunosuppression) and radiologic findings consistent with IFD.† Mycological evidence was not required; however, patients with a single serum galactomannan value ≥ 0.5 to < 0.7 or a positive BAL galactomannan were included in this group.

Probable IFD: Patients were categorized in this group if the DRC determined there was adequate evidence of invasive infectious disease based on at-risk host factors (e.g., neutropenia, HSCT, immunosuppression) and radiologic findings consistent with IFD.† Patients in this group had mycological evidence of IFD based on cytology, microscopy, culture from a non-sterile site or two consecutive serum galactomannan values ≥ 0.5 or one serum galactomannan value ≥ 0.7.

Proven IFD: Patients were categorized in this group if the DRC determined there was adequate evidence of invasive infectious disease based on positive microscopy or culture from a sterile site or with tissue damage.

† If pulmonary disease was not present, clinical evidence of sino-nasal or CNS infection was necessary.

Overall Response

The DRC categorized overall response into 4 categories based on the 2008 EORTC/MSG guidelines.[57] The 4 categories for overall response are complete response, partial response, stable and progression. Each of the 4 categories was based on specific clinical, radiological and mycological response criteria, which are detailed in [Appendix 3].

Other

Additional details on the pathogen, disease location and attributable mortality coding are provided in [Appendix 3].

7.2.7 Statistical Analysis Plan

7.2.7.1 Sample Size Calculation

The sample size calculation was based on the primary efficacy endpoint, all-cause mortality through day 42. Approximately 255 patients per group or approximately 510 patients in total

were to be enrolled to ensure at least 80% power to demonstrate that the upper bound of the 95% CI for a treatment difference (isavuconazole–voriconazole) was not greater than 10%. This sample size calculation was based on a one-sided, large sample, normal approximation and non-inferiority test at a 2.5% significance level. A 20% mortality rate through day 42 for both voriconazole and isavuconazole was assumed for the ITT analysis population.

7.2.7.2 Analysis of the Primary Efficacy Endpoint and Non-inferiority Margin Justification

The primary endpoint, all-cause mortality through day 42, was summarized for each treatment group as a crude rate including all ITT patients (the primary analysis population). The treatment difference (isavuconazole–voriconazole) and the 95% CI of the adjusted treatment difference were calculated based on the stratified Cochran-Mantel-Haenszel (CMH) method adjusting for three randomization strata: geographical region, allogeneic HSCT status and active malignancy status at baseline. A patient with an unknown survival status at the time point at which the all-cause mortality endpoint was analyzed (i.e., days 42 or 84) was treated as a death for that analysis.

The survival probability through day 84 was calculated based on the Kaplan-Meier method by censoring the lost-to-follow-up patients at the last assessment day that was calculated from the first dose of study drug.

The upper bound of the 95% CI for the adjusted treatment difference was compared to the prespecified NIM of 10%. Isavuconazole was to be considered non-inferior to voriconazole in the treatment of IA if the upper limit of the 95% CI for the adjusted treatment difference in mortality rates was less than 10%.

A high level outline of the formal justification of the 10% NIM follows:

- In the absence of historical placebo-controlled trials, an estimation of the all-cause mortality through day 42 in the untreated patients was 84.8% with a 95% CI of (75.1, 94.5), which was based on a meta-analysis of the historical literature. This estimation was consistent with a mortality of 100% in untreated patients reported by Denning.[58]
- The historical all-cause mortality rate through day 42 for voriconazole was 18.8% (95% CI: 12.4, 25.1), based on the randomized comparative study evaluating voriconazole and amphotericin B.[12]

A conservative estimate of effect size (M_1) for voriconazole compared to untreated (placebo) IA patients for all-cause mortality through day 42 was 50.0, which was calculated as follows:

Lower bound of placebo 95% CI minus Upper bound of voriconazole 95% CI = 75.1% – 25.1% = 50.0%

A 10% NIM provides statistically robust evidence that isavuconazole is superior to placebo, preserves at least 80% of the estimated voriconazole treatment effect and is clinically acceptable.

Additionally, sensitivity analyses were performed for the primary endpoint: minimum-risk method using the same three randomization stratification factors and crude treatment difference without the stratification factors.

7.2.7.3 Analyses of Secondary Efficacy Endpoints

The key secondary efficacy endpoint was the DRC-assessed overall response at EOT. Other secondary efficacy endpoints included DRC-assessed clinical response, mycological response and radiological response at EOT. The primary analysis population for these endpoints was the mITT, which consisted of patients with proven and probable IFD assessed by the DRC at baseline.

The same CMH method as the primary efficacy analysis was used to calculate the adjusted treatment difference (voriconazole–isavuconazole) and its 95% CI for all secondary efficacy endpoints. For the key secondary efficacy endpoint of success rate for DRC-assessed overall response at EOT, the upper bound of the 95% CI for the adjusted treatment difference was compared to a 15% interpretive margin agreed upon with the FDA.

Other secondary efficacy endpoints included all-cause mortality through day 84 and DRC-assessed clinical response, mycological response and radiological response.

7.2.7.4 Analysis Populations and Subgroup Analysis

Intent-to-treat (ITT)

The primary analysis population in Study 0104 was the ITT population and consisted of all randomized patients who took at least one dose of study drug. Data were analyzed according to the treatment the patient was randomized to.

Modified Intent-to-treat (mITT)

The mITT analysis population consisted of a subset of ITT patients with proven or probable IFD (i.e., IA or other filamentous fungi) at baseline as determined by the DRC. A description of DRC baseline categorization of IFD is provided in [Section 7.2.6].

Mycological Intent-to-treat (myITT)

The mycological ITT (myITT) analysis population consisted of a subset of mITT patients with microbiologically-confirmed IA at baseline. Patients with other filamentous fungi were not included in this population.

Other Analysis Populations

Additional analysis populations include the per protocol sets (PPS), which are a subset of the ITT analysis population (i.e., PPS-ITT) or a subset of the mITT analysis population (PPS-mITT) and included patients that did not deviate from the pre-specified Classification Criteria (e.g., excluded patients who met key exclusionary criteria, received at least 3 consecutive days of prohibited concomitant medications, received < 7 days of study drug). Details regarding the prespecified PPS criteria can be found in [Appendix 4].

The safety population included all randomized patients who received at least one dose of study drug with data analyzed according to the study drug that patients received as the first dose, even if it was different from the randomized study drug.

Subgroup Analyses

The subgroup analyses were conducted for the primary and the key secondary efficacy endpoints. Within the subgroup analysis, the Treatment-by-Subgroup interaction was evaluated using a logistic regression model with the following factors: Treatment Group, Geographical Regions, Allogeneic HSCT Status, Active Malignancy Status, Subgroup Factor and Treatment-by-Subgroup interaction. The interaction was evaluated at the significance level of 0.15. The subgroups are presented with crude treatment group differences and 95% CIs calculated based on normal approximation.

7.2.7.5 Handling of Missing Data

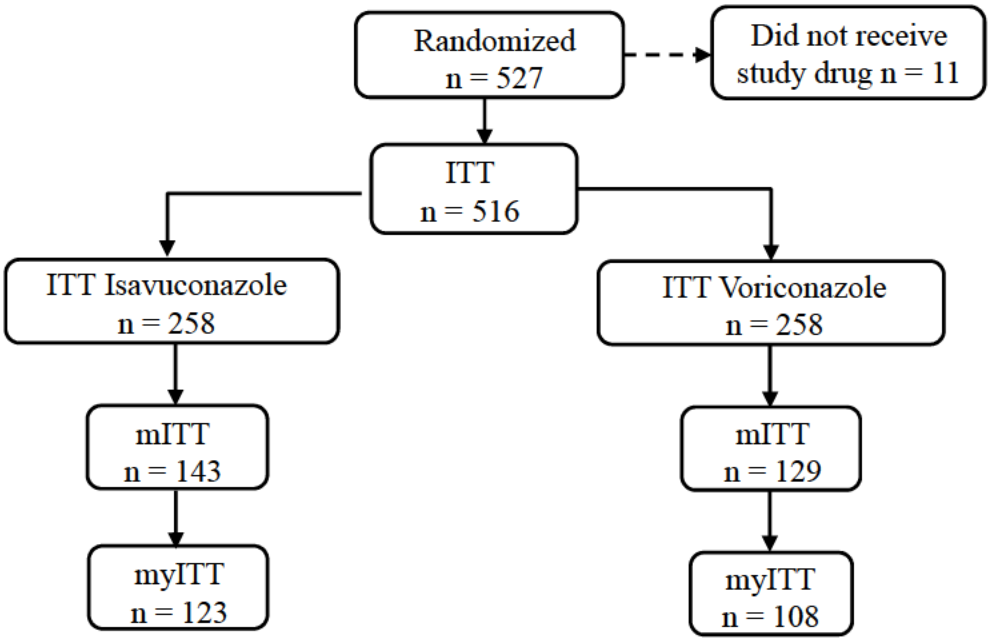
Unknown survival status was counted as a death for calculation of crude mortality and was censored for the Kaplan-Meier method. When change from baseline to a postbaseline value was calculated, only patients with both baseline and at least one postbaseline value were included in the calculation. In the time to event analysis, patients who were lost-to-follow-up were censored at the last assessment day that was calculated from the first dose of study drug.

7.3 Distribution, Demographics and Duration of Exposure

7.3.1 Distribution

In Study 0104, 516 patients were randomized to isavuconazole (258) and voriconazole (258), received at least one dose of study drug and were included in the ITT population. The mITT population consisted of 272 patients (143 isavuconazole and 129 voriconazole) [Figure 16]. See [Section 7.2.7.4] for further description of the patient populations.

Figure 16 Analysis Populations (0104)



Intent-to-treat (ITT): All randomized patients who received at least one dose of study medication.
Modified ITT (mITT): A subset of ITT patients with proven or probable IFD as determined by the DRC.
Mycological ITT (myITT): A subset of mITT patients with microbiologically-confirmed IA.
DRC: Data Review Committee; IA: invasive aspergillosis.

Analysis populations based on DRC categorization of IFD at baseline include the ITT, mITT and myITT populations [Table 7].

Table 7 DRC Categorization of IFD by Analysis Population (0104)

Analysis Population DRC Classification	Isavuconazole n (%)	Voriconazole n (%)	Total n (%)
ITT Population	**(n = 258)**	**(n = 258)**	**(n = 516)**
Proven IFD	29 (11.2)	36 (14.0)	65 (12.6)
Probable IFD	114 (44.2)	93 (36.0)	207 (40.1)
Possible IFD	88 (34.1)	108 (41.9)	196 (38.0)
No IFD	27 (10.5)	21 (8.1)	48 (9.3)
mITT Population	**(n = 143)**	**(n = 129)**	**(n = 272)**
Proven IFD	29 (20.3)	36 (27.9)	65 (23.9)
Probable IFD	114 (79.7)	93 (72.1)	207 (76.1)
myITT Population	**(n = 123)**	**(n = 108)**	**(n = 231)**
Proven IA	18 (14.6)	18 (16.7)	36 (15.6)
Probable IA	105 (85.4)	90 (83.3)	195 (84.4)

Intent-to-treat (ITT): All randomized patients who received at least one dose of study medication.
Modified ITT (mITT): A subset of ITT patients with proven or probable IFD as determined by the DRC.
Mycological ITT (myITT): A subset of mITT patients with microbiologically-confirmed IA.
DRC: Data Review Committee; IA: invasive aspergillosis; IFD: invasive fungal disease.

Overall, the number of patients discontinuing treatment was similar in the 2 treatment groups. The 3 most common reasons for discontinuation of treatment, based on the investigator's

categorization, were Adverse Event/Intercurrent Illness, Insufficient Therapeutic Response and Death [Table 8]. Differences were observed between treatment groups for some of the categories of reasons for treatment discontinuation. The number of patients who discontinued treatment primarily due to Adverse Event/Intercurrent Illness was lower in the isavuconazole treatment group (12.0%, 31/258) than in the voriconazole treatment group (20.5%, 53/258). The number of patients who discontinued treatment primarily due to Insufficient Therapeutic Response, as assessed by the investigator, was higher in the isavuconazole treatment group (15.1%, 39/258) than in the voriconazole treatment group (8.9%, 23/258).

Table 8 Primary Reasons for Study Drug Discontinuation (ITT Population; 0104)

Parameter **Category, n (%) of patients**	**Isavuconazole** **(n = 258)**	**Voriconazole** **(n = 258)**
Discontinued	**140 (54.3)**	**138 (53.5)**
Primary Reasons for Study Drug Discontinuation		
Death	17 (6.6)	21 (8.1)
Adverse Event/Intercurrent Illness	31 (12.0)	53 (20.5)
Insufficient Therapeutic Response	39 (15.1)	23 (8.9)
Failure to Return/Lost-to-follow-up	2 (0.8)	1 (0.4)
Violation of Selection at Entry	17 (6.6)	10 (3.9)
Other Protocol Violation	10 (3.9)	6 (2.3)
Did Not Cooperate	12 (4.7)	9 (3.5)
Admin/Other	12 (4.7)	15 (5.8)

Intent-to-treat (ITT): All randomized patients who received at least one dose of study medication.

Death: Patient death while on study treatment.

Adverse Event/ Intercurrent Illness: Patient had an adverse event leading to discontinuation of study treatment.

Insufficient Therapeutic Response: Per investigator assessment of response, the patient was a failure and/or required alternative antifungal therapy.

Failure to Return/Lost-to-follow-up: Patient unable to adhere to study requirements and unable to be contacted for follow up visits.

Violation of Selection at Entry: Patient was assessed as not meeting all entry criteria after initiation of study drug. Reasons included but were not limited to: invasive fungal disease (IFD) not confirmed within 7 days or ineligible creatinine clearance level.

Other Protocol Violation: Patient had a protocol violation causing discontinuation per the investigator. Reasons include, but were not limited to: were not compliant with study medication or took prohibited medication.

Did Not Cooperate: Patient withdrew consent.

Admin/Other: Encompassed any reason other than the above. Examples of reasons include: patient moved and patient withdrawn due to hold in enrollment.

7.3.2 Demographics and Baseline Characteristics

For the ITT population, the treatment groups were balanced for baseline characteristics [Table 9]. The majority of patients randomized into the study were White (81.8% isavuconazole and 74.3% voriconazole). Overall, the study recruited more men (56.2% isavuconazole and 63.2% voriconazole) than women. There were no clinically relevant differences between the two treatment groups for baseline characteristics. The stratification factors at randomization (i.e., geographic region [US and Canada, Western Europe plus Australia and New Zealand and Other Region], allogeneic HSCT and active malignancy) were balanced between the 2 treatment groups.

More than 80% of patients had underlying hematologic malignancies, approximately 65% were neutropenic and approximately 20% had had a prior allogeneic HSCT.

Table 9 Demographics and Baseline Characteristics (ITT Population; 0104)

Parameter Statistics	Isavuconazole (n = 258)	Voriconazole (n = 258)
Age, Mean (SD; years)	**51.1 (16.2)**	**51.2 (15.9)**
Sex, Male, n (%)	**145 (56.2)**	**163 (63.2)**
Race, n (%)		
White	211 (81.8)	191 (74.3)
Asian	45 (17.4)	64 (24.9)
African American	1 (0.4)	1 (0.4)
Other	1 (0.4)	1 (0.4)
Missing	0	1
Ethnicity, n (%)		
Hispanic or Latino	22 (8.5)	9 (3.5)
Not Hispanic or Latino	236 (91.5)	248 (96.5)
Missing	0	1
Baseline Condition, n (%)		
Hematologic malignancy	211 (81.8)	222 (86.0)
Neutropenia†	163 (63.2)	175 (67.8)
Use of corticosteroids	48 (18.6)	39 (15.1)
Use of T-cell immunosuppressant	111 (43.0)	109 (42.2)
Stratification Variables, n (%)		
Prior Allogeneic HSCT	54 (20.9)	51 (19.8)
Active malignancy at baseline	173 (67.1)	187 (72.5)
Geographical region‡		
North America	30 (11.6)	28 (10.9)
Western Europe plus Australia and New Zealand	105 (40.7)	107 (41.5)
Other regions	123 (47.7)	123 (47.7)

Intent-to-treat (ITT): All randomized patients who received at least one dose of study medication.

Age was calculated relative to informed consent date.

ANC: absolute neutrophil count; HSCT: hematopoietic stem cell transplant.

† Neutropenia was defined as ANC < 0.5 x 10^9/L (< 500/mm^3) and was determined by the investigator.

‡ North America consists of Canada and the US. Western Europe consists of Belgium, France, Germany, Italy, The Netherlands, Spain and Switzerland. Other Regions consists of Argentina, Brazil, Chile, China, Egypt, Hungary, India, Israel, Malaysia, Mexico, Poland, Russia, South Korea, Thailand and Turkey.

In the overall ITT population, the majority of patients (445, 86.2%) had a malignancy as the primary underlying condition, predominantly hematologic malignancies (433 patients, 83.9%). The 4 most common hematologic malignancies were AML (225 patients), acute lymphocytic leukemia (54 patients), non-Hodgkin's lymphoma (26 patients) and chronic lymphocytic leukemia (23 patients).

The distribution of the pathogens causing the IFD for the mITT population, as assessed by the DRC, is presented in [Table 10]. Approximately half of the mITT Population (51.5%) had evidence for *Aspergillus* infection based on galactomannan. The most common pathogen in both treatment groups was *Aspergillus fumigatus*.

Table 10 Mycological Criteria for IFD at Baseline (mITT Population; 0104)

Category Pathogen, n (%) of patients	Isavuconazole (n = 143)	Voriconazole (n = 129)
Galactomannan Positive†	72 (50.3)‡	68 (52.7)
ASPERGILLUS species ONLY§	49 (34.3)	39 (30.2)
Aspergillus fumigatus	32 (22.4)	21 (16.3)
Aspergillus flavus	10 (7.0)	12 (9.3)
Aspergillus terreus	4 (2.8)	2 (1.6)
Aspergillus niger	6 (4.2)	2 (1.6)
Aspergillus ustus	0	1 (0.8)
Aspergillus NOS	1 (0.7)	3 (2.3)
Aspergillus sydowi	1 (0.7)	0
ASPERGILLUS Species PLUS OTHER MOULD Species	3 (2.1)	1 (0.8)
NON-*ASPERGILLUS* Species ONLY	5 (3.5)	6 (4.7)
MOULD Species NOS	14 (9.8)	15 (11.6)

Modified intent-to-treat (mITT): A subset of ITT patients with proven or probable IFD as determined by the DRC.

DRC: Data Review Committee; IFD: invasive fungal disease; NOS: not otherwise specified.

† Galactomannan criteria were 1 serum result ≥ 0.7 or 2 consecutive serum results ≥ 0.5.

‡ One patient in the isavuconazole treatment group is included in this group and did not have positive galactomannan, but was identified by the DRC as having a probable IFD on the basis of adequate host factors, adequate clinical and radiological features and the mycological criterion of non-sterile cytology, direct microscopy or culture evidence of presence of a species of mould.

§ Within *Aspergillus* species only, a patient may have more than one pathogen causing IFD. The frequency for each category is mutually exclusive.

The majority of patients who had proven or probable IFD as determined by the DRC had an IFD determined to be lower respiratory tract disease (LRTD) only (isavuconazole 81.1%, 116/143; voriconazole 82.9%, 107/129). Overall, more than 90% of these patients had pulmonary involvement.

The population of patients enrolled in Study 0104 is representative of the patient population likely to receive antifungal treatment for proven, probable or possible IFD caused by *Aspergillus* spp.

7.3.3 Duration of Study Drug Administration

Duration of study drug administration was similar between treatment groups [Table 11].

Table 11 Duration of Study Drug Administration (ITT Population; 0104)

Characteristics	Isavuconazole (n = 258)	Voriconazole (n = 258)
Total Duration (Days)	**(n = 258)**	**(n = 258)**
Mean (SD)	47.0 (32.35)	46.4 (32.06)
Median	45.0	46.5
Min – Max	1 – 102	1 – 88
Duration of IV Dosing (Days)	**(n = 258)**	**(n = 258)**
Mean (SD)	8.1 (8.51)	8.9 (9.58)
Median	5.0	5.0
Min – Max	1 – 84	1 – 63

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Characteristics	Isavuconazole (n = 258)	Voriconazole (n = 258)
Duration of Oral Dosing (Days)	**(n = 195)**	**(n = 205)**
Mean (SD)	51.6 (27.98)	47.2 (28.91)
Median	60.0	52.5
Min – Max	0.5 – 99.5	1.0 – 85.5

Intent-to-treat (ITT): All randomized patients who received at least one dose of study medication.

Total duration is defined as the number of days between the start and the end date of study drug, where the duration will be calculated by: (end date-start date + 1). Duration of IV dosing only and duration of oral dosing only are calculated separately in a similar way as total duration. For the days when both IV and oral dosing occur on the same day, the day will be split by 0.5 day in the duration calculation.

All patients started on IV therapy and 77.5% of these patients switched from IV to oral therapy during the course of the study.

7.4 Study 0104 Efficacy Results

7.4.1 All-cause Mortality

7.4.1.1 Primary Efficacy Endpoint Analysis – All-cause Mortality Through Day 42

In the double-blind study, all-cause mortality through day 42 in the ITT population was 18.6% and 20.2% in the isavuconazole and voriconazole treatment groups, respectively [Table 12]. This met the primary objective of demonstrating the non-inferiority of isavuconazole relative to voriconazole since the upper bound of the 95% CI (5.683) for the adjusted treatment difference (isavuconazole-voriconazole: -1.0) was lower than the prespecified NIM of 10%.

Table 12 All-cause Mortality through Day 42 (ITT Population; 0104)

	Isavuconazole (n = 258)	Voriconazole (n = 258)
All-cause Mortality, n (%)	48 (18.6)	52 (20.2)
Adjusted Treatment Difference (isavuconazole-voriconazole) 95% CI	-1.0 (-7.759, 5.683)	
Unknown Survival Status, n (%)†	3 (1.2)	2 (0.8)

Intent-to-treat (ITT): All randomized patients who received at least one dose of study medication.

The adjusted treatment difference (isavuconazole-voriconazole) and 95% CI were calculated by a stratified CMH method with the strata of Geographical Region, Allogeneic HSCT Status and Active Malignancy Status.

CMH: Cochran-Mantel-Haenszel; HSCT: hematopoietic stem cell transplant.

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

Two sensitivity analyses were performed for all-cause mortality through day 42. One sensitivity analysis was based on a minimum-risk method and the other calculated the treatment difference and associated 95% CI based on the crude mortality rate without stratification factors. The minimum risk method used the same stratification factors as the primary analysis (CMH method). The outcomes in both of the sensitivity analyses support the results of the primary analysis [Table 13].

Table 13 Sensitivity Analyses for All-cause Mortality through Day 42 (ITT Population; 0104)

Analysis Method Outcomes, n (%)	Isavuconazole (n = 258)	Voriconazole (n = 258)
Minimum Risk		
All-cause mortality†	48 (18.6)	52 (20.2)
Adjusted treatment difference (95% CI)‡	-1.1 (-7.842, 5.624)	
Without Adjustment for Stratification Factors		
All-cause mortality†	48 (18.6)	52 (20.2)
Crude treatment difference (95% CI)§	-1.6 (-8.771, 5.670)	

Intent-to-treat (ITT): All randomized patients who received at least one dose of study medication.

HSCT: hematopoietic stem cell transplant.

† 5 patients (3 isavuconazole and 2 voriconazole) with unknown survival status were counted as deaths.

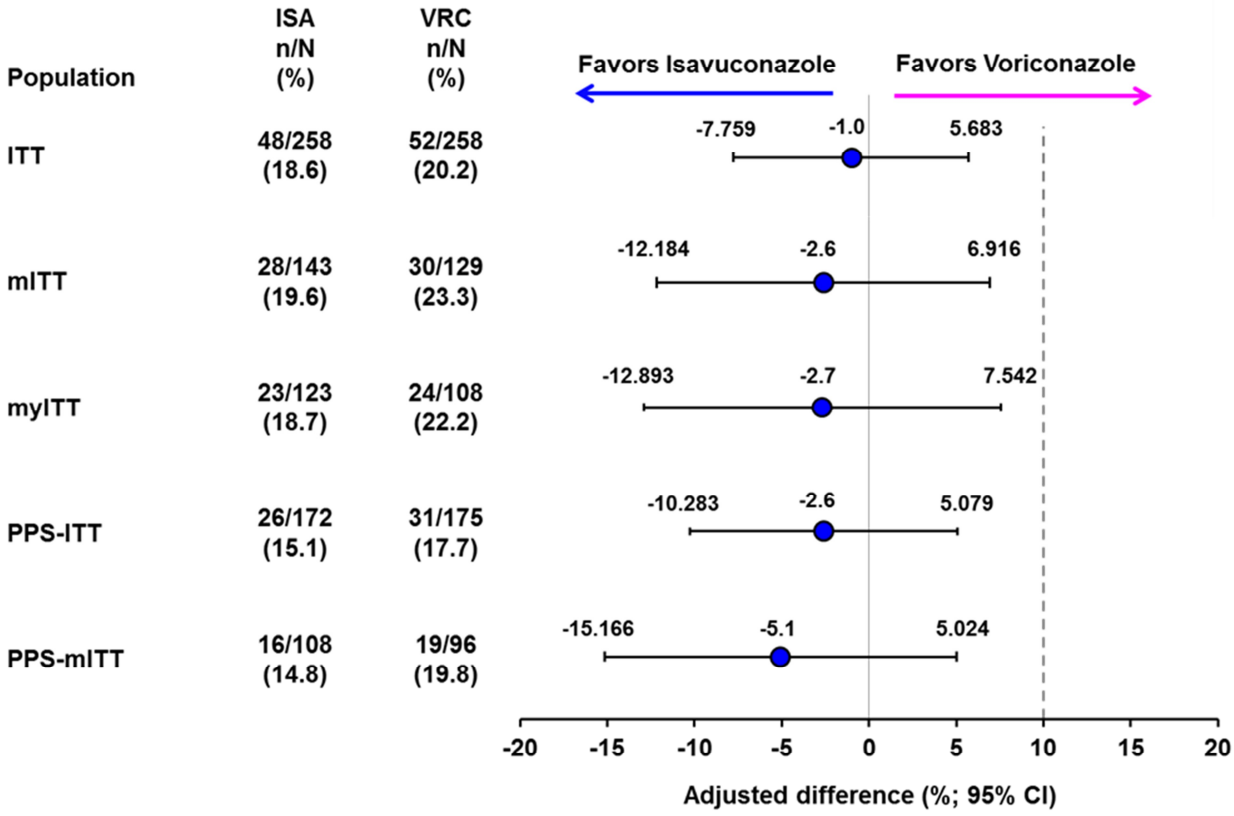
‡ Adjusted treatment difference (isavuconazole−voriconazole) and 95% CIs are calculated by a stratified Minimum Risk method with stratification factors: Geographical Regions, Allogeneic HSCT Status and Active Malignancy Status.

§ Crude treatment difference is calculated by subtracting voriconazole from isavuconazole (isavuconazole−voriconazole) without stratification factors and the 95% CI is calculated based on a normal approximation.

7.4.1.2 All-cause Mortality Through Day 42 for Various Populations

Mortality rates were consistent across populations demonstrating the robustness of the outcomes. The adjusted treatment differences and associated 95% CIs for mortality through day 42 across the various prespecified analytical populations were similar to those observed for the ITT population [Figure 17].

Figure 17 All-Cause Mortality through Day 42 – Number of Patients, Adjusted Treatment Differences and 95% CIs for Various Populations (0104)



Intent-to-treat (ITT): All randomized patients who received at least one dose of study medication.

Modified ITT (mITT): A subset of ITT patients with proven or probable IFD as determined by the DRC.

Mycological ITT (myITT): A subset of mITT patients with microbiologically-confirmed IA.

Per Protocol Set-ITT (PPS-ITT) or mITT (PPS-mITT): A subset of ITT (or mITT) patients who did not deviate from the prespecified Classification Criteria.

DRC: Data Review Committee; IA: invasive aspergillosis; ISA: isavuconazole; VRC: voriconazole.

7.4.1.3 All-cause Mortality Through Day 42 by DRC Categorization of IFD

All-cause mortality through day 42 by DRC categories for IFD at baseline are shown in [Table 14].

Table 14 All-cause Mortality through Day 42 by IFD Category (ITT Population)

IFD Category, n/n (%)	Isavuconazole (n = 258)	Voriconazole (n = 258)
Proven	7/29 (24.1)	7/36 (19.4)
Probable	21/114 (18.4)	23/93 (24.7)
Possible	15/88 (17.0)	19/108 (17.6)
No IFD	5/27 (18.5)	3/21 (14.3)

Intent-to-treat (ITT): All randomized patients who received at least one dose of study medication.

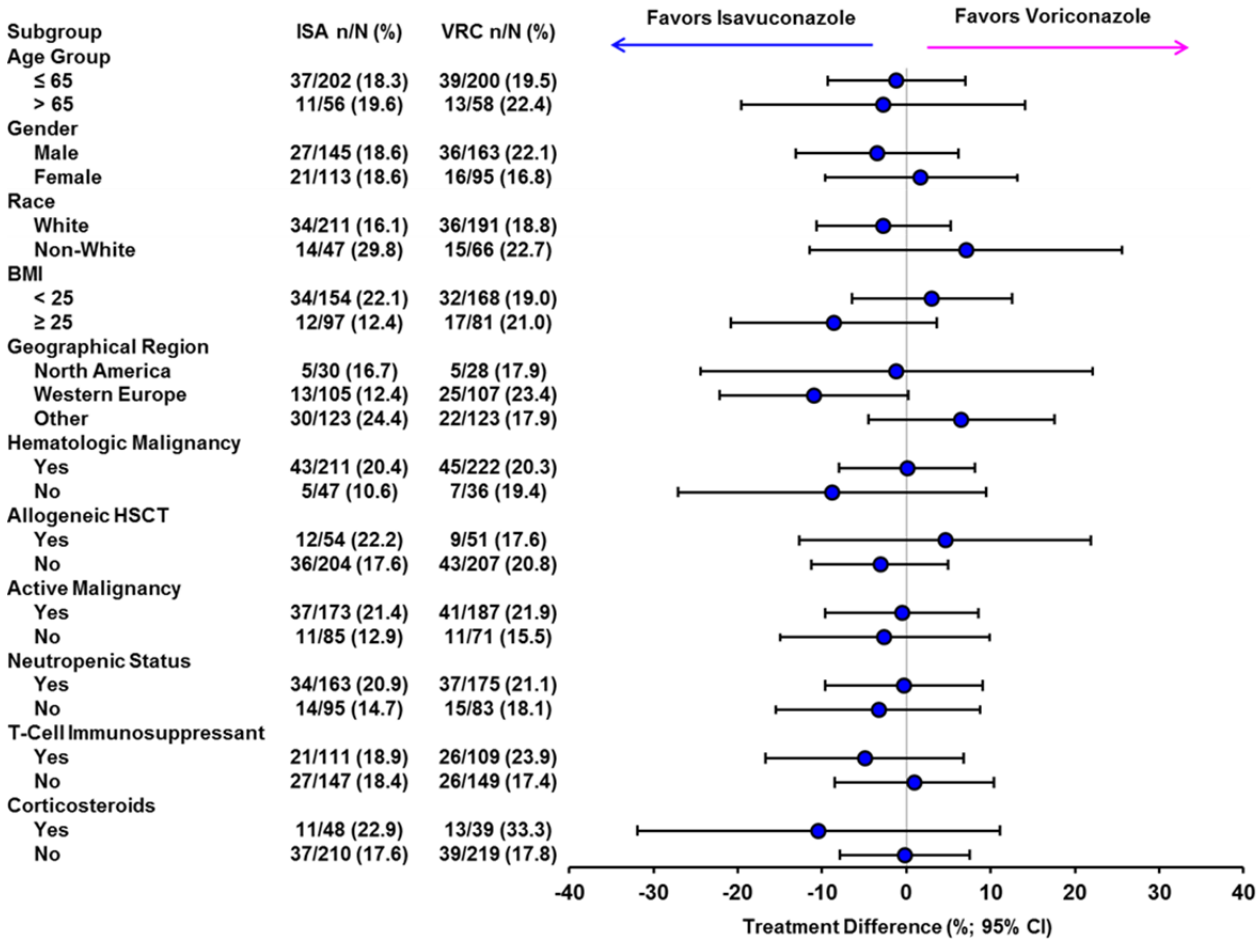
Patients with unknown survival status are counted as deaths.

IFD: invasive fungal disease.

7.4.1.4 All-cause Mortality Through Day 42 by Subgroup

All-cause mortality through day 42 was further analyzed for various intrinsic (age, gender, race and other baseline characteristics) and extrinsic factors (e.g., geographic region) for the ITT population. The crude treatment group differences and 95% CIs for all-cause mortality through day 42 in each of the subgroups for the ITT population are presented in [Figure 18]. These results, along with those from the various populations shown in [Figure 17], further support the robustness of the result of the primary endpoint and the consistent treatment effect of isavuconazole. No dose adjustments for reasons pertaining to efficacy are warranted for any of the subgroups.

Figure 18 All-cause Mortality Through Day 42 – Number of Patients and Treatment Differences with 95% CIs by Subgroup (ITT Population; 0104)



Intent-to-treat (ITT): All randomized patients who received at least one dose of study drug.
Non-White includes Black or African American, Asian or Other.

Footnotes continued on next page

North America consists of Canada and the US. The category of Western Europe consists of New Zealand, Australia, Belgium, France, Germany, Italy, The Netherlands, Spain and Switzerland. Other Regions consists of Argentina, Brazil, Chile, China, Egypt, Hungary, India, Israel, Malaysia, Mexico, Poland, Russia, South Korea, Thailand and Turkey.

Neutropenia was defined as ANC < 0.5 x 10^9/L (< 500/mm^3) and was determined by the investigator.

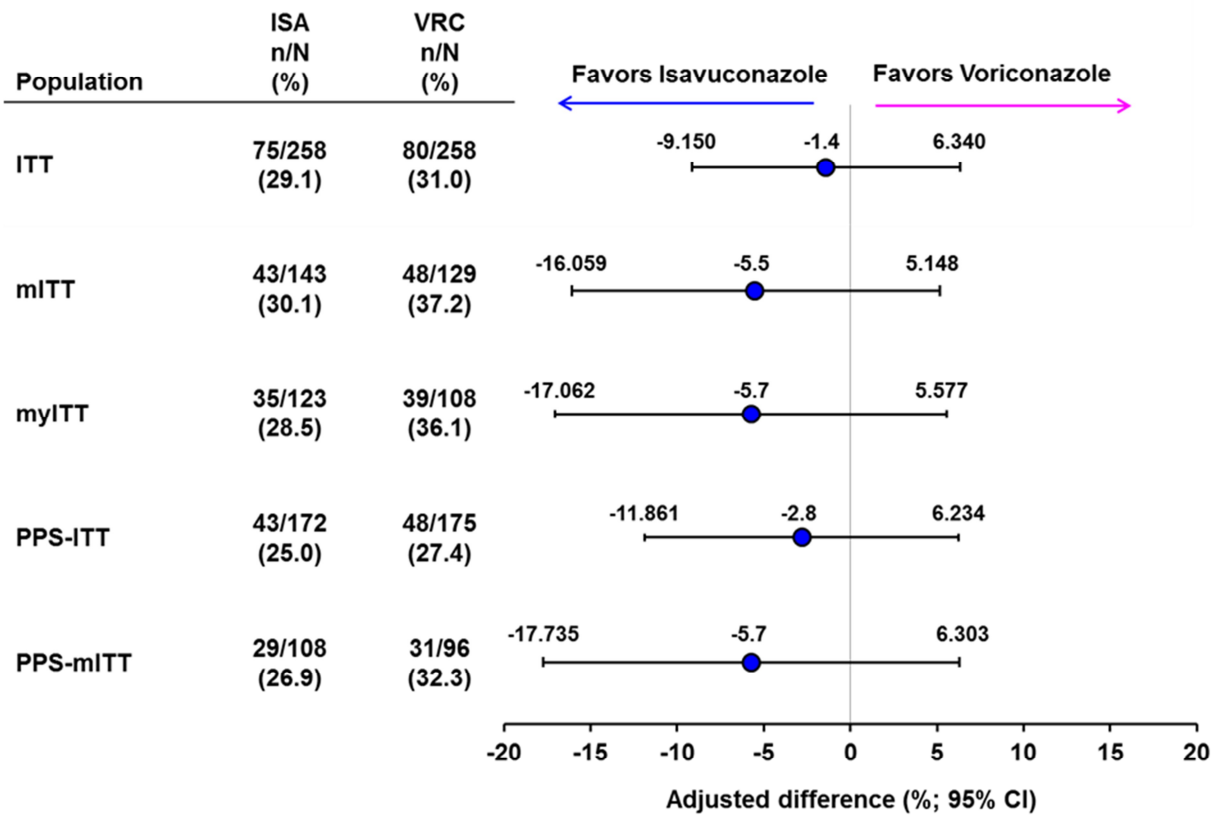
ANC: absolute neutrophil count; BMI: body mass index; HSCT: hematopoietic stem cell transplant; ISA: isavuconazole; VRC: voriconazole.

Results from subgroup analyses of all-cause mortality through day 42 in the mITT population are shown in [Appendix 5].

7.4.1.5 All-cause Mortality Through Day 84 for Various Populations

Adjusted treatment differences and 95% CIs for all-cause mortality through day 84 for the ITT and other populations are similar to those of the primary endpoint [Figure 19].

Figure 19 All-cause Mortality through Day 84 – Number of Patients and Adjusted Treatment Differences with 95% CIs for Various Populations (0104)



Intent-to-treat (ITT): All randomized patients who received at least one dose of study medication.

Modified ITT (mITT): A subset of ITT patients with proven or probable IFD as determined by the DRC.

Mycological ITT (myITT): A subset of mITT patients with microbiologically-confirmed IA.

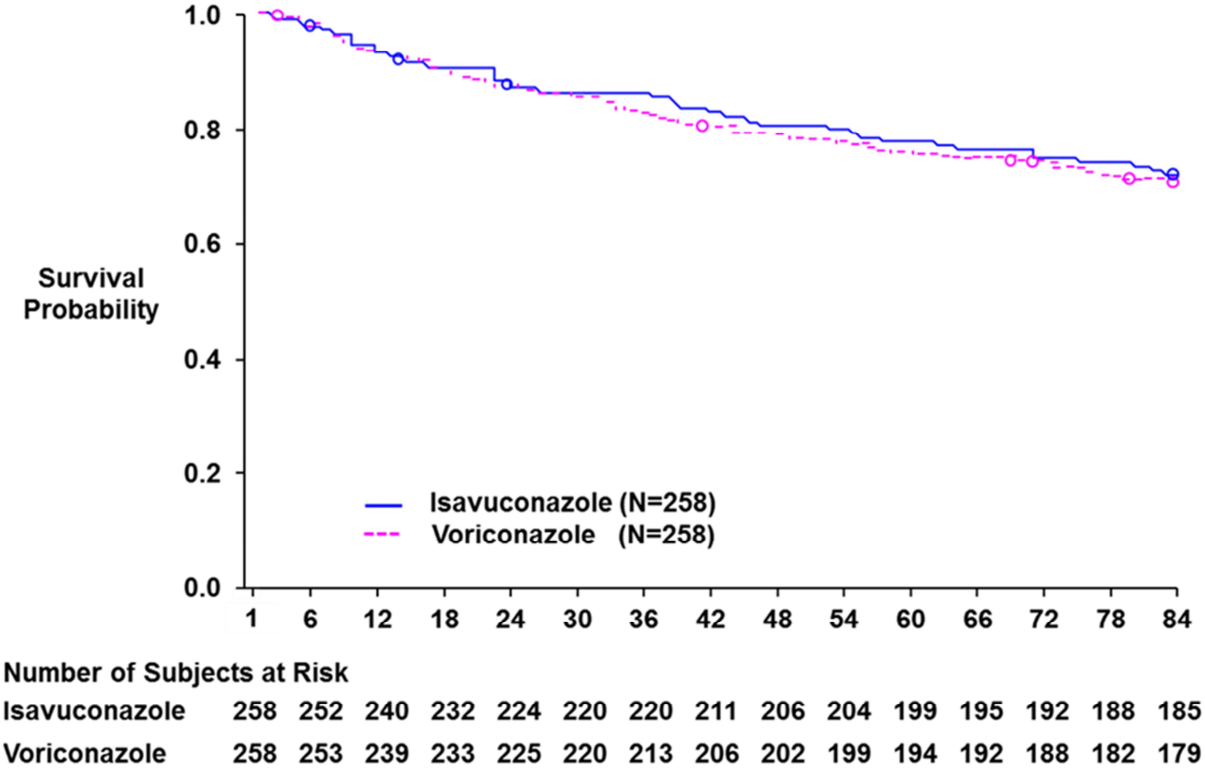
Per Protocol Set-ITT (PPS-ITT) or mITT (PPS-mITT): A subset of ITT (or mITT) patients who did not deviate from the prespecified Classification Criteria.

DRC: Data Review Committee; IA: invasive aspergillosis; ISA: isavuconazole; VRC: voriconazole.

7.4.1.6 Kaplan-Meier Estimates of the Probability of Survival

A stable trend was shown for probability of survival through day 84 using the Kaplan-Meier method in the ITT and mITT analysis populations as presented in [Figure 20 and Figure 21].

Figure 20 Kaplan-Meier Estimates of Probability of Survival through Day 84 (ITT Population; 0104)

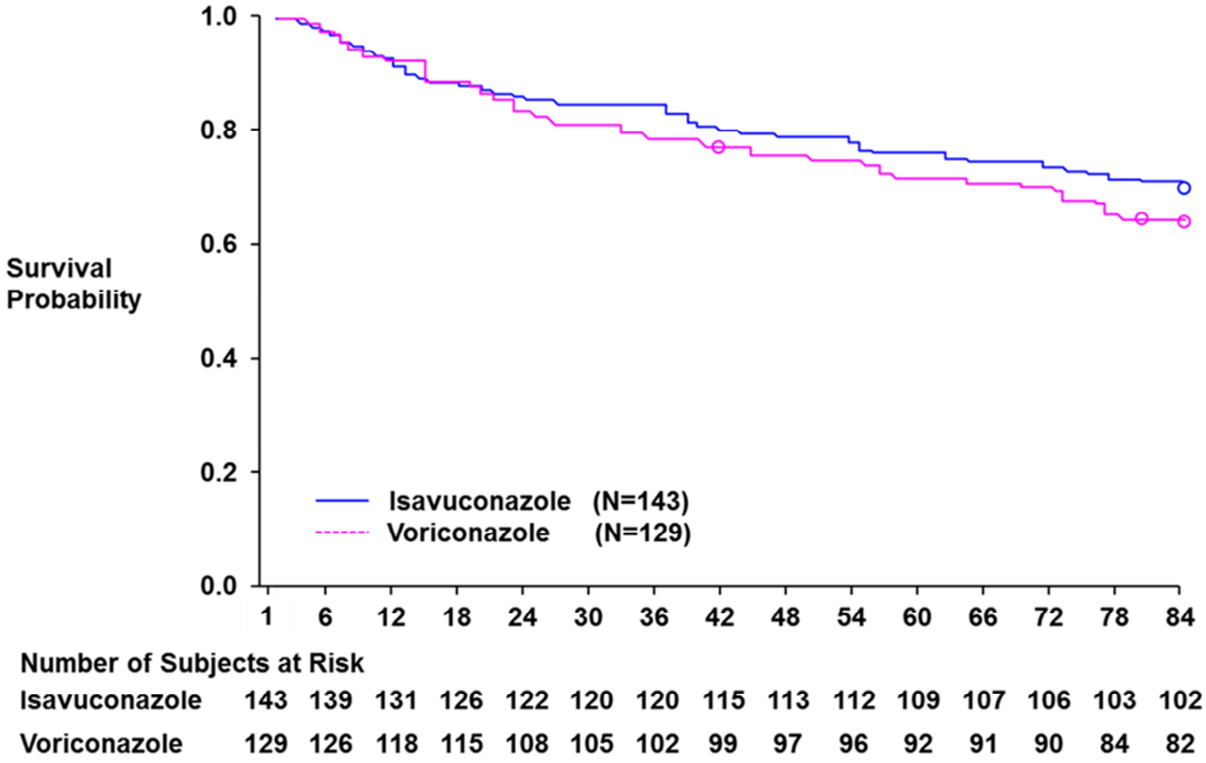


Number of Subjects at Risk

Isavuconazole	258	252	240	232	224	220	220	211	206	204	199	195	192	188	185
Voriconazole	258	253	239	233	225	220	213	206	202	199	194	192	188	182	179

Intent-to-treat (ITT): All randomized patients who received at least one dose of study medication.
Patients were censored on the patient's last assessment day.

Figure 21 Kaplan-Meier Estimates of Probability of Survival through Day 84 (mITT Population; 0104)



Modified intent-to-treat (mITT): A subset of ITT patients with proven or probable IFD as determined by the DRC.

Patients were censored on the patient's last assessment day.

DRC: Data Review Committee; IFD: invasive fungal disease.

7.4.2 DRC-assessed Overall Response

7.4.2.1 Key Secondary Endpoint – DRC-assessed Overall Response at EOT

The results from analysis of the key secondary endpoint of success for DRC-assessed overall response support the efficacy of isavuconazole. Success rates for DRC-assessed overall response at EOT were similar between isavuconazole and voriconazole treated patients (35.0% and 36.4%, respectively) in the mITT population [Table 15]. The 95% CI for the adjusted treatment difference (voriconazole-isavuconazole: 1.6) was (-9.336, 12.572). The upper bound of the 95% CI is below the 15% interpretive margin agreed upon with the FDA.

Table 15 DRC-assessed Overall Response at EOT (mITT Population; 0104)

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

Modified intent-to-treat (mITT): A subset of ITT patients with proven or probable IFD as determined by the DRC.

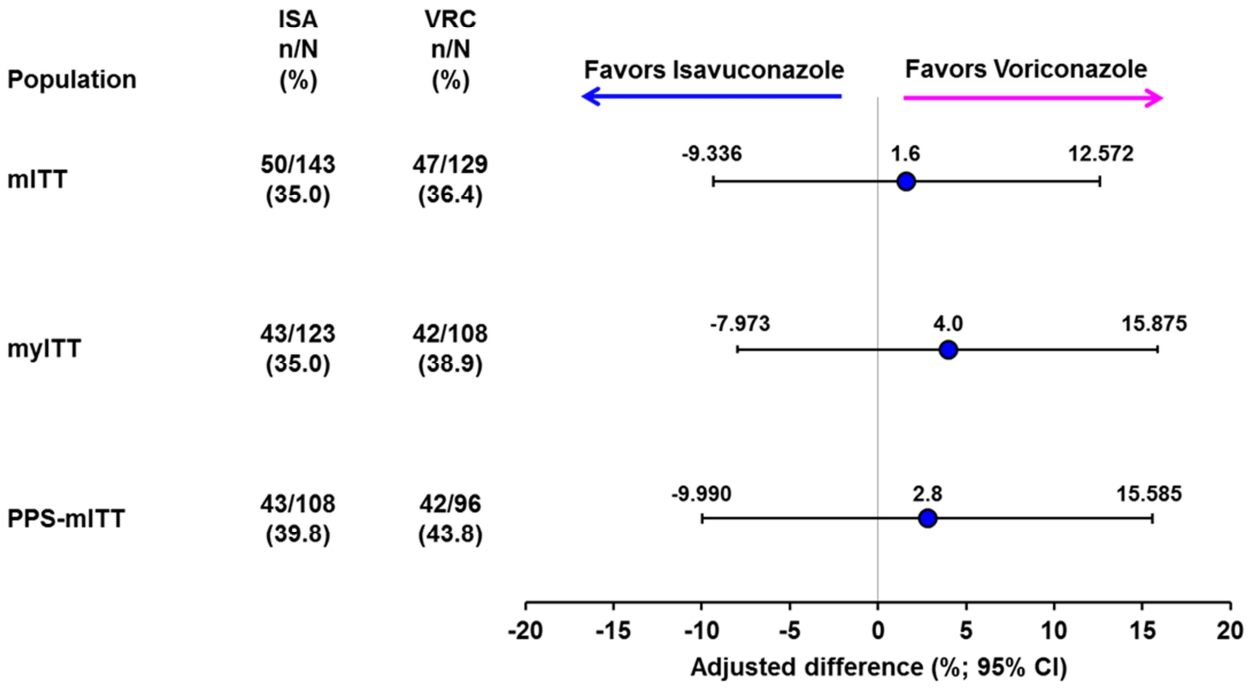
The adjusted treatment difference (voriconazole-isavuconazole) was calculated by a stratified CMH method with the strata of Geographical Region, Allogeneic HSCT Status and Active Malignancy Status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

CMH: Cochran-Mantel-Haenszel; DRC: Data Review Committee; EOT: end of treatment; IFD: invasive fungal disease; HSCT: hematopoietic stem cell transplant.

7.4.2.2 DRC-assessed Overall Response at EOT for Various Populations

The adjusted treatment differences and associated 95% CIs for DRC-assessed overall response at EOT across the various prespecified analytical populations were similar to those observed for the mITT population [Figure 22].

Figure 22 Success Rates for DRC-assessed Overall Response at EOT – Adjusted Treatment Differences with 95% CIs for Various Populations (0104)



Footnotes appear on next page

Modified intent-to-treat (mITT): A subset of ITT patients with proven or probable IFD as determined by the DRC.

Mycological ITT (myITT): A subset of mITT patients with microbiologically-confirmed IA.

Per Protocol Set-mITT (PPS-mITT): A subset of mITT patients who did not deviate from the prespecified Classification Criteria.

DRC: Data Review Committee; IA: invasive aspergillosis; IFD: invasive fungal disease; ISA: isavuconazole; VRC: voriconazole.

7.4.2.3 DRC-assessed Overall Response at EOT by DRC Categorization of IFD

DRC-assessed overall response by treatment group and by IFD categories are shown in [Table 16].

Table 16 DRC-assessed Overall Response at EOT by IFD Category (Patients with Proven, Probable and Possible IFD per DRC)

IFD Category, n/n (%)†	Isavuconazole (n = 231)	Voriconazole (n = 237)
Proven	7/29 (24.1)	11/36 (30.6)
Probable	43/114 (37.7)	36/93 (38.7)
Possible	41/88 (46.6)	51/108 (47.2)

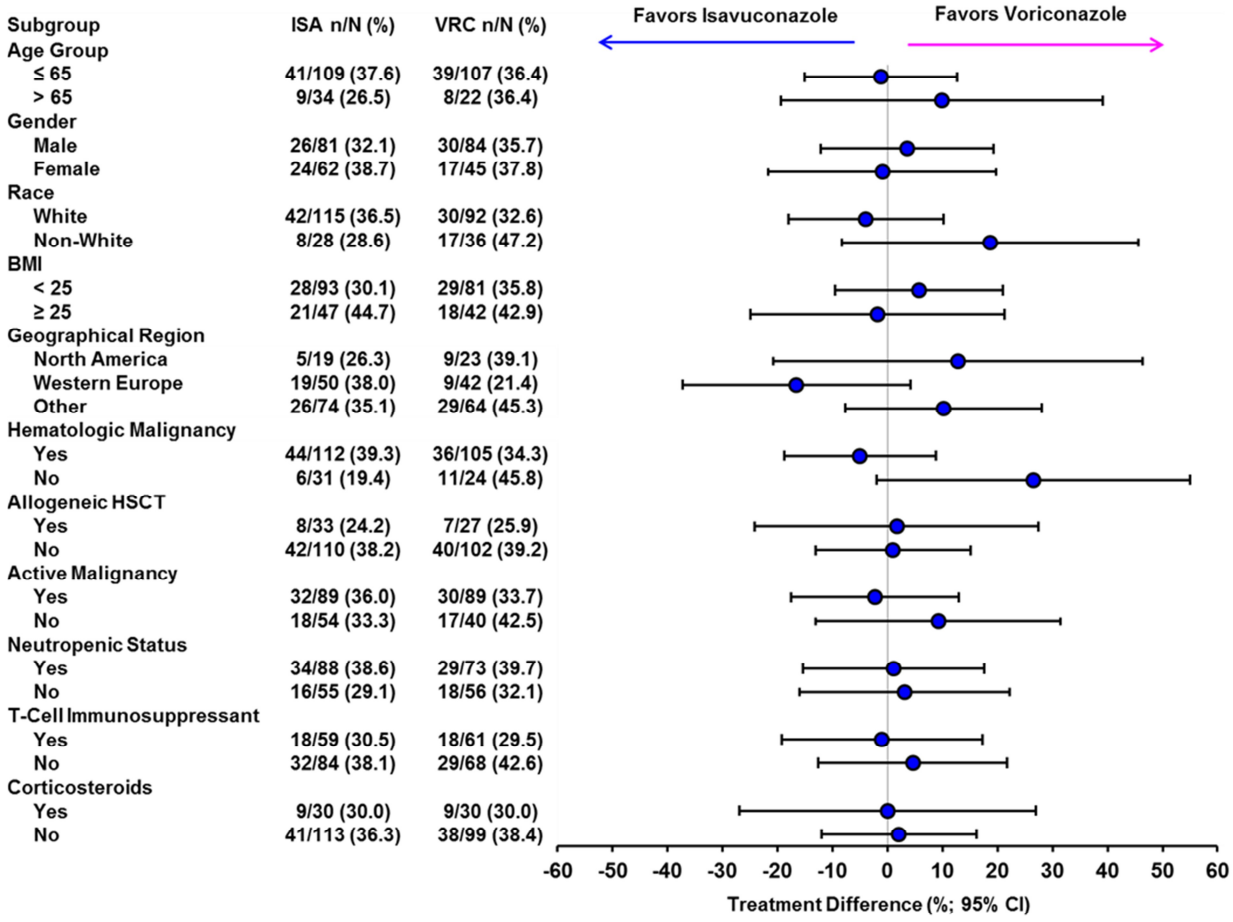
DRC: Data Review Committee; EOT: end of treatment; IFD: invasive fungal disease.

† Response outcomes were not recorded by the DRC for patients in the DRC-assessed no IFD category.

7.4.2.4 DRC-assessed Overall Response at EOT by Subgroup

The treatment group differences and 95% CIs for DRC-assessed overall response by subgroup are presented in [Figure 23]. These results, along with those from the various populations in [Figure 22], further support the consistency of the key secondary efficacy results and the treatment effect of isavuconazole.

Figure 23 Success Rates for DRC-assessed Overall Response at EOT – Number of Patients and Treatment Differences with 95% CIs by Subgroup (mITT Population; 0104)



Modified intent-to-treat (mITT): A subset of ITT patients with proven or probable IFD as determined by the DRC.

Success is defined as a complete or partial overall response.

Non-White includes Black or African American, Asian or Other.

Neutropenia was defined as ANC < 0.5 x 10^9/L (< 500/mm^3) and was determined by the investigator.

ANC: absolute neutrophil count; BMI: body mass index; HSCT: hematopoietic stem cell transplant; DRC: Data Review Committee; EOT: end of treatment; ISA: isavuconazole; VRC: voriconazole.

7.4.2.5 DRC-assessed Clinical, Mycological and Radiological Response at EOT

Success rates for DRC-assessed clinical, mycological and radiological responses at EOT are presented in [Table 17].

Table 17 DRC-assessed Clinical, Mycological and Radiological Response at EOT (mITT Population; 0104)

Success	Isavuconazole (n = 143)		Voriconazole (n = 129)		Adjusted Treatment Difference 95% CI†
	n	n (%)	n	n (%)	
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)

Modified intent-to-treat (mITT): A subset of ITT patients with proven or probable IFD as determined by the DRC.

CMH: Cochran-Mantel-Haenszel; DRC: Data Review Committee; EOT: end of treatment; HSCT: hematopoietic stem cell transplant; IFD: invasive fungal disease.

† The adjusted treatment difference (voriconazole-isavuconazole) and 95% CIs are calculated by a stratified CMH method with the strata of Geographical Region, Allogeneic HSCT Status and Active Malignancy Status.

The rates of success for radiological response were low in both treatment groups. At least part of the reason for this relates to missing data. The number of patients with no postbaseline radiological assessments was approximately 22.0% in both treatment groups. This was due to the fact that patients with radiological disease at baseline were required to have scans only if clinically indicated. In addition, radiological improvement is known to lag behind clinical improvement.

7.4.3 Assessment of Impact of Enrollment Hold on Efficacy Outcomes

The FDA requested an evaluation of outcomes before and after the enrollment hold (January 2009 to March 2011). For the posthoc analysis, demographics, baseline characteristics and outcome measures were summarized by patients randomized prior to and after the enrollment hold. Statistical tests were performed to assess any potential interaction with the treatment group for the primary and secondary efficacy endpoints in the respective analysis population for each endpoint.

In summary, some numerical differences in baseline characteristics and outcomes were observed; however, these differences did not result in a significant impact on the interpretation of the study results.

7.4.3.1 Baseline Characteristics Pre- and Post-enrollment Hold

Demographic and baseline characteristics were summarized for patients enrolled before and after the enrollment hold (i.e., pre-Hold and post-Hold).

To a great extent, demographics and baseline characteristics were comparable between patients enrolled before the hold in enrollment and those enrolled after the hold in enrollment. A summary of select baseline characteristics are provided in [Table 18 (ITT) and Table 19 (mITT)]. Further details of baseline characteristics before and after the hold in enrollment are summarized in [Appendix 6].

The following observations were made that may assist in understanding the variations between pre-Hold and post-Hold outcomes:

- There was an increase in the proportion of patients the DRC-classified as proven and probable from before the hold in enrollment to after the hold in enrollment in the isavuconazole treatment group [Table 18].
- There was an increase in the proportion of patients with active malignancy at baseline in the ITT and mITT of both treatment groups for the post-Hold period [Table 18 and Table 19].
- There was an increase in the proportion of patients with neutropenia at baseline from before to after the hold in enrollment in the isavuconazole treatment group for the ITT population [Table 18], and in both treatment groups for the mITT population [Table 19].

Table 18 Select Baseline Characteristics in Patients Enrolled Before and After the Enrollment Hold (ITT Population; 0104)

	Isavuconazole & Voriconazole		Isavuconazole		Voriconazole	
Parameter Statistics	**Pre-Hold (n = 304)**	**Post-Hold (n = 212)**	**Pre-Hold (n = 154)**	**Post-Hold (n = 104)**	**Pre-Hold (n = 150)**	**Post-Hold (n = 108)**
Proven/Probable	153 (50.3)	119 (56.1)	78 (50.6)	65 (62.5)	75 (50.0)	54 (50.0)
Active Malignancy at Baseline, n (%)	201 (66.1%)	159 (75.0%)	97 (63.0%)	76 (73.1%)	104 (69.3%)	83 (76.9%)
Neutropenia†, n (%)	196 (64.5%)	142 (67.0%)	94 (61.0%)	69 (66.3%)	102 (68.0%)	73 (67.6%)

Intent-to-treat (ITT): All randomized patients who received at least one dose of study medication.

ANC: absolute neutrophil count.

† Neutropenia was defined as ANC < 0.5 x 10^9/L (< 500/mm^3) and was determined by the investigator.

Table 19 Select Baseline Characteristics in Patients Enrolled Before and After the Enrollment Hold (mITT Population; 0104)

	Isavuconazole & Voriconazole		Isavuconazole		Voriconazole	
Parameter Statistics	**Pre-Hold (n = 153)**	**Post-Hold (n = 119)**	**Pre-Hold (n = 78)**	**Post-Hold (n = 65)**	**Pre-Hold (n = 75)**	**Post-Hold (n = 54)**
Active Malignancy, n (%)	95 (62.1)	83 (69.7)	46 (59.0)	43 (66.2)	49 (65.3)	40 (74.1)
Neutropenia†, n (%)	85 (55.6)	76 (63.9)	46 (59.0)	42 (64.6)	39 (52.0)	34 (63.0)

Modified intent-to-treat (mITT): A subset of ITT patients with proven or probable IFD as determined by the DRC.

ANC: absolute neutrophil count; DRC: Data Review Committee; IFD: invasive fungal disease.

† Neutropenia was defined as ANC < 0.5 x 10^9/L (< 500/mm^3) and was determined by the investigator.

7.4.3.2 Assessment of Impact of Enrollment Hold on All-cause Mortality through Day 42

The impact of enrollment hold was assessed by testing the interaction between treatment groups and enrollment periods. The analysis was performed utilizing the subgroup approach, which was prespecified in the Statistical Analysis Plan (SAP) for Study 0104. The adjusted treatment differences and associated 95% CIs for each enrollment period were calculated

based on the same method as was used in the primary analysis using the CMH method with the stratification of HSCT status, active malignancy and geographic regions.

There was no change in all-cause mortality from before to after the enrollment hold in the voriconazole group. There was a numerical increase in all-cause mortality from before to after the enrollment hold in the isavuconazole group [Table 20]. The interaction between treatment groups and enrollment period was not statistically significant (P = 0.332), indicating that the enrollment period did not significantly influence the results of the primary efficacy analysis.

Table 20 Assessment of Enrollment Hold on All-cause Mortality through Day 42 (ITT Population; 0104)

Interaction P value	Period	Isavuconazole (n = 258) n/n (%)	Voriconazole (n = 258) n/n (%)	Per Period Adjusted Treatment Difference (ISA–VRC) (95% CI)†	Treatment Difference Adjusting for Period Effect (ISA–VRC) (95% CI)‡
0.332	Pre-Hold	24/154 (15.6)	30/150 (20.0)	-3.6 (-12.066, 4.863)	-1.5 (-8.303, 5.323)
	Post-Hold	24/104 (23.1)	22/108 (20.4)	3.2 (-6.998, 13.451)	

Intent-to-treat (ITT): All randomized patients who received at least one dose of study medication.

Interaction P value is from a logistic regression model with Treatment Group, Enrollment-Hold Period, Geographic Regions, HSCT Status, Active Malignancy Status and Treatment Group by Enrollment-Hold Period factors.

CMH: Cochran-Mantel-Haenszel; HSCT: hematopoietic stem cell transplant; ISA: isavuconazole; VRC: voriconazole.

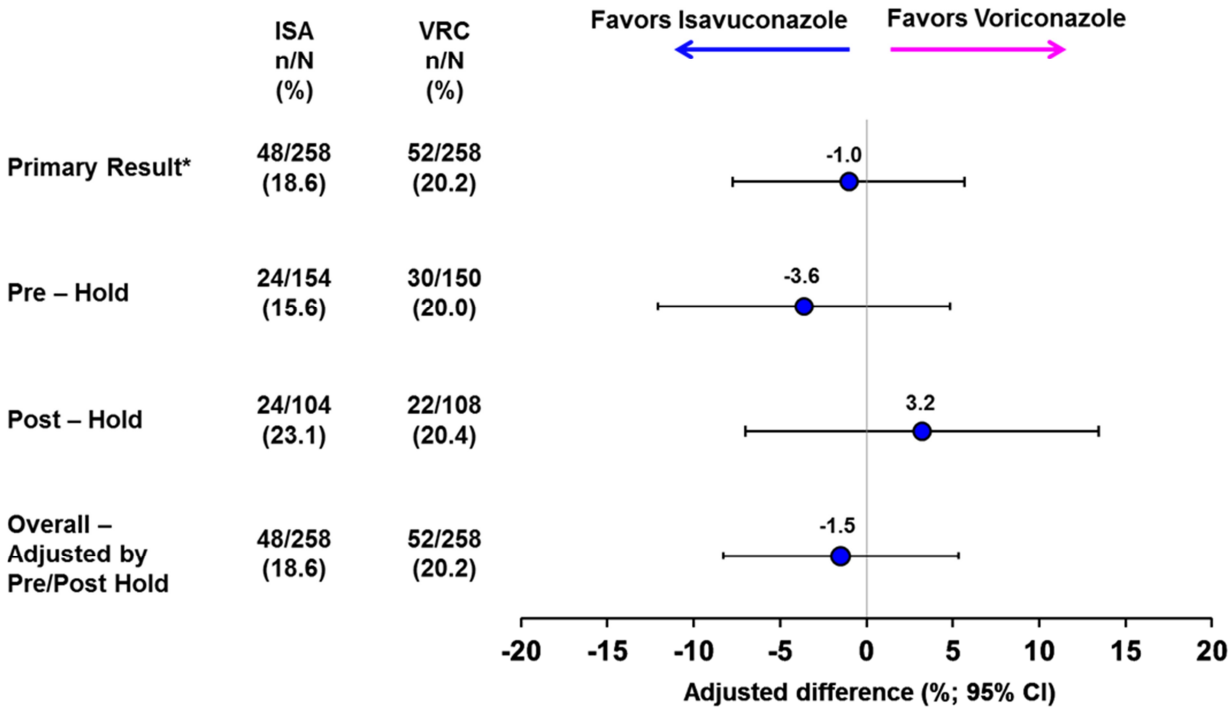
† Adjusted treatment difference per period based on the CMH method with Geographic Regions, HSCT and Active Malignancy as stratification factors.

‡ Adjusted treatment difference based on the CMH method with the Enrollment Hold Period as the only adjustment factor.

An additional analysis of all-cause mortality through day 42 was performed by the CMH method adjusting for enrollment period. The adjusted treatment difference with associated 95% CI was -1.5 (-8.303, 5.323), which was consistent with the primary analysis results of -1.0 (-7.759, 5.683). These data support the overall treatment effect on all-cause mortality.

The relevance of the above findings to the comparison of isavuconazole versus voriconazole is graphically represented in [Figure 24].

Figure 24 All-cause Mortality Through Day 42 – Number of Patients, Adjusted Treatment Differences and 95% CIs for Overall and Before and After the Enrollment Hold (ITT Population; 0104)



Intent-to-treat (ITT): All randomized patients who received at least one dose of study medication.

ISA: isavuconazole; VRC: voriconazole.

* Primary result is presented in [Table 12].

7.4.3.3 Assessment of Impact of Enrollment Hold on DRC-assessed Overall Response at EOT

Based on the same approach as was done for the primary endpoint, the interaction for treatment group by enrollment hold was assessed for overall response at EOT for the mITT population.

The results of DRC-assessed overall response at EOT for patients enrolled before and after the hold are summarized for the total mITT population and by treatment group in [Table 21]. The interaction between treatment groups and enrollment periods was not statistically significant (P = 0.849), indicating that the enrollment period did not significantly influence the results of the primary analysis for overall response, the key secondary endpoint of Study 0104.

Table 21 Assessment of Enrollment Hold on DRC-assessed Overall Response at EOT (mITT Population; 0104)

Interaction P value	Period	Isavuconazole (n = 143) n/n (%)	Voriconazole (n = 129) n/n (%)	Per Period Adjusted Treatment Difference (VRC–ISA) (95% CI)†	Treatment Difference Adjusting for Period Effect (VRC–ISA) (95% CI)‡
0.849	Pre-Hold	31/78 (39.7)	30/75 (40.0)	0.4 (-13.740, 14.449)	1.1 (-10.235, 12.485)
	Post-Hold	19/65 (29.2)	17/54 (31.5)	2.7 (-12.873, 18.334)	

Modified intent-to-treat (mITT): A subset of ITT patients with proven or probable IFD as determined by the DRC.

Interaction p-value is from a logistic regression model with Treatment Group, Enrollment-Hold Period, Geographic Regions, HSCT Status, Active Malignancy Status and Treatment Group by Enrollment-Hold Period factors.

CMH: Cochran-Mantel-Haenszel; DRC: Data Review Committee; EOT: end of treatment; HSCT: hematopoietic stem cell transplant; IFD: invasive fungal disease; ISA: isavuconazole; VRC: voriconazole.

† Adjusted treatment difference per period based on the CMH method with Geographic Regions, HSCT and Active Malignancy as stratification factors.

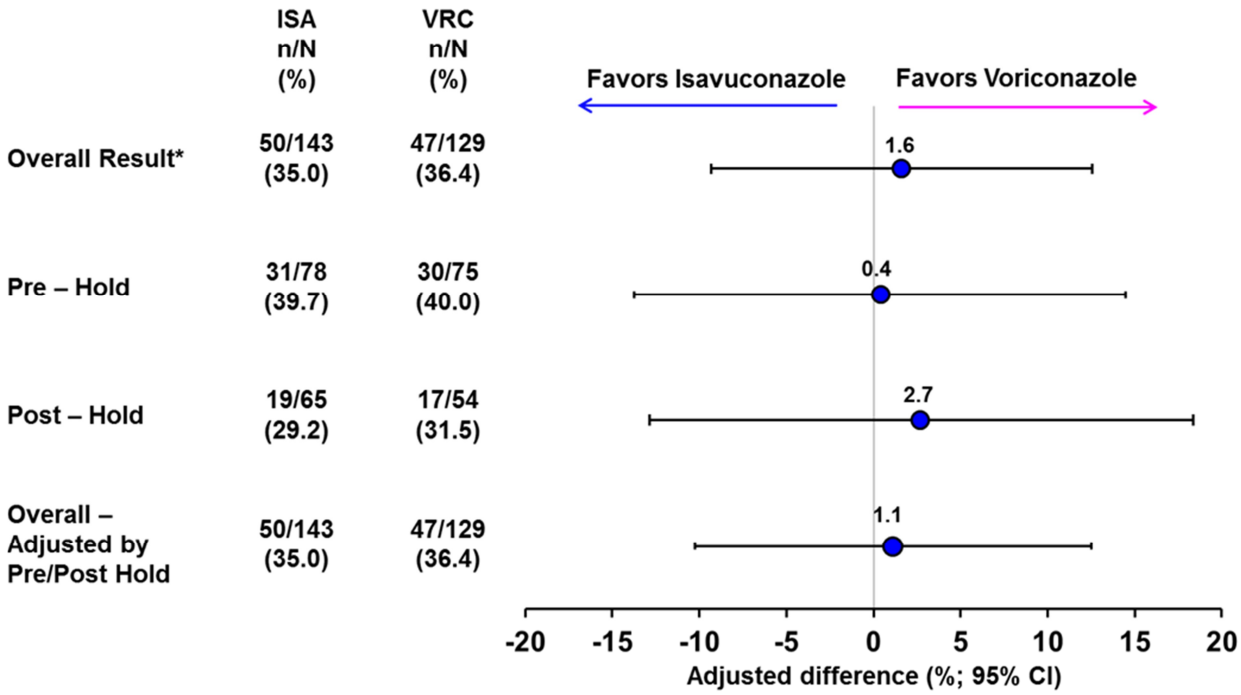
‡ Adjusted treatment difference based on the CMH method with the Enrollment Hold Period as the only adjustment factor.

A decline in DRC-assessed overall response from before to after the enrollment hold was observed for the mITT population in both treatment groups.

An additional analysis for overall response at EOT was performed by the CMH method adjusting for enrollment period. The adjusted treatment difference with associated 95% CI was 1.1 (-10.235, 12.485), consistent with the findings from the primary analysis of this key secondary endpoint 1.6 (-9.336, 12.572). This supports that the treatment effect on this key secondary efficacy endpoint was not affected by the enrollment hold.

The relevance of the above findings to the comparison of isavuconazole versus voriconazole is graphically represented in [Figure 25].

Figure 25 DRC-assessed Overall Response at EOT – Number of Patients, Adjusted Treatment Differences and 95% CIs for Overall and Before and After the Enrollment Hold (mITT Population; 0104)



Modified intent-to-treat (mITT): A subset of ITT patients with proven or probable IFD as determined by the DRC.

DRC: Data Review Committee; EOT: end of treatment; IFD: invasive fungal disease; ISA: isavuconazole; VRC: voriconazole.

*Overall Result presented in [Table 15].

7.4.4 *Aspergillus* Species Minimum Inhibitory Concentrations (MICs) and Responses (0104)

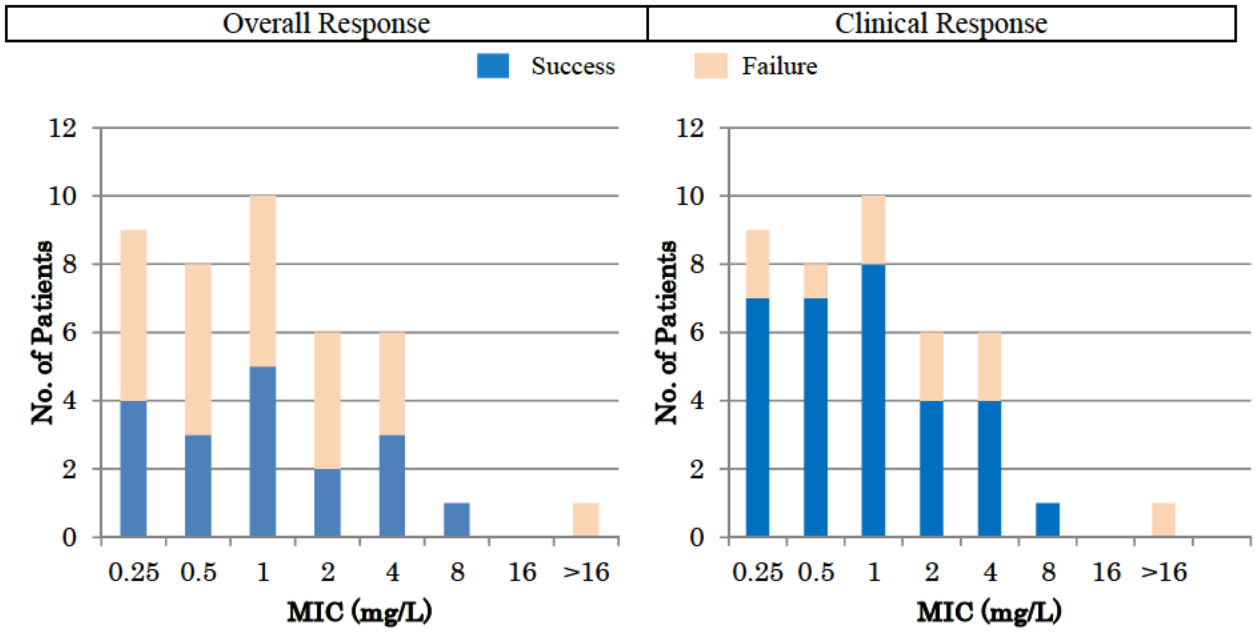
A total of 76 isolates of *Aspergillus* spp. were cultured at baseline from patients enrolled in clinical Study 0104.

Isavuconazole treated patients (n = 37) had a total of 51 baseline isolates of *Aspergillus* spp. tested. Using CLSI methods, isavuconazole demonstrated MIC_{50} and MIC_{90} values against these baseline *Aspergillus* spp. of 1 and 4 mg/L, respectively, with MICs ranging from 0.25 to 32 mg/L. Voriconazole MIC values for these isolates were similar (MIC_{50}: 1; MIC_{90}: 2; range: 0.12-32 mg/L).

Voriconazole treated patients (n = 23) had a total of 25 baseline *Aspergillus* isolates tested. Using CLSI methods, voriconazole MIC_{50} and MIC_{90} values against these baseline *Aspergillus* isolates were 1 and 2 mg/L, respectively, with MICs ranging from 0.25 to 2 mg/L. Isavuconazole MIC values for these isolates were similar (MIC_{50}: 1; MIC_{90}: 2; range: 0.25-4 mg/L).

For isavuconazole treated patients, there was no obvious relationship between outcomes across the range of MICs [Figure 26]. Similarly, no relationship was seen for the voriconazole treated patients between outcomes and MIC values.

Figure 26 Overall and Clinical Response at EOT by Isavuconazole MIC Values (CLSI; 0104)



CLSI: Clinical and Laboratory Standards Institute; EOT: end of treatment; MIC: minimum inhibitory concentration.

The following non-*Aspergillus* spp. were isolated at baseline from 5 isavuconazole treated patients: 1 *Fusarium oxysporum*, 1 *Fusarium solani*, 1 *Fusarium subglutinans*, 1 *Lichtheimia (Absidia) corymbifera*, and 1 *Penicillium sizovae*. The following non-*Aspergillus* spp. were collected from 3 voriconazole treated patients: 1 *Fusarium fujikuroi*, 1 *Fusarium solani* and 1 *Penicillium piceum*.

Fifteen patients had postbaseline fungal organisms cultured (12 isavuconazole and 3 voriconazole).

- For 7 of the 15 patients, MIC values for both isavuconazole and voriconazole were within 1 to 2 dilution steps of the MICs measured for the corresponding baseline pathogen.
- In 6 of the 15 patients, a postbaseline fungal pathogen was the only organism isolated (4 isavuconazole and 2 voriconazole).
- In 2 of the 15 patients (1 in each treatment group) a new infecting pathogen was isolated during the course of therapy.
    - For an isavuconazole treated patient with *A. terreus* isolated at baseline, isolates of *A. westerdijkiae* and *Lichtheimia [Absidia] corymbifera* were obtained on days 6 and 13, respectively.

- For a voriconazole treated patient with baseline fusariosis, an isolate of *R. oryzae* was obtained on day 42 of therapy.

Overall, there was no indication of resistance development during treatment.

7.4.5 Consistency of Voriconazole Efficacy in Study 0104 with Historical Literature

Importantly, the voriconazole treatment group performed consistent with the US package insert and the literature.[12,13] The protocol was designed assuming approximately 20% all-cause mortality through day 42 for voriconazole and the actual all-cause mortality through day 42 in the ITT population was 20.2%. The baseline characteristics of patients in Study 0104 were also generally comparable to those reported in the Herbrecht study; for example, mean age was approximately 50 years, a majority (> 65%) was male and a vast majority (> 80%) were White and had underlying hematologic malignancies or HSCT (Voriconazole Briefing Document for FDA Antiviral Drugs Advisory Committee dated October 4, 2001, Tables 7-7 and 7-9).[12]

The efficacy results for the voriconazole treatment arm in Study 0104 were also consistent with data from the following, as presented in [Table 22].

- Voriconazole treatment arm in the Pfizer Global Comparative Aspergillosis Study (307/602) (Voriconazole Briefing Document for FDA Antiviral Drugs Advisory Committee dated October 4, 2001, Table 7-26)
- Study 307/602, after data were reclassified according to the 2008 EORTC/MSG definitions[59]
- A recent clinical study comparing voriconazole monotherapy versus voriconazole + anidulafungin in hematologic malignancy patients with IA[34]

Table 22 Overview of Voriconazole Mortality Results

	Global Comparative Aspergillosis Study (307/602) ITT (n = 194) mITT (n = 144)	Reclassification of Global Aspergillosis Study (307/602)[59]	Combination Trial Voriconazole Monotherapy (n = 142)[34]	Study 0104 Voriconazole ITT (n = 258) mITT (n = 129) Heme mITT (n = 105)
ITT (day 42/week 6)	19.6%	NA	NA	20.2%
ITT (day 84/week 12)	28.4%	NA	NA	31.0%
mITT (day 42/week 6)	18.7%	NA	NA	23.3%
mITT (day 84/week 12)	29.2%	30.1%	NA	37.2%
Hematologic Malignancy mITT (day 42/week 6)	NA	NA	27.5%	23.8%
Hematologic Malignancy mITT (day 84/week 12)	NA	NA	39.4%	37.1%

Intent-to-treat (ITT): All randomized patients who received at least one dose of study drug.

Modified ITT (mITT): All patients with DRC confirmed proven or probable IA.

Heme mITT: mITT patients with hematological malignancy at baseline.

DRC: Data Review Committee; IA: invasive aspergillosis; NA: not available.

7.4.6 Efficacy Summary (IA)

In summary, the results of Study 0104 demonstrated that isavuconazole is as effective as voriconazole, the current gold standard, for the treatment of IA. The primary efficacy objective of the study was met demonstrating that isavuconazole was non-inferior to voriconazole for all-cause mortality through day 42 in the ITT population. Comparable results were seen for all-cause mortality across sensitivity analyses, populations, time points and subgroups, further supporting the effectiveness of isavuconazole in IA. The results from the analysis of the key secondary endpoint of success for DRC-assessed overall response in the mITT population also support the efficacy of isavuconazole in the treatment of IA.

8 EFFICACY IN INVASIVE MUCORMYCOSIS

8.1 Summary of Efficacy Results in IM

Isavuconazole demonstrated effectiveness for the treatment of patients with IM:

- All-cause mortality through day 42 was 37.8% in the mITT-Mucorales population (0103).
- The success rate for DRC-assessed overall response at EOT was 31.4% in the overall mITT-Mucorales population (0103).
- Isavuconazole demonstrated activity for the treatment of IM.
    - In the matched-case control analysis, crude mortality through day 42 in patients receiving isavuconazole as primary therapy in Study 0103 was 33.3% relative to 39.4% in patients receiving amphotericin-based treatment as primary therapy from matched controls from the Fungiscope Registry database.
    - The overall mortality rate (37.8%) for isavuconazole treated patients was similar to the mortality rate for amphotericin treated patients reported in the literature (37.8%). Isavuconazole was also shown to have a clear treatment effect for all-cause mortality relative to untreated literature controls, which have a mortality rate approaching 100%.
- The activity of isavuconazole was demonstrated to be superior to that of placebo and similar to that of liposomal amphotericin in animal models of mucormycosis [see Figure 6, Figure 7 and Figure 8].

8.2 Study 0103 Design

8.2.1 Background on Efficacy in IM

Given the rarity of IM, no randomized, well-controlled comparative studies of mould-active antifungal treatments have been conducted or published. The only antifungal treatment approved for IM is amphotericin B deoxycholate and the most recent guidelines (2013) issued in Europe by the ECIL-3 and the ESCMID/ECMM recommend the use of lipid formulations of amphotericin B as first-line therapy based primarily on case series and expert opinion.[17,18] Currently, there are no guidelines issued in the US for the treatment of IM.

Since IM is a very rare and life-threatening fungal disease, consideration of the totality of evidence is warranted. The FDA specified that for rare fungal pathogens, such as Mucorales, efficacy should be demonstrated in a minimum of 20 well-documented cases where the study drug is used as primary therapy or in refractory disease in patients who received limited prior antifungal treatment. While such data could not be utilized alone to support an approval, it

could be assessed within the context of appropriate animal model testing, a larger NDA submission supporting efficacy in a more common invasive fungal infection and in a literature review describing comparative mortality in untreated patients and patients treated with other mould-active agents.

The efficacy of isavuconazole in the treatment of patients with IA in a randomized, double-blind, comparative study is described in [Sections 7.4.1 and 7.4.2].

For IM, the in vivo efficacy of isavuconazole was assessed in intratracheal infection models in DKA and neutropenic mice that were specifically developed and validated via NIH funding to test drugs and immunotherapeutic interventions against mucormycosis. A sensitive strain of *Rhizopus oryzae* was used in mice made susceptible to infection by inducing DKA or neutropenia. These data show that the effectiveness of isavuconazole was superior to that of placebo controls and similar to that of liposomal amphotericin B [see Section 5.4].

Study results for 37 patients with IM who were treated with isavuconazole, 21 of whom received isavuconazole as primary therapy, are provided in the following sections. This represents one of the largest series of prospectively evaluated and systemically treated patients with IM. To provide context for the interpretation of outcomes, a matched-case control analysis was conducted [Section 8.4.5].

Additional support for the interpretation of IM outcomes is provided from information on the natural history of mucormycosis, including mortality rates in untreated and treated patients from the literature and the Fungiscope database, which are described in [Section 8.4.6]. In short, overall mortality rates declined to approximately 40% after amphotericin B deoxycholate was widely introduced, but have remained essentially unchanged since the 1960s. If IM is not treated, it is almost universally fatal![19]

8.2.2 Overview of Study 0103 Design

Study 0103 was an open-label, multicenter, single arm, phase 3 study, which evaluated isavuconazole for the treatment of IA in patients with renal impairment or in patients with IFD caused by rare moulds, yeasts or dimorphic fungi, regardless of renal function.

Isavuconazole was administered either as an IV infusion or orally, first as a loading dose followed by maintenance dosing [Table 23]. The isavuconazole dosing regimen in this study was the same as in Study 0104, except that patients could continue therapy for up to 180 days. In some countries (Israel, Belgium and the US), patients who were deriving clinical benefit could continue treatment beyond 180 days.

Table 23 Summary of Study Periods and Treatment (0103)

Isavuconazole Treatment		Follow-up
Loading Dose	**Maintenance Dose**	
Study days 1 and 2	Study day 3 to EOT	EOT + 4 weeks ± 7 days
IV or oral 200 mg (q8h ± 2h)	IV or oral 200 mg (q24h ± 2h)	

EOT: end of treatment (last administration of study drug).

8.2.3 Inclusion/Exclusion Criteria

Eligible patients in Study 0103 included patients ≥ 18 years of age with proven, probable or possible IA with renal impairment or with proven or culture positive IFD caused by rare moulds, yeasts or dimorphic fungi (excluding *Aspergillus fumigatus* and *Candida* spp.). Patients were eligible for enrollment if they required primary treatment or if the patient's IFD was refractory to their prior antifungal treatment or if the patient was intolerant of their prior antifungal treatment.

Primary therapy patients could not have received > 4 days of systemic mould-active antifungal therapy within 7 days prior to the administration of isavuconazole study drug.

Refractory patients were to have clear documentation of progression or failure to improve clinically despite receiving at least 7 days of a standard antifungal therapy.

Intolerant patients were to have a doubling of serum creatinine to higher than the ULN within 48 hours; a serum creatinine > 2.0 mg/mL and current treatment with polyene or IV voriconazole; or other adverse events requiring discontinuation of current therapy such as persistence of visual disturbances, allergic reaction, phototoxicity or severe infusion reactions.

Key exclusion criteria from Study 0103:

- Hepatic dysfunction, defined as:
  - Total bilirubin ≥ 3 x ULN, ALT or AST ≥ 5 x ULN or known cirrhosis or chronic hepatic failure
- Chronic aspergillosis, aspergilloma or allergic aspergillosis
- Advanced HIV (CD4 < 50 cells/mm^3) or uncontrolled AIDS condition
- Unlikely to survive 30 days

A full list of inclusion/exclusion criteria per the 0103 protocol can be found in [Appendix 2].

8.2.4 Study Endpoints

The relevant endpoints evaluated in this study of patients with a variety of rare mould infections were mortality and DRC-assessed overall response. The study protocol identified the DRC-assessed overall response at day 42 as the primary endpoint, given the variety of fungal infections where mortality may or may not be appropriate. In IM, Astellas believes mortality is the most relevant endpoint particularly as it allows comparison of the results from Study 0103 to those reported in historic literature and Fungiscope registry. For overall response, results at the EOT are presented, consistent with the key secondary endpoint for Study 0104.

8.2.4.1 All-cause Mortality and Survival Estimates

All-cause mortality through day 42 and day 84 was described including patients who died and those with unknown survival status. To account for patients whose survival status was unknown and because the systematic collection of survival status was limited to up to day 84,

a Kaplan-Meier analysis was employed to estimate the survival rate up to day 180 by censoring the patients with unknown survival status at their last assessment day.

8.2.4.2 DRC-Assessed Overall Response

In Study 0103, patient data were reviewed and adjudicated by an independent DRC consisting of experts in fungal infections. The DRC was responsible for categorizing the baseline diagnosis of IFD (i.e., proven, probable, possible and no IFD), pathogen causing IFD, therapy status (i.e., primary, refractory, intolerant) and overall response outcomes (i.e., complete, partial, stable, progressive disease) at EOT, day 42 and day 84. For overall response, patients with complete or partial responses were considered a success and patients with stable or progression responses were considered a failure. Patients who died before or on day 42 were considered failures in the day 42 assessment, even if the DRC considered them a success. Patients who died before or on day 84 were also considered failures in the day 84 assessment, even if the DRC considered them a success.

Overall response is derived from clinical, mycological and radiologic criteria. Success rates for clinical, mycological and radiological responses were also evaluated at EOT, day 42 and day 84.

Response to treatment was assessed by the DRC based on the study protocol and the DRC Charter, which were consistent with the EORTC/MSG 2008 consensus criteria.[57] Mucormycosis diagnostic and response criteria definitions used in Study 0103 are provided in [Appendix 7].

Review of patient data by the DRC was done using patient profiles. The information in the patient profiles did not include the investigator assessment of baseline mycological criteria nor the investigator assessments of clinical, mycological or radiological responses at the various time points.

An independent radiology expert was responsible for providing a written evaluation of each image and an assessment of radiological response. The radiology assessment data from the radiology expert were included in the patient profiles reviewed by the DRC.

The DRC consisted of 3 experts in fungal infections who reviewed each patient's data. Consensus for all data was required by all 3 DRC members. If consensus was not reached, the DRC chair would adjudicate a review meeting to reach consensus on all data points.

8.2.5 Independent Data Safety Monitoring Committee (IDSMB)

An IDSMB monitored the data from Study 0103 on an ongoing basis to ensure the continuing safety of patients. The IDSMB could stop the study for safety reasons. The study was not stopped due to safety concerns and no alterations in study design or conduct were requested by the IDSMB.

8.2.6 Sample Size

This study was open-label with an isavuconazole treatment group and there was no formal statistical calculation for sample size. The analysis in this study was pathogen-specific as

assessed by the independent DRC at baseline. The sample size was increased in protocol Amendment 6.1 (February 2013) from 100 patients to 150 patients and enrollment of patients with certain infections was limited in order to enroll approximately 30 renally impaired (RI) patients with IFD as well as an adequate number of patients with proven or probable IM.

8.3 Distribution, Demographics and Duration of Exposure

8.3.1 Distribution

A total of 149 patients enrolled in the study, 146 patients (98.0%) took at least 1 dose of study drug. A summary of the analysis populations is provided in [Table 24].

Table 24 Analysis Populations (0103)

Analysis Populations, n (%) of patients	Total (n = 149)
Enrolled	**149 (100.0)**
Intent-to-Treat (ITT)	**146 (98.0)**
Modified Intent-to-Treat (mITT)	**140 (94.0)**
mITT-Mucorales	**37 (24.8)**
mITT-*Aspergillus*	24 (16.1)
mITT-Other filamentous fungi (not *Aspergillus* or Mucorales)	17 (11.4)
mITT-Mould species not otherwise specified	7 (4.7)
mITT-Dimorphic fungi	29 (19.5)
mITT-Non-*Candida* yeast	11 (7.4)
mITT-Mixed infection	15 (10.1)
Safety (SAF)	**146 (98.0)**

Intent-to-treat (ITT)/Safety (SAF): all enrolled patients who received at least one dose of study drug.

Modified Intent-to-treat (mITT): ITT patients who had proven or probable IFD as determined by the DRC (overall and by organism).

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

DRC: Data Review Committee; eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease.

The analysis populations in Study 0103 include 140 patients who were determined by the DRC to have proven or probable IFD. In this document, we focus on the mITT-Mucorales population as these patients provide support for the IM indication. Mortality and overall response outcomes for the other patients are provided in [Appendix 8].

A total of 46 patients enrolled into Study 0103 with IM. Of these, 8 patients had mixed mould infection, at least one of which was a Mucorales order pathogen and data are provided in [Appendix 8]. Thirty-eight (38) patients had invasive mould infection caused by a single Mucorales order pathogen. The independent DRC assessed 37 patients to have proven or probable IM, making up the mITT-Mucorales population. These 37 patients were categorized by the DRC as either primary, refractory or intolerant. Twenty-one (21) of these patients received isavuconazole as primary therapy, 11 had IFD refractory to their current antifungal treatment and 5 patients were intolerant of their current antifungal treatment.

In the mITT-Mucorales population, the DRC baseline assessment was 32 patients (86.5%) with proven IM and 5 patients (13.5%) with probable IM, which was similar for primary therapy patients (18, 85.7% and 3, 14.3%, respectively).

The 3 most common primary reasons for premature study drug discontinuation in the mITT-Mucorales population, based on the investigator's categorization, were Death, Adverse Event/Intercurrent Illness and Did Not Cooperate [Table 25].

Table 25 Primary Reason for Treatment Discontinuation (mITT-Mucorales Population; 0103)

n (%) of patients	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Treatment Discontinuation	13 (61.9)	9 (81.8)	2 (40.0)	24 (64.9)
Primary reason for treatment 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)

mITT-Mucorales: ITT patients who had proven or probable IM as determined by the DRC.

Only the primary reason for discontinuation was collected.

DRC: Data Review Committee; IM: invasive mucormycosis; ITT: intent-to-treat; mITT: modified intent-to-treat.

Of the 24 patients who are recorded as discontinuing treatment for various reasons, 16 discontinued study drug prior to day 84 with a treatment duration ranging from 2 to 68 days. These 16 patients died prior to day 84 [Table 29]. The other 8 patients discontinued study drug on days 33, 86, 87, 102, 106, 144, 509 and 735 and are described in [Section 8.4.4].

8.3.2 Demographics and Baseline Characteristics

The median age of mITT-Mucorales patients was 49 years; 13.5% of patients were > 65 years (19.0% of primary therapy patients) and 8.1% of patients were > 75 years (9.5% of primary therapy patients). Overall, 43.2% of patients resided in North America; however, the majority of primary therapy patients (61.9%) resided in Other Regions [Table 26].

Table 26 Summary of Demographics and Baseline Characteristics by Therapy Status (mITT-Mucorales Population; 0103)

Parameter Category/Statistic	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Age, Mean (SD), years	51.7 (14.72)	46.4 (16.55)	39.6 (15.22)	48.5 (15.51)
Sex, Male, n (%)	17 (81.0)	8 (72.7)	5 (100.0)	30 (81.1)
Race, n (%)				
White	12 (57.1)	10 (90.9)	3 (60.0)	25 (67.6)
Black or African American	1 (4.8)	1 (9.1)	2 (40.0)	4 (10.8)
Asian	8 (38.1)	0	0	8 (21.6)
Table continued on next page				

Parameter Category/Statistic	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Ethnicity, n (%)				
Hispanic or Latino	1 (4.8)	0	0	1 (2.7)
Not Hispanic or Latino	20 (95.2)	11 (100.0)	5 (100.0)	36 (97.3)
Geographic Region, n (%)				
North America	7 (33.3%)	4 (36.4%)	5 (100.0%)	16 (43.2%)
Western Europe	1 (4.8%)	4 (36.4%)	0	5 (13.5%)
Other Regions†	13 (61.9%)	3 (27.3%)	0	16 (43.2%)
Baseline Condition, n (%)				
Hematologic malignancy	11 (52.4)	7 (63.6)	4 (80.0)	22 (59.5)
Active malignancy	11 (52.4)	6 (54.5)	1 (20.0)	18 (48.6)
T-cell immunosuppressant use	7 (33.3)	6 (54.5)	5 (100.0)	18 (48.6)
Corticosteroid use	5 (23.8)	3 (27.3)	2 (40.0)	10 (27.0)
Allogeneic HSCT status	4 (19.0)	4 (36.4)	5 (100.0)	13 (35.1)
Neutropenia¶	4 (19.0)	5 (45.5)	1 (20.0)	10 (27.0)
Diabetes§	4 (19.0)	0	0	4 (10.8)
Solid organ transplant	1 (4.8)	2 (18.2)	0	3 (8.1)

mITT-Mucorales: ITT patients who had proven or probable IM as determined by the DRC.

Age was calculated relative to informed consent date.

Hematologic malignancy status and T-cell immunosuppressant use involved an Astellas medical review.

DRC: Data Review Committee; HSCT: hematopoietic stem cell transplant; IM: invasive mucormycosis; ITT: intent-to-treat; mITT: modified intent-to-treat.

† Other Regions included Russia, Mexico, Brazil, Thailand, South Korea, India, Lebanon and Israel.

‡ Neutropenia was defined as ANC < 0.5 x 10^9/L (< 500/mm^3) and was determined by the investigator.

§ Diabetes included diabetes mellitus and diabetic ketoacidosis.

Overall, the majority of patients had a history of hematologic malignancy (59.5%), 48.6% had previously received T-cell immunosuppressants, 48.6% had active malignancy, 35.1% had allogeneic HSCT status, 27.0% had neutropenia and 27.0% had previously received corticosteroids. This pattern was also seen for primary therapy patients, with the exception of active malignancy, which occurred in the majority (52.4%) of primary therapy patients.

The most commonly reported primary underlying diseases were AML in 10 patients (27.0%) and acute lymphocytic leukemia and diabetes mellitus in 3 patients each (8.1%). In primary therapy patients, the most commonly reported primary underlying diseases were AML and diabetes mellitus in 3 patients each (14.3%).

In the mITT-Mucorales population, the majority of patients had LRTD only (10, 27.0%) or with other involved organs (12, 32.4%). The majority of primary therapy patients had non-LRTD only (12, 57.1%). The 3 most common non-LRTD locations were sinus (16, 43.2%), eye (7, 18.9%) and CNS (6, 16.2%), which was also seen in primary therapy patients (13, 61.9%; 7, 33.3%; and 6, 28.6%, respectively).

The 3 most commonly reported pathogens at baseline, as assessed by the DRC, were *Mucormycetes* not otherwise specified (NOS) (35.1%) and *Mucor* NOS and *Rhizopus oryzae* (both reported in 18.9% of patients) [Table 27]. For primary therapy patients, the 3 most

commonly reported pathogens at baseline, as assessed by the DRC, were *Mucor* NOS (33.3%), *Mucormycetes* NOS (28.6%) and *Rhizopus oryzae* (19.0%).

Table 27 DRC Assessment of Pathogens Causing IFD (mITT-Mucorales Population; 0103)

	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Pathogen n (%)				
Mucormycetes NOS	6 (28.6)	5 (45.5)	2 (40.0)	13 (35.1)
Mucor NOS	7 (33.3)	0	0	7 (18.9)
Rhizopus oryzae	4 (19.0)	3 (27.3)	0	7 (18.9)
Rhizomucor spp.	2 (9.5)	2 (18.2)	1 (20.0)	5 (13.5)
Lichtheimia (Absidia) corymbifera	2 (9.5)	0	0	2 (5.4)
Rhizopus NOS	0	1 (9.1)	1 (20.0)	2 (5.4)
Cunninghamella spp.	0	0	1 (20.0)	1 (2.7)

mITT-Mucorales: ITT patients who had proven or probable IM as determined by the DRC.

DRC: Data Review Committee; IM: invasive mucormycosis; ITT: intent-to-treat; mITT: modified intent-to-treat; NOS: not otherwise specified.

The population of patients enrolled in Study 0103 is representative of the patient population likely to receive antifungal treatment for proven or probable IFD caused by species of the Mucorales order.

8.3.3 Duration of Study Drug Administration

For the mITT-Mucorales population, the overall median duration of treatment was 84.0 days [Table 28]. Seven of these patients received isavuconazole for > 180 days.

Table 28 Duration of Study Drug Administration by Therapy Status (mITT-Mucorales Population; 0103)

Exposure Component Statistic/Category	Primary Therapy	Refractory	Intolerant	Total
Total duration (days)				
n†	21	11	5	37
Mean (SD)	149.0 (206.28)	117.0 (211.50)	97.4 (89.34)	132.5 (193.28)
Min – Max	2 - 882	6 - 735	10 - 232	2 - 882
Median	102.0	33.0	85.0	84.0
IV duration (days)				
n‡	18	8	4	30
Mean (SD)	15.5 (14.46)	22.8 (25.45)	17.3 (12.45)	17.7 (17.47)
Min – Max	2 - 51	6 - 77	5 - 33	2 - 77
Median	9.5	11.5	15.5	10.0
Oral duration (days)				
n‡	16	9	4	29
Mean (SD)	178.1 (222.41)	122.8 (219.45)	104.5 (81.23)	150.8 (204.82)
Min – Max	16 - 882	8 - 690	7 - 199	7 - 882
Median	142.8	33.0	106.0	80.0

mITT-Mucorales: ITT patients who had proven or probable IM as determined by the DRC.

Footnotes continued on next page

For the 2 active patients who remain ongoing in the study, a last dose date of September 30, 2013 was used for the purpose of this analysis.

DRC: Data Review Committee; IM: invasive mucormycosis; ITT: intent-to-treat; mITT: modified intent-to-treat.

† The total duration of study drug exposure was calculated as (last date of study drug administration - first date of study drug administration + 1). For the days when IV and oral doses were administered on the same day, the day was split into one-half day for each route's duration.

‡ Duration for IV or oral dosing was only calculated for patients who received at least 1 dose via this route of administration.

8.4 Study 0103 Efficacy Results

8.4.1 All-cause Mortality Through Day 42 and Day 84

All-cause mortality through day 42 and day 84 in the mITT-Mucorales population was 37.8% and 43.2%, respectively [Table 29]. All-cause mortality through day 42 and day 84 in primary therapy patients was 33.3% and 42.9%, respectively.

Table 29 Crude All-cause Mortality Rates through Day 42 and Day 84 (mITT Mucorales Population; 0103)

Outcomes, n (%) of patients	Primary (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)

mITT-Mucorales: ITT patients who had proven or probable IM as determined by the DRC

† A patient with a last known survival status before day 42 was counted as dead.

‡ A patient with a last known survival status before day 84 was counted as dead.

DRC: Data Review Committee; IM: invasive mucormycosis; ITT: intent-to-treat; mITT: modified ITT.

The Kaplan-Meier estimate of probability of survival was 52.9% through day 180 in the mITT-Mucorales population.

8.4.2 DRC-Assessed Overall Response

8.4.2.1 DRC-Assessed Overall Response at EOT (mITT-Mucorales)

The success rate for DRC-assessed overall response at EOT in the mITT-Mucorales population was 31.4%, with 14.3% of patients assessed to be a complete success and 17.1% assessed to be a partial success. An additional 28.6% of patients in the mITT-Mucorales population were assessed to be stable [Table 30].

For primary therapy patients, 31.6% of patients were assessed to be a success, with 15.8% of patients assessed to be a complete success and 15.8% a partial success. An additional 31.6% of primary therapy patients were assessed to be stable, which is a clinically relevant favorable outcome in this patient population.

Table 30 DRC Assessed Overall Response at EOT by Therapy Status (mITT-Mucorales Population; 0103)

Outcome Response, n (%) of patients	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)

mITT-Mucorales: ITT patients who had proven or probable IM as determined by the DRC.

DRC: Data Review Committee; EOT: end of treatment; IM: invasive mucormycosis; ITT: intent-to-treat; mITT: modified ITT.

Patients who were still actively participating in the study at the interim cut of the database do not have EOT data available for this analysis. In the Primary Therapy arm, 2 patients were on long-term extension and had not completed the EOT visit.

8.4.2.2 DRC-assessed Clinical, Mycological and Radiological Response at EOT (mITT-Mucorales)

The proportions of patients with outcomes of success for clinical, mycological and radiological response at the EOT are provided in [Table 31]. Clinical response rates are higher than those for mycological and radiological, which may reflect lack of follow-up cultures and lag in radiographic improvement.

Table 31 Success Rates for DRC-Assessed Clinical, Mycological and Radiological Response at EOT by Therapy Status (mITT-Mucorales Population; 0103)

Success, n (%) of patients	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 Response	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)

mITT-Mucorales: ITT patients who had proven or probable IM as determined by the DRC.

Patients who were still actively participating in the study at the interim cut of the database were not included in this analysis at the EOT time point. In the Primary Therapy arm, 2 patients were on long-term extension and had not completed an EOT visit.

DRC: Data Review Committee; EOT: end of treatment; IM: invasive mucormycosis; ITT: intent-to-treat; mITT: modified intent-to-treat.

8.4.3 Mucorales Minimum Inhibitory Concentrations (MICs; 0103)

Baseline Mucorales isolates were available from a subset of patients (n = 19) who were enrolled in clinical Study 0103. The isavuconazole MICs ranged from 0.25 to 32 µg/mL and successful clinical outcomes were observed across the range of MIC values.

A small proportion of patients (n = 9) had postbaseline isolates. Four of the postbaseline isolates were the only strains isolated from the patient. There was no evidence of resistance development during the study.

8.4.4 Invasive Mucormycosis – Clinical Summary

The review of the case reports of patients treated with isavuconazole provides further evidence that isavuconazole is an alternative therapy for the treatment of IM. Sixteen (16) of 37 patients with proven or probable IM died on or before day 84 [Table 29], 13 of whom had progressive disease. One of the 16 patients who discontinued treatment on day 22 with stable disease was last known alive on day 35 and was considered a death because survival information was not known at day 42.

Of the 21 who survived beyond day 84, one patient (*Rhizomucor pusillus,* isavuconazole MIC > 16 mg/L [CLSI]) had progressive disease and discontinued study drug and died on day 87. One patient (*Mucormycetes* NOS - no MIC) discontinued treatment on day 33 due to elevated liver tests and posaconazole was initiated. This patient had stable disease at the end of isavuconazole treatment and was last known alive on day 91.

Of the remaining 19 patients who survived beyond day 84, 10 were considered by the independent DRC to have successful outcomes (5 with complete overall response and 5 with partial overall response) and 9 were considered to have stable disease at EOT or the last DRC assessment.

Complete Overall Response

Of the 5 patients with a complete overall response at the EOT:

- 3 patients with proven IM had an underlying hematologic malignancy and disseminated disease including pulmonary involvement.
    - 2 of these patients (both *Mucor* NOS - no MIC) received isavuconazole for primary therapy for 179 and 180 days. No other Mucorales-active antifungal therapy was administered. One patient had a laparotomy on day 73, but neither patient had surgical resection of the pulmonary involvement. Greater than 90% improvement in the pulmonary infiltrates and complete resolution of clinical symptoms was confirmed by the independent DRC, supporting the classification of these patients as overall complete responders. Both patients were alive at the last follow-up on days 241 and 236, respectively.
    - The third patient (*Mucormycetes* NOS - no MIC) with hematologic malignancy was classified by the independent DRC as having disseminated disease involving the ear and lung that was refractory to prior antifungal therapy (amphotericin, voriconazole and posaconazole). The patient discontinued isavuconazole on day 735, did not receive other antifungal therapy after the start of isavuconazole and did not have surgical debridement of the lung. Greater than 90% improvement in pulmonary infiltrates and complete resolution of clinical symptoms was confirmed by the independent DRC, supporting the classification of this patient as an overall complete responder. The patient died on day 737 due to AML.
- The fourth patient with proven IM (*Actinomucor elegans* - isavuconazole MIC 0.25 mg/L [CLSI]) had metastatic small cell lung cancer that was active at baseline

with involvement of the sinuses. Surgical debridement was performed one day prior to the patient starting isavuconazole as primary therapy. This patient discontinued isavuconazole therapy on day 509 and died on day 517 due to progression of his underlying malignancy.

- The fifth patient with proven IM (*Rhizopus azygosporus* - isavuconazole MIC 1 mg/L) had two lung transplants for Chronic Obstructive Pulmonary Disease (COPD) and pulmonary involvement of disease that was refractory to amphotericin B and posaconazole. This patient discontinued isavuconazole on day 86. A left pneumonectomy was performed 9 days prior to initiation of isavuconazole. The patient was alive at the last follow-up on day 153.

Partial Overall Response

Of the 5 patients with partial overall response at the EOT:

- The first patient with proven IM (*Mucormycetes* NOS - no MIC) had a hematologic malignancy and disseminated disease including pulmonary and bone involvement. Debridement of T-spine occurred 139 days before study enrollment with no further therapeutic surgical intervention. The patient was intolerant of posaconazole and received isavuconazole for 232 days. The patient was alive at the last follow-up on day 296.
- Two of these 5 patients had proven IM and received isavuconazole for primary therapy.
    - The second patient (*Mucormycetes* NOS- no MIC) did not have an underlying disease documented, but had IM involvement of the sinuses. Isavuconazole was administered for 42 days with complete resolution of clinical signs and symptoms and was alive at the last follow-up visit on day 101. This patient had nasal mass excision 20 days prior to initiation of isavuconazole.
    - The third patient (*Mucor* NOS - no MIC) had diabetes mellitus with IM involvement of the eye and sinuses. This patient also had surgical intervention (days 1 and 21) of both involved organs. Isavuconazole was administered for 182 days with complete resolution of clinical signs and symptoms and was alive at the last follow-up visit on day 235.
- The remaining two patients received isavuconazole and had IFD that were refractory to amphotericin.
    - The fourth patient with proven IM (*Mucormycetes* NOS- no MIC) had COPD with pulmonary involvement and received isavuconazole for 182 days. This patient was alive at the last follow-up on day 238, without surgical intervention.
    - The fifth patient with proven IM (*Rhizopus oryzae* - isavuconazole MIC 16 mg/L [CLSI]) had ulcerative colitis with involvement of the sinuses. The patient underwent initial facial resection 99 days prior to initiation of isavuconazole and had debridement of a muscle graft on days 16 and 25.

Isavuconazole was administered for 84 days and the patient was alive at the last follow-up on day 182.

Stable Disease

Of the 9 patients with stable disease at the EOT or last DRC assessment (*Cunninghamella spp.* - no MIC; *Mucor amphibiorum* - no MIC; *Mucor* NOS - no MIC; *Rhizopus oryzae* - isavuconazole MIC 2 mg/L [CLSI]; *Rhizopus microsporus* - isavuconazole MIC 16 mg/L [CLSI]; and 4 patients with *Mucormycetes* NOS - no MIC), all were proven IM except the patient with *Mucor* NOS who was determined by the DRC to have probable IM:

- Four (4) patients had hematologic malignancies, 5 had pulmonary involvement including 2 patients with disseminated disease. Seven patients received isavuconazole for primary therapy and 2 were intolerant to amphotericin (both due to renal impairment). Treatment duration ranged from 85 to 882 days. Eight of the 9 patients were known to be alive between 107 and 882 days after the start of isavuconazole therapy. One of the 9 patients had metastatic esophageal adenocarcinoma and disseminated disease including pulmonary involvement, received isavuconazole as primary therapy, discontinued study drug on day 144 and died on day 145. It should be noted that 5 of the 9 patients with stable disease, including the one that died, and a patient who refused further treatment and discontinued study drug on day 106, had complete or partial clinical responses based on the last independent DRC assessment at day 84. Another of these 9 patients was recorded to have discontinued study drug on day 102 and was last known to be alive on day 328.

Summary

Complete or partial overall responses have been observed in patients receiving isavuconazole for primary treatment and in patients with disease refractory to other systemic antifungal therapy. In particular, cases of complete overall response provide unambiguous evidence of antifungal activity in this life-threatening disease.

8.4.5 Mucor Matched Control Analysis

The FDA suggested that a case series of approximately 20 well-documented cases receiving isavuconazole as initial therapy may be sufficient to support a labeled indication, in the context of a randomized, controlled study and supporting literature.

To provide additional support to evaluate the activity of isavuconazole to treat IM, a matched control analysis was conducted to compare results from patients assessed by the DRC as having received isavuconazole as primary therapy for proven or probable IM in Study 0103 with patients from the Fungiscope Registry database who received primary therapy with amphotericin-based formulations for proven or probable IM. The Fungiscope Registry is a global web-based database and is a contemporary observational study coordinated from the Clinical Trials Centre at the University of Cologne, Germany. This database contains the largest collection of information on rare fungal infections, with over 150 cases of IM treated between 2003 and 2013.

The primary therapy patients were selected for this matched control analysis because they represent the least confounded evidence to assess the isavuconazole monotherapy treatment effect. Amphotericin was chosen as the comparator as it is only approved therapy for IM. Mortality was chosen as the outcome measure because it is objective and available.

8.4.5.1 Matched Control Methods

The case matching was governed by a prospectively defined methodology and allowed for up to 3 controls to match to each Study 0103 case. The matching activity was conducted independent of the Sponsor by a physician blinded to outcomes in both the case and control groups. The blinded physician received data from Study 0103 cases from the Sponsor without outcomes. The blinded physician was also provided the potential controls without outcomes, which were programmatically identified from the Fungiscope database by an independent statistician from the University of Cologne. The blinded physician conducted matching. Once the entire cohort of matched controls was selected and locked, the data from the matched controls was provided to the Sponsor with outcomes from the independent statistician.

Matching Criteria

The case matching used three primary criteria, which were selected on the basis of a literature search and considered the most relevant factors predictive of outcome in patients with IM.

Case matching criteria:

- Severe Disease (yes/no), which included patients with CNS involvement or disseminated disease. Disseminated disease was defined as disease involving more than 1 non-contiguous organ.
- Underlying hematologic malignancy (yes/no).
- Surgical Resection or Debridement (yes/no), which was intended as therapeutic intervention for IM 7 days prior to or after the start of their primary therapy.

Secondary matching criteria included age, underlying disease other than hematologic malignancy and type of amphotericin formulation used with preference given to lipid-based preparations.

8.4.5.2 Results of Study 0103 Cases and Matched Controls

All 21 of the Study 0103 cases were matched to at least one control. A total of 33 matched controls, treated between January 2005 and March 2013, were identified. The distribution of matched controls identified per Study 0103 case is shown in [Table 32].

Table 32 Case Control Matching

Study 0103 Cases (n = 21), n (%) of patients	Number of Matched Controls
5 (23.8)	3
2 (9.5)	2
14 (66.7)	1

Demographics of patients in this analysis are provided in [Table 33].

Table 33 Demographics (0103 Cases and Matched Controls)

Parameter Category/Statistic	Study 0103 Cases (n = 21)	Fungiscope Matched Controls (n = 33)
Age (years)		
n	21	33
Mean (SD)	51.7 (14.72)	56.5 (12.98)
Median	51.0	57.0
Min - Max	25 - 77	22 - 81
Gender n (%)		
Male	17 (81.0)	22 (66.7)
Female	4 (19.0)	11 (33.3)
Race n (%)		
White	12 (57.1)	31 (93.9)
Black or African American	1 (4.8)	0
Asian	8 (38.1)	2 (6.1)
Geographic region n (%)		
North America and Western Europe†	8 (38.1%)	21 (63.6%)
Other‡	13 (61.9%)	12 (36.4%)

† The North America and Western Europe region consists of Canada, US, Austria, Belgium, France and Germany.

‡ The Other region consists of Brazil, the Czech Republic, Greece, India, Israel, Lebanon, Russia and Thailand.

The most common pathogens identified in the Study 0103 cases, as assessed by the DRC, were *Mucormycetes* NOS (28.6%), *Mucor* NOS (23.8%) and *Rhizopus oryzae* (19.0%). The most common pathogens for the matched controls were similar, although the controls had a higher proportion of patients with infections due to *Rhizopus*, either *Rhizopus* NOS, *R. microspores* and/or *R. oryzae* [Table 34].

Table 34 Baseline Fungal Disease Characteristics (0103 Cases and Matched Controls)

Parameter Category/Statistic	Study 0103 Cases (n = 21)	Fungiscope Matched Controls (n = 33)
Categorization of IFD n (%)		
Proven	18 (85.7)	20 (60.6)
Probable	3 (14.3)	13 (39.4)
Pathogen Identified n (%)		
Lichtheimia (Absidia) corymbifera	2 (9.5)	6 (18.2)
Actinomucor elegans	1 (4.8)	0
Mucor NOS	5 (23.8)	5 (15.2)
Mucor amphibiorum	1 (4.8)	0
Mucormycetes NOS	6 (28.6)	7 (21.2)
Rhizomucor	1 (4.8)	0
Rhizomucor pusillus	1 (4.8)	2 (6.1)
Rhizopus NOS	0	6 (18.2)
Rhizopus microsporus	0	4 (12.1)
Rhizopus oryzae	4 (19.0)	3 (9.1)
Table continued on next page		

Parameter Category/Statistic	Study 0103 Cases (n = 21)	Fungiscope Matched Controls (n = 33)
Location of IFD		
LRTD Locations n (%)		
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 Locations n (%)		
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)

CNS: Central Nervous System; GI: Gastrointestinal; IFD: invasive fungal disease; LRTD: Lower Respiratory Tract Disease; NOS: not otherwise specified.

The number and percentage of each group represented in each matching criterion is presented in [Table 35]. For surgery and hematologic malignancy, the percentage of patients was similarly distributed. There was a somewhat lower proportion of matched controls identified with severe disease.

Table 35 Matching Criteria and Baseline Characteristics (0103 Cases and Matched Controls)

Parameter Category/Statistic	Study 0103 Cases (n = 21)	Fungiscope Matched Controls (n = 33)
Matching Criteria, n (%)		
Severe Disease	12 (57.1)	13 (39.4)
CNS Involvement	6 (28.6)	8 (24.2)
Disseminated Disease	8 (38.1)	8 (24.2)
Hematologic Malignancy	11 (52.4)	18 (54.5)
Surgery	9 (42.9)	13 (39.4)
Baseline Characteristics, n (%)		
Immunosuppressant Use	9 (42.9)	9 (27.3)
Baseline Neutropenia†	4 (19.0)	8 (24.2)
HSCT	4 (19.0)	5 (15.2)
Diabetes	4 (19.0)	6 (18.2)
Solid Organ Transplant	1 (4.8)	3 (9.1)

CNS: Central Nervous System; HSCT: hematopoietic stem cell transplant.

† Neutropenia was defined as ANC < 0.5 x 10^9/L (< 500/mm^3) and was determined by the investigator.

The mortality rate through day 42 from Study 0103 cases was similar to the mortality rate of the Fungiscope matched controls [Table 36]. As the matching allowed 1 case to be matched to 1, 2 or 3 controls, weighted mortality was calculated by averaging the mortality rates from the clusters of matched controls to each of the 21 cases.

Table 36 Mortality from Study 0103 Cases and Crude and Weighted Mortality from the Matched Controls

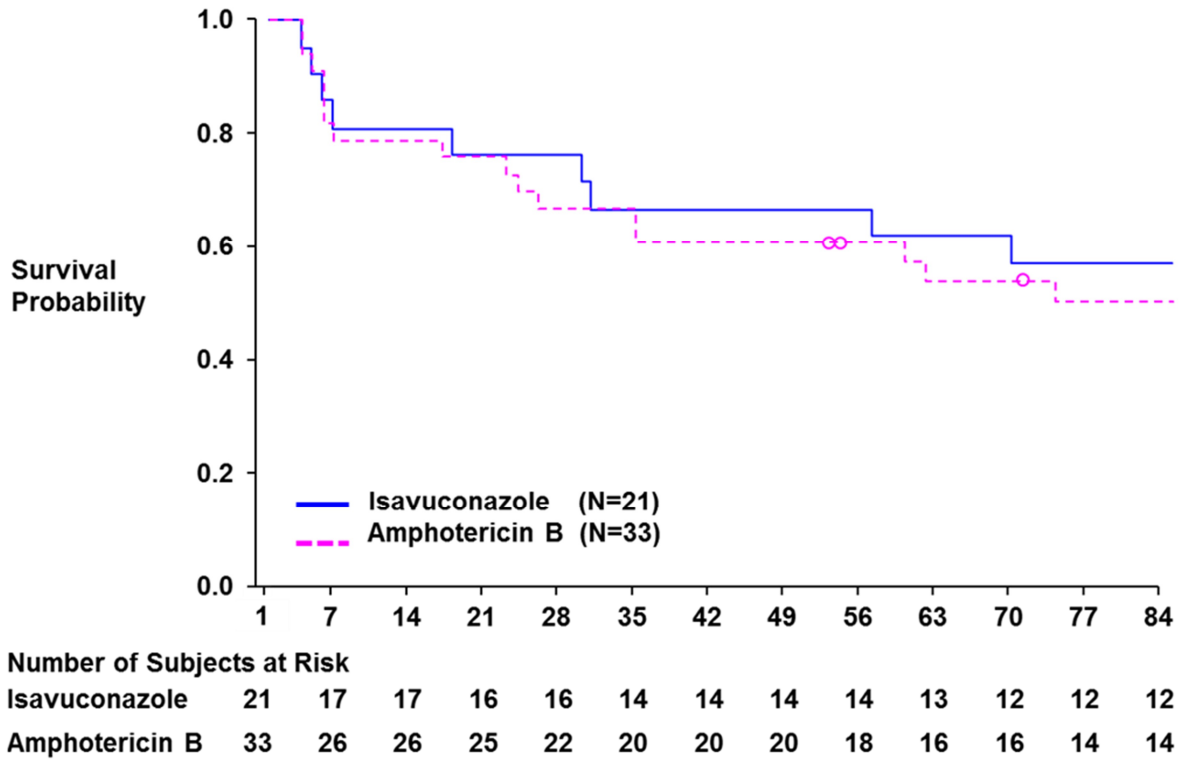
	All-cause Mortality n/n (%)	95% CI
Study 0103 Mucorales Primary Therapy Cases	7/21 (33.3)	(14.588, 56.968)†
Amphotericin-treated Matched Controls – Crude Mortality	13/33 (39.4)	(22.907, 57.861)†
Amphotericin-treated Matched Controls – Weighted Mortality	(41.3)	(20.213, 62.326)‡

† Exact binomial CIs were calculated

‡ 95% CI was calculated based on a normal approximation.

Day 84 Kaplan-Meier survival estimates for the 0103 cases were similar to those for the matched controls (57.1% for 0103 cases, 49.7% for the matched controls) [Figure 27].

Figure 27 Kaplan-Meier Estimates of the Probability of Survival (0103 Cases and Matched Controls)



While there are several limitations to comparisons between clinical trials and historical registries, the analyses performed indicate that isavuconazole has efficacy comparable to that of amphotericin B.

The Sponsor believes that this approach to providing a control group may be a better reflection of current outcomes than the historic literature, as it is a contemporary observational database relevant to current standard of care. It should be noted that a sample

size of approximately 800 (395 per arm) patients would be required to conduct an adequately powered (80%) study to demonstrate non-inferiority of isavuconazole with amphotericin B assuming a 39.4% mortality rate from the amphotericin B matched controls and a 10% NIM.

8.4.6 Mucormycosis Historical Literature Review

The ECIL 3 and ESCMID/ECMM recommend liposomal or lipid-complex amphotericin B as first-line therapy for the treatment of IM.[17,18] Given the rarity of IM, no randomized, well-controlled clinical efficacy trials have been conducted. Therefore, the guidelines issued in Europe are based on a review of the case series in the published literature and expert opinion. Posaconazole was recommended by ECIL as a second-line treatment option for patients refractory to or intolerant of amphotericin B or in patients who require prolonged maintenance therapy.[17] There are no treatment guidelines for IM issued in the US.

In order to provide context in which to interpret outcomes of isavuconazole for the treatment of IM obtained from Study 0103, a thorough review of the existing literature was conducted for publications that reported mortality rates in various patient populations with IM treated with an amphotericin-based formulation or in patients who received no treatment or delayed treatment.

Publications that reported mortality rates in patients with IM (1991 through 2011) who had mixed underlying conditions (e.g., hematological malignancies, SOT, diabetes, etc. – similar to patients in Study 0103) and received amphotericin-based treatment were reviewed. Mortality rates ranged from 35% to 61% and were generally comparable with the mortality rates in Study 0103 (38% and 43% through days 42 and 84, respectively). The literature also reported mortality rates in a high risk patient population with hematological malignancy that ranged from 55% to 80%, compared to rates of 55% to 59% observed through day 42 and day 84 in patients with hematological malignancy in Study 0103. A list of references utilized in the historical review is provided in [Appendix 9].

Clinical Benefit in Treated and Untreated Patients with IM

IM, if left untreated, is almost universally fatal. In a review article by Roden, which included 929 cases of IM reported in the literature from 1940 through 2003, 241 cases were not treated, of which 233 (97%) died.[19] A more recent review by Skiada and colleagues included information on more than 200 cases from 2005 to 2007, which included information on 31 untreated cases, of which 26 (83.9%) died.[16]

To supplement the available data, we contacted Dr. Oliver Cornely who provided mortality outcomes in patients with IM who were entered into the Fungiscope database.[60] In this database, there are 136 cases of IM with available survival data through day 42, 29 of whom did not receive adequate treatment and all 29 died. In the untreated patients, most were diagnosed postmortem or shortly before death, similar to the Roden and Skiada papers. The Sponsor acknowledges the inherent limitations of postmortem diagnoses, but believes that these data are the best available when trying to estimate mortality rates if IM is left untreated. The diagnosis of mucormycosis is challenging and, when diagnosed, all patients would be treated with systemic Mucorales-active antifungal therapy. With no serologic biomarker for

IM, patients with disease that is not readily accessible by biopsy may go undiagnosed until autopsy.[10,11] Postmortem diagnosis underscores the rapid fatality of this disease and the difficulty in diagnosis.

Mortality outcomes from these sources, along with 95% CIs are presented in [Table 37]. Across these three data sources, the mortality rates in amphotericin-treated patients range from 37.7% to 38.3%, while mortality rates in untreated patients range from 95.5% to 100%. A meta-analysis (using a random-effect model accounting for the heterogeneous nature among these three data sources) was conducted yielding an overall mortality rate of 37.8% (95% CI: 34.7, 41.0) in amphotericin treated patients and an overall mortality rate of 96.2% (95% CI: 94.0, 98.4) in untreated patients.

Even allowing for the limitation inherent in comparing outcomes of amphotericin treated versus untreated (largely autopsy diagnosed) patients, these data demonstrate a large apparent amphotericin treatment effect.

Table 37 Mortality Rates and 95% CIs in Amphotericin Treated and Untreated Patients

Study	Amphotericin Treated Patients All-cause Mortality n/n (%) (95% CI)†	Untreated Patients All-cause Mortality n/n (%) (95% CI)†
Roden[19]	244/648 (37.7) (33.9, 41.5)	233/241 (96.7) (93.6, 98.6)
Skiada[16]	58/152 (38.2) (30.4, 46.4)	21/22 (95.5) (77.2, 99.9)
Fungiscope[60] ‡	41/107 (38.3) (29.1, 48.2)	29/29 (100) (88.1, 100)
Meta-analysis§	37.8 (34.7, 41.0)	96.2 (94.0, 98.4)

† CIs were calculated by exact binomial method; 95% CIs from the meta-analysis were based on normal approximation.

‡ Day 42: 13 with premortem diagnosis, typically within a week of death, plus post-mortem diagnosis

§ Based on Roden, Skiada and Fungiscope data. The number of treated patients = 907. The number of untreated patients = 292.

The mortality rates and 95% CIs for all patients with proven or probable IM from Study 0103, as well as for the subset of patients who received isavuconazole as primary therapy, are presented alongside the mortality data from the untreated meta-analysis [Table 38]. Similar to data with amphotericin, there is a large treatment effect with isavuconazole relative to no treatment.[19,16,60]

Table 38 All-Cause Crude Mortality in Isavuconazole Treated and Untreated Patients

Time Point	Isavuconazole Treated Patients All Mucor† n/n (%) (95% CI)‡	Isavuconazole Treated Patients Primary Therapy Mucor n/n (%) [95% CI]‡	Untreated Patients Mucor Meta-analysis§ n/n (%) [95% CI]‡
Day 42	14/37 (37.8) (22.5, 55.2)	7/21 (33.3) (14.6, 57.0)	96.2 (94.0, 98.4)
Day 84	16/37 (43.2) (27.1, 60.5)	9/21 (42.9) (21.8, 66.0)	

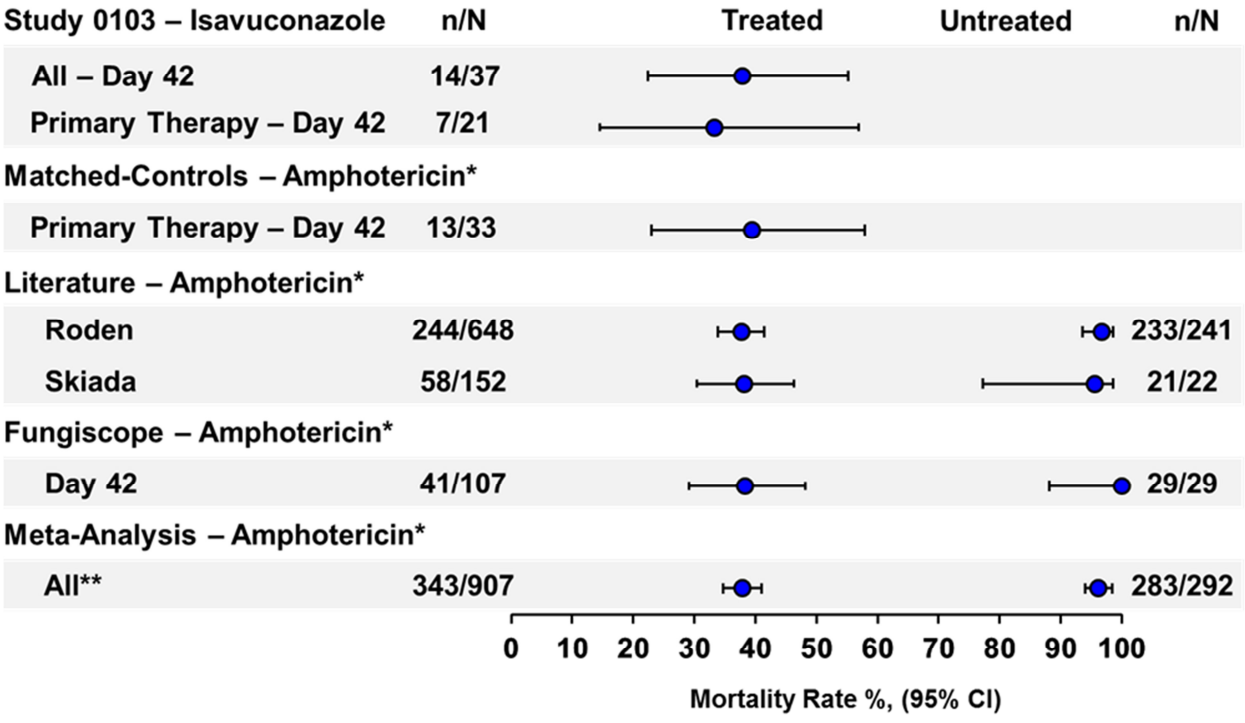
† 1 patient with unknown survival status at day 42 was assumed to be dead.

‡ 95% CIs were calculated using the exact binomial method. The 95% CI from the meta-analysis was based on normal approximation.

§ Based on Roden[19], Skiada[16] and Fungiscope[60] data. Number of untreated patients = 292.

Data from the above tables are presented graphically in [Figure 28]. It is important to note that isavuconazole treated patients are representative of the population of patients with various underlying risk factors that would be candidates to receive isavuconazole in the clinical setting.

Figure 28 Mortality in Amphotericin B and Isavuconazole Treated and Untreated Patients with IM



IM: invasive mucormycosis.

*Amphotericin refers to both amphotericin B deoxycholate and lipid formulations of amphotericin.

**The meta-analysis is based on Roden[19], Skiada[16] and Fungiscope[60] data. The number of treated patients = 907 and the number of untreated patients = 292.

Taken collectively, these data support the current treatment guidelines that advocate the use of amphotericin as treatment for IM and would similarly support isavuconazole as having a treatment effect relative to no treatment.

Clinical Benefit in Patients with IM and Underlying Hematologic Malignancy

Chamilos and colleagues[61] reported that patients with underlying hematologic malignancies who developed IM at their institution between 1989 and 2006, were at high risk to progress and die without appropriate treatment. Patients who had a delay (> 6 days from diagnosis) in the initiation of treatment had a mortality rate of 82.9% at week 12. This represents an almost doubling of the mortality rate relative to patients who had therapy initiated in a more timely fashion. The authors also reported that further delays in initiation of adequate therapy results in a mortality rate approaching 100%. This report clearly points to the fact that patients with IM and underlying hematologic malignancy are at a high risk to progress and die without appropriate treatment.

To supplement this data in the subgroup of patients with underlying hematologic malignancies, Dr. Oliver Cornely also provided mortality outcomes in patients with IM and underlying hematologic malignancies from the Fungiscope database.[60] In this dataset, there are 96 cases of IM with available survival data through day 84 (the time point reported in the Chamilos paper), 26 of whom did not receive adequate treatment and all 26 died. As depicted in [Table 39], the mortality rates in amphotericin treated patients range from 48.6% (Chamilos)[61] to 52.9% (Fungiscope)[60], while the mortality rate in untreated patients is 100%, mirroring the Chamilos report.[61]

A meta-analysis (using a random effect model) was conducted yielding an overall mortality rate of 51.4% (95% CI: 41.9, 61.0) in amphotericin treated patients with underlying hematologic malignancies. A 95% CI was also calculated for the mortality rate of 100% (86.8, 100) in untreated patients from the Fungiscope database.[60] These data also demonstrate an apparent treatment effect for amphotericin treated patients relative to untreated patients as depicted by the separation of the 95% CIs.

Table 39 All-cause Mortality in Patients with Underlying Hematologic Malignancy

Study	Amphotericin Treated Patients with Hematologic Malignancy n/n (%) (95% CI)†	Delayed Treatment‡ Patients with Hematologic Malignancy n/n (%) (95% CI)†	Untreated Patients with Hematologic Malignancy n/n (%) (95% CI)†
Chamilos[61] (Week 12)	17/35 (48.6) (31.4, 66.0)	29/35 (82.9)¶ (66.4, 93.4)	NA
Fungiscope[60] (Day 84)	37/70 (52.9) (40.6, 64.9)	NA	26/26 (100)§ (86.8, 100.0)
Meta-analysis††	51.4 (41.9, 61.0)	NA	NA

NA: not available.

Footnotes continued on next page

† 95% CIs were calculated using exact binomial method. The 95% CI from the meta-analysis was based on normal approximation.

‡ Early treatment (< 6 days from diagnosis) vs Delayed treatment (≥ 6 days from diagnosis)[61]

¶ Chamilos[61] reported that further delays in initiation of adequate therapy results in a mortality rate that approaches 100%.

§ 12 with premortem diagnosis, typically within a week of death, plus postmortem diagnosis.[60]

†† Based on Chamilos[61] and Fungiscope[60] (n = 105).

There were 22 patients enrolled in Study 0103 with IM and an underlying hematologic malignancy, 11 of whom received isavuconazole for primary therapy. All-cause mortality rates and 95% CIs are presented in [Table 40].

Table 40 All-cause Mortality in Isavuconazole Treated Patients with Underlying Hematologic Malignancy (mITT-Mucorales; 0103)

Time Point	ISA Treated Patients All Mucor Hematologic Malignancy§ n/n (%) (95% CI)†	ISA Treated Patients Primary Therapy Mucor Hematologic Malignancy n/n (%) (95% CI)†	Untreated Patients Hematologic Malignancy n/n (%) (95% CI)†
Day 42	12/22 (54.5) (32.2, 75.6)	5/11 (45.5) (16.8, 76.6)	26/26 (100)‡ (86.8, 100.0)
Day 84	13/22 (59.1) (36.4, 79.3)	6/11 (54.5) (23.4, 83.3)	

ISA: isavuconazole.

† 95% CIs were calculated using exact binomial method.

‡ Fungiscope database: 12 patients with premortem diagnosis, typically within a week of death, plus postmortem diagnosis.[60]

§ 1 patient with unknown survival status at day 42 was assumed to be dead.

Despite the lower denominators, which yield wider CIs, these data support the current treatment guidelines that advocate the use of amphotericin as first-line antifungal treatment for IM in hematologic malignancy patients and would similarly support a treatment effect with isavuconazole versus no treatment.

8.4.7 Efficacy Summary (IM)

In conclusion, the data collected from various sources shows that isavuconazole is an effective therapy in the treatment of IM including in patients with hematologic malignancies. The activity of isavuconazole is supported by in vitro susceptibility data, animal models and clinical experience demonstrating better outcomes relative to untreated patients and comparable to amphotericin treated patients. The review of the cases for isavuconazole treated patients show evidence of efficacy in the treatment of IM with isavuconazole monotherapy. In particular, cases of overall complete response provide unambiguous evidence of antifungal activity in this life-threatening disease.

Both the above and the successful outcomes from the large, randomized, double-blind, multicenter, non-inferiority, comparative Study 0104, which evaluated isavuconazole for the treatment of IA, support the use of isavuconazole as a safe and effective alternative to amphotericin B deoxycholate, which has significant toxicity, is only available in an IV formulation and is the only approved treatment for IM.

9 OVERVIEW OF SAFETY

9.1 Summary of Safety Results

The safety profile of isavuconazole has been well characterized with a large global safety population. In total, over 1600 subjects received isavuconazole in the clinical development program.

Characteristics of the safety profile of isavuconazole:

- The safety profile of isavuconazole is favorable compared to the safety profile of voriconazole for study drug-related adverse events and adverse events in the system organ classes of skin, eye and hepatobiliary disorders.
- Isavuconazole shortens QTc while voriconazole results in lengthening of QTc.
- The safety profile of isavuconazole is generally similar across target indications.

9.2 Overall Safety Population

The safety profile of isavuconazole has been well characterized with a large, global safety population [Table 41]. In total, more than 1600 subjects received isavuconazole in the clinical development program. In phase 1 studies, more than 1100 subjects were exposed to isavuconazole in standard pharmacokinetic studies, pharmacodynamic studies and extensive drug-drug interaction studies. Two phase 2 and two phase 3 studies characterize the efficacy and/or safety of isavuconazole in patients. The two phase 2 studies evaluated isavuconazole in patients with esophageal candidiasis and as prophylaxis in neutropenic patients with AML. The phase 2 studies are not considered directly supportive of the efficacy of the proposed indications since they evaluated isavuconazole in different patient populations and clinical settings. The phase 3 program for the proposed indications included 403 patients who received isavuconazole.

Table 41 Global Clinical Development Safety Program

	Studies n	All Subjects n	Isavuconazole Treated Subjects n
Total	**44**	**2166**	**1692**
Phase 1	40	1322	1145
Phase 2	2	182	144
Phase 3	2	662	403

The extent of patient exposure in Phase 3 Studies 0104 and 0103 is presented in [Table 42]. A substantial number of patients received isavuconazole for durations relevant to the proposed indications with a median exposure of 57 days. The proportion of patients receiving

isavuconazole for more than 4 months consists mostly of patients with mucormycosis or rare moulds in the open-label phase 3 study. Prolonged therapy was allowed in these patients by protocol as deemed necessary by their managing physicians.

Table 42 Duration of Study Drug Administration in the Phase 3 Studies (0104 and 0103)

Duration of Study Drug Administration	Phase 3 Isavuconazole Treated (n = 403)
Total Duration (days)	
Mean (SD)	76.1 (91.2)
Median	57.0
Cumulative Total Duration Category (days), n (%)	
≥ 14	318 (78.9)
≥ 28	269 (66.7)
≥ 42	241 (59.8)
≥ 84	144 (35.7)
≥ 126	67 (16.6)

The population of patients enrolled in Study 0104 and the phase 3 population as a whole are representative of the patient population likely to receive antifungal treatment for proven, probable or possible IFD. The phase 3 population is of sufficient magnitude and extent of exposure to allow a reasonable assessment of the safety of the compound in the intended clinical indications.

An overview of safety results from the clinical development program for isavuconazole is provided below with a focus on Study 0104 and comparative safety with voriconazole in the Safety Population (all randomized patients who received at least one dose of study drug with data analyzed according to the study drug that patients received as the first dose even if it was different from what they were randomized to).

9.3 Demographics and Duration of Study Drug Administration

In Study 0104, the overall mean age of patients was 51 years and the majority of patients were White (78.1%), ≤ 65 years of age (77.9%) and male (59.7%). The high morbidity of this population was shown by the high prevalence of hematologic malignancy (83.9%), with many patients in an immunocompromised state because of neutropenia (65.5%; defined as ANC < 0.5 x 10^9/L), T-cell immunosuppressants use (42.6%) and corticosteroid use (16.9%). In addition, the patient's immunocompromised state was likely exacerbated by the high rate of active malignancy (69.8%), which also requires chemotherapy. These characteristics are present in a similar proportion of patients in both treatment groups as shown for the ITT Population in [Section 7.3.2].

One patient was randomized to isavuconazole, but received voriconazole and, therefore, was analyzed in the isavuconazole group for the ITT population and in the voriconazole group for the safety population.

The duration of study drug administration in the ITT Population was similar between treatment groups and is presented in [Section 7.3.3].

9.4 Treatment-emergent Adverse Events (TEAEs)

All adverse event data are presented for TEAEs, defined as an adverse event starting after first study drug administration up to 28 days after the last dose of study drug. Study drug-related TEAEs include those considered by the investigator to be remotely, possibly or probably related to study drug and those with a missing relationship.

A high level summary of the safety findings from Study 0104 is provided in [Table 43]. Adverse events were reported almost universally for patients enrolled in the study. One-half of the patients experienced serious adverse events. The high level of adverse events is characteristic of this patient population with high underlying morbidity and life-threatening invasive fungal infection. All patients in the study were enrolled while hospitalized for their illness and IV antifungal therapy was initiated during said hospitalization.

The overall safety data reveal that the two drugs were generally comparable. The two treatment groups had similar proportions of patients with overall adverse events and serious adverse events as well as serious study drug related adverse events. Despite the high background of adverse events, differences were noted between treatment groups specifically in study drug-related adverse events and adverse events leading to permanent discontinuation of study drug.

Table 43 Overview of TEAEs and Deaths (0104)

Category of TEAEs, n (%) of patients	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)

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.

A TEAE 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.

TEAE(s): treatment-emergent adverse event(s).

In the analysis of TEAEs by SOC, the proportion of patients with TEAEs was similar between treatment groups for the majority of SOCs [Table 44]. However, differences between the isavuconazole and voriconazole treatment groups, respectively, were observed for the following SOCs: Skin and Subcutaneous Tissue Disorders (33.5% vs 42.5%), Eye Disorders (15.2% vs 26.6%) and Hepatobiliary Disorders (8.9% vs 16.2%). Isavuconazole treated patients had a statistically significantly lower number of patients with events in the Skin disorders, Eye disorders and Hepatobiliary disorders SOCs.

Table 44 TEAEs by System Organ Class (SOC) (0104)

MedDRA v12.1 System Organ Class, n (%) of patients	Isavuconazole (n = 257)	Voriconazole (n = 259)
Overall	**247 (96.1)**	**255 (98.5)**
Gastrointestinal Disorders	174 (67.7)	180 (69.5)
Infections and Infestations	152 (59.1)	158 (61.0)
General Disorders and Administration Site Conditions	148 (57.6)	144 (55.6)
Respiratory, Thoracic and Mediastinal Disorders	143 (55.6)	147 (56.8)
Metabolism and Nutrition Disorders	108 (42.0)	121 (46.7)
Nervous System Disorders	95 (37.0)	89 (34.4)
Skin and Subcutaneous Tissue Disorders	86 (33.5)*	110 (42.5)
Investigations	85 (33.1)	96 (37.1)
Blood and Lymphatic System Disorders	77 (30.0)	82 (31.7)
Psychiatric Disorders	70 (27.2)	86 (33.2)
Musculoskeletal and Connective Tissue Disorders	69 (26.8)	77 (29.7)
Vascular Disorders	67 (26.1)	77 (29.7)
Renal and Urinary Disorders	55 (21.4)	58 (22.4)
Cardiac Disorders	43 (16.7)	57 (22.0)
Eye Disorders	39 (15.2)*	69 (26.6)
Injury, Poisoning and Procedural Complications	33 (12.8)	39 (15.1)
Hepatobiliary Disorders	23 (8.9)*	42 (16.2)
Immune System Disorders	20 (7.8)	25 (9.7)
Neoplasms Benign, Malignant and Unspecified	19 (7.4)	31 (12.0)
Ear and Labyrinth Disorders	14 (5.4)	13 (5.0)
Reproductive System and Breast Disorders	8 (3.1)	13 (5.0)
Endocrine Disorders	5 (1.9)	3 (1.2)
Congenital, Familial and Genetic Disorders	3 (1.2)	2 (0.8)
Social Circumstances	0	1 (0.4)

Sorting order: descending percentage in isavuconazole group by system organ class.

TEAE(s): treatment-emergent adverse event(s).

*Statistical significance at ≤ 0.05 (Fisher's exact test)

Review of the TEAEs reported within the SOCs of Skin Disorders, Eye Disorders and Hepatobiliary Disorders suggests that the lower proportion of TEAEs in patients receiving isavuconazole than voriconazole was primarily influenced by the following TEAEs:

- Skin and Subcutaneous Tissue Disorders SOC: rash (17, 6.6% vs 28, 10.8%), erythema (9, 3.5% vs 15, 5.8%) and drug eruption (3, 1.2% vs 11, 4.2%)
- Eye Disorders SOC: visual impairment (4, 1.6% vs 19, 7.3%), photophobia (2, 0.8% vs 6, 2.3%) and reduced visual acuity (1, 0.4% vs 6, 2.3%)
- Hepatobiliary Disorders SOC: hyperbilirubinemia (5, 1.9% vs 10, 3.9%), abnormal hepatic function (4, 1.6% vs 9, 3.5%), jaundice (1, 0.4% vs 6, 2.3%) and cholestasis (1, 0.4% vs 6, 2.3%)

The proportion of patients who experienced the 10 most frequently reported TEAEs regardless of relationship to study drug was similar in both treatment groups as shown in [Table 45].

Table 45 10 Most Frequently Reported TEAEs by Preferred Term (0104)

MedDRA v12.1 Preferred Term, n (%) of patients	Isavuconazole (n = 257)	Voriconazole (n = 259)
Total Number of Patients with ≥ 1 TEAE	**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)

Preferred Terms ordered by decreasing frequency in the isavuconazole treatment arm.

TEAE(s): treatment-emergent adverse event(s).

9.5 Study Drug Related TEAEs

In Study 0104, TEAEs considered by the investigator to be related to study drug were experienced by fewer isavuconazole treated patients (42.4%) than voriconazole treated patients (59.8%) [Table 46].

Table 46 Study Drug Related TEAEs by SOC (0104)

MedDRA v12.1 System Organ Class, n (%) of patients	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)

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

Sorting order: descending percentage in isavuconazole group by system organ class.

TEAE(s): treatment-emergent adverse event(s).

Consistent with the results observed for overall TEAEs, fewer isavuconazole than voriconazole treated patients experienced study drug-related TEAEs for the following SOCs (events influencing the treatment differences): Eye Disorders (visual impairment and visual acuity reduced), Hepatobiliary Disorders (abnormal hepatic function, hyperbilirubinemia, cholestasis, hepatic failure and jaundice), Investigations (liver chemistries and prolonged electrocardiogram [ECG] QT) and Psychiatric Disorders (hallucination-type events). A numerically higher proportion of isavuconazole than voriconazole treated patients experienced study drug-related TEAEs in the Respiratory, Thoracic and Mediastinal Disorders SOC (dyspnea).

The 10 most common study drug-related TEAEs are shown in [Table 47].

Table 47 10 Most Common Study Drug-related TEAEs by Preferred Term (0104)

MedDRA v12.1 Preferred Term, n (%) of patients	Isavuconazole (n = 257)	Voriconazole (n = 259)
Nausea	19 (7.4)	21 (8.1)
Vomiting	13 (5.1)	22 (8.5)
Gamma-glutamyl transferase increased	6 (2.3)	14 (5.4)
Aspartate aminotransferase increased	5 (1.9)	11 (4.2)
Blood alkaline phosphatase increased	5 (1.9)	11 (4.2)
Alanine aminotransferase increased	4 (1.6)	11 (4.2)
Hepatic function abnormal	2 (0.8)	9 (3.5)
Hallucination	1 (0.4)	11 (4.2)
Visual impairment	1 (0.4)	15 (5.8)
Hallucination, visual	0	9 (3.5)

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

TEAE(s): treatment-emergent adverse event(s).

9.6 Deaths

All-cause mortality through day 42 was the primary endpoint of the study and mortality rates at specific time points were reported in detail in the efficacy section of this document [Section 7.4.1].

For the safety evaluation, deaths were summarized from first dose of study drug through 28 days after the last dose. The proportion of patient deaths from the first dose through 28 days after the last dose of study drug was similar between the isavuconazole and voriconazole treatment groups (24.1%, 62/257 vs 27.0%, 70/259, respectively).

Causes of death in the study were examined at two levels. The first approach was to examine the TEAEs leading to death as determined by the investigator. The second approach was to review the DRC-assessed attribution of death to IFD, which allowed delineation of the contribution of the underlying infectious process to the death.

The overall proportion of patients who had TEAEs leading to death was similar between the isavuconazole and voriconazole treatment groups [Table 48]. The more common TEAEs leading to death (occurred in ≥ 2% of patients in either the isavuconazole or voriconazole group, respectively) were septic shock (8/257, 3.1% vs 4/259, 1.5%), sepsis (7/257, 2.7% vs

5/259, 1.9%), respiratory failure (6/257, 2.3% vs 6/259, 2.3%), acute myeloid leukemia (3/257, 1.2% vs 7/259, 2.7%) and multi-organ failure (1/257, 0.4% vs 6/259, 2.3%).

Table 48 TEAEs Leading to Death (0104)

MedDRA V12.1 System Organ Class Preferred Term	ISA n = 257 n (%)	VRC n = 259 n (%)
Patients with ≥ 1 TEAE with an Outcome of Death	**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 (incl cysts and polyps)	**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)

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MedDRA V12.1 System Organ Class Preferred Term	ISA n = 257 n (%)	VRC n = 259 n (%)
Blast cell crisis	1 (0.4)	1 (0.4)
Burkitt's leukaemia	0	1 (0.4)
Chronic lymphocytic leukaemia	0	2 (0.8)
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

ISA: isavuconazole; TEAE: treatment-emergent adverse event; VRC: voriconazole.

† Cause of death unknown

The DRC examination of the attribution of death to IFD was limited to a subset of patients who had proven, probable or possible IFD. The DRC did not assess the attribution of death to IFD for patients determined to have no IFD (isavuconazole: 27; voriconazole: 21). A summary of the DRC assessment showed that the majority of deaths in both treatment groups were reported to be associated with evidence of residual or ongoing IFD at both time points (mortality through day 42 and day 84) [Table 49].

Table 49 DRC Attribution of Death to IFD (ITT-excluding no IFD Population)

Attributable Mortality	Isavuconazole (n = 231)	Voriconazole (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; ITT: intent-to-treat.

† Clear evidence that mortality is due to progressive IFD

‡ Evidence of residual or ongoing IFD at the time of death, but death may be due to IFD or progression of underlying disease.

9.7 Serious TEAEs

In Study 0104, more than half of all patients experienced at least one serious TEAE including deaths (isavuconazole 52.1%, voriconazole 57.5%), which is expected based on the significant underlying diseases in these patients. The overall proportion of patients with serious events was similar between the isavuconazole and voriconazole treatment groups [Table 50].

Table 50 Serious TEAEs by SOC (0104)

MedDRA v12.1 System Organ Class, n (%) of patients	Isavuconazole (n = 257)	Voriconazole (n = 259)
Overall	**134 (52.1)**	**149 (57.5)**
Infections and infestations	51 (19.8)	61 (23.6)
Respiratory, thoracic and mediastinal disorders	41 (16.0)	43 (16.6)
Blood and lymphatic system disorders	28 (10.9)	17 (6.6)
Neoplasms benign, malignant and unspecified	18 (7.0)	29 (11.2)
Nervous system disorders	17 (6.6)	16 (6.2)
General disorders and administration site conditions	11 (4.3)	19 (7.3)
Cardiac disorders	11 (4.3)	12 (4.6)
Renal and urinary disorders	10 (3.9)	10 (3.9)
Gastrointestinal disorders	9 (3.5)	12 (4.6)
Immune system disorders	4 (1.6)	6 (2.3)
Vascular disorders	4 (1.6)	6 (2.3)
Hepatobiliary disorders	3 (1.2)	6 (2.3)
Investigations	3 (1.2)	6 (2.3)
Injury, poisoning and procedural complications	3 (1.2)	3 (1.2)
Skin and subcutaneous tissue disorders	3 (1.2)	2 (0.8)
Musculoskeletal and connective tissue disorders	3 (1.2)	0
Metabolism and nutrition disorders	2 (0.8)	7 (2.7)

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MedDRA v12.1 System Organ Class, n (%) of patients	Isavuconazole (n = 257)	Voriconazole (n = 259)
Eye disorders	2 (0.8)	1 (0.4)
Psychiatric disorders	1 (0.4)	6 (2.3)

A TEAE with a missing seriousness was considered a serious TEAE.

Sorting order: descending percentage in isavuconazole group by system organ class.

TEAE(s): treatment-emergent adverse event(s).

The more common serious TEAEs by preferred term (PT) that occurred in ≥ 1% of patients in either the isavuconazole or voriconazole treatment groups are shown in [Table 51]. The number of patients who experienced a serious TEAE was generally similar between treatment groups.

Table 51 Serious TEAEs (≥ 1% in Either Treatment Group; 0104)

MedDRA v12.1 Preferred Term, n (%) of patients	Isavuconazole (n = 257)	Voriconazole (n = 259)
Overall	**134 (52.1)**	**149 (57.5)**
Respiratory failure	14 (5.4)	12 (4.6)
Septic shock	14 (5.4)	10 (3.9)
Febrile neutropenia	14 (5.4)	5 (1.9)
Pyrexia	8 (3.1)	10 (3.9)
Sepsis	7 (2.7)	8 (3.1)
Renal failure acute	6 (2.3)	8 (3.1)
Pneumonia	5 (1.9)	10 (3.9)
Acute respiratory failure	5 (1.9)	5 (1.9)
Dyspnoea	5 (1.9)	1 (0.4)
Aspergillosis	4 (1.6)	3 (1.2)
Neutropenia	4 (1.6)	3 (1.2)
Pancytopenia	4 (1.6)	3 (1.2)
Respiratory distress	4 (1.6)	3 (1.2)
Acute myeloid leukaemia	3 (1.2)	8 (3.1)
Thrombocytopenia	3 (1.2)	4 (1.5)
Fungal infection	3 (1.2)	3 (1.2)
Renal failure	3 (1.2)	2 (0.8)
Convulsion	3 (1.2)	1 (0.4)
Haemorrhage intracranial	2 (0.8)	3 (1.2)
Multi-organ failure	1 (0.4)	7 (2.7)
Cardiac arrest	1 (0.4)	5 (1.9)
Gastrointestinal haemorrhage	0	3 (1.2)
Bacterial sepsis	0	4 (1.5)
Staphylococcal bacteraemia	0	3 (1.2)
Acute myeloid leukaemia recurrent	0	5 (1.9)
Epistaxis	0	4 (1.5)
Lung infiltration	0	3 (1.2)
Pulmonary embolism	0	3 (1.2)

A TEAE with a missing seriousness was considered a serious TEAE.

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

TEAE(s): treatment-emergent adverse event(s).

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.

9.8 Discontinuation of Study Drug Due to TEAEs

In Study 0104, fewer isavuconazole than voriconazole patients (14.4% vs 22.8%) had at least one TEAE leading to permanent discontinuation of study drug.

Patients in the isavuconazole group had numerically fewer TEAEs leading to discontinuation of study drug compared to the voriconazole group in the Psychiatric Disorders (0.8% vs 2.3%) and Hepatobiliary Disorders (0.4% vs 2.3%) SOCs. There were 4 voriconazole treated patients who discontinued study drug due to events of hallucination or visual hallucination compared to no isavuconazole treated patients.

Study drug-related TEAEs leading to permanent discontinuation of study drug were also experienced by numerically fewer isavuconazole than voriconazole treated patients (8.2% vs 13.5%, respectively).

9.9 Events of Interest

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

Most of the events of interest were evaluated using groupings of TEAEs (PTs) associated with various types of events that were selected based on medical input or by using standard Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs). SMQs are used to capture potential events relevant to a particular condition. The events captured by these selected grouping or by SMQ are not necessarily reflective of the true condition, but are potentially related to the condition.

Details are provided below on the manner of safety evaluation for events of interest:

- Hepatotoxicity was evaluated based on categorization of elevations in ALT/AST and in ALT/AST plus total bilirubin
- Infusion/injection site reactions were evaluated by selected MedDRA high level terms and preferred terms for those who received at least one IV dose of study drug
- Potential hypersensitivity reactions:
    - Anaphylaxis was evaluated by narrow SMQ
    - Severe cutaneous adverse events were evaluated by narrow SMQ
- Effects of isavuconazole on cardiac repolarization and the clinical significance of those effects were evaluated by the performance of a thorough QT study and a careful examination of arrhythmogenic signals in the clinical database. The latter were performed by evaluation of select MedDRA preferred terms.
- Potential ocular toxicity was evaluated by selected MedDRA preferred terms
- Psychiatric events were evaluated by selected MedDRA preferred terms
- Acute pancreatitis was evaluated by acute pancreatitis narrow SMQ

- Infusion-related reactions were evaluated by MedDRA preferred term infusion-related reaction
- Convulsions and epilepsy-type events were evaluated by convulsions SMQ

9.9.1 Elevated Liver Tests

In general, fewer isavuconazole than voriconazole treated patients experienced increases in liver tests [Table 52].

Table 52 Assessment of Potential Hepatotoxicity at Any Time Point Postbaseline (0104)

Parameter	Criteria	Isavuconazole (n =257) n/n (%)	Voriconazole (n =259) n/n (%)
ALT	> 3 x ULN	31/249 (12.4)	35/255 (13.7)
	> 5 x ULN	17/249 (6.8)	18/255 (7.1)
	> 10 x ULN	5/249 (2.0)	12/255 (4.7)
AST	> 3 x ULN	24/249 (9.6)	39/255 (15.3)
	> 5 x ULN	13/249 (5.2)	19/255 (7.5)
	> 10 x ULN	4/249 (1.6)	8/255 (3.1)
ALT or AST	> 3 x ULN	39/250 (15.6)	48/255 (18.8)
	> 5 x ULN	21/250 (8.4)	27/255 (10.6)
	> 10 x ULN	6/250 (2.4)	14/255 (5.5)
ALP	> 1.5 x ULN	73/249 (29.3)	98/254 (38.6)
	> 3 x ULN	24/249 (9.6)	34/254 (13.4)
Total Bilirubin	> 2 x ULN	28/249 (11.2)	23/255 (9.0)
(ALT or AST) and Total Bilirubin†	(ALT or AST) > 3 x ULN and Total Bilirubin > 2 x ULN	8/251 (3.2)	10/255 (3.9)
(ALT or AST), ALP and Total Bilirubin†	(ALT or AST) > 3 x ULN, ALP < 2 x ULN and Total Bilirubin > 2 x ULN	3/251 (1.2)	7/255 (2.7)

ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate transaminase; ULN: upper limit of normal.

† The corresponding criteria were assessed within 3 days apart for each pair of parameters selected for this analysis.

In addition, effects on liver tests were evaluated using two nominal lab definitions of Hy's law. The first consists of patients with concurrent elevations of ALT or AST exceeding 3 x ULN and total bilirubin exceeding 2 x ULN. The second uses the same criteria as the first, but excludes patients with elevations in alkaline phosphatase (ALP; > 2 x ULN) in an attempt to discriminate between cholestatic and hepatotoxic injury. The proportions of patients fulfilling the nominal lab definitions of Hy's law appeared to be similar in the two groups. A detailed review of the records of patients in both treatment groups was done to determine the presence or absence of confounding factors or alternate etiologies. This examination revealed potential alternative etiologies for the observed laboratory abnormalities, such as concomitant sepsis, multi-organ failure and/or concomitant use of hepatotoxic drugs.

9.9.2 TEAEs in the Infusion/Injection Site Reaction Events of Interest

In Study 0104, infusion/injection site reaction events of interest were evaluated by review of a group of select MedDRA preferred terms. Infusion/injection site reactions are characterized by local symptoms around the site of the injection occurring in association with IV administration of study drug.

TEAEs in the Infusion/Injection Site Reaction events of interest occurring at any time during the study were reported in a numerically higher proportion of isavuconazole than voriconazole treated patients (4.3%, 11 patients vs 1.5%, 4 patients, respectively) [Table 53].

Table 53 TEAEs in the Infusion/Injection Site Reaction Events of Interest (0104)

MedDRA v12.1 **High Level Term** Preferred Term	**Isavuconazole** **(n = 257)** **n (%)**	**Voriconazole** **(n = 259)** **n (%)**
Patients with ≥ 1 TEAE in EOI	**11 (4.3)**	**4 (1.5)**
Infections NEC	**1 (0.4)**	**0**
Injection site infection	1 (0.4)	0
Infusion related reactions	**7 (2.7)**	**2 (0.8)**
Infusion related reaction	3 (1.2)	1 (0.4)
Infusion site extravasation	0	1 (0.4)
Infusion site irritation	1 (0.4)	0
Infusion site oedema	1 (0.4)	0
Infusion site pain	2 (0.8)	0
Injection site reactions	**1 (0.4)**	**1 (0.4)**
Injection site phlebitis	0	1 (0.4)
Injection site reaction	1 (0.4)	0
Vascular infections	**2 (0.8)**	**1 (0.4)**
Infusion site abscess	1 (0.4)	1 (0.4)
Infusion site infection	1 (0.4)	0

Events that are presented here occurred throughout the treatment period.

EOI: events of interest; NEC: not elsewhere classified; TEAE(s): treatment-emergent adverse event(s).

Local infusion/injection site reactions were further evaluated for temporal relationship to the study drug IV infusion. Reactions that occurred during the study drug IV period or no more than 1 day after study drug IV infusion are shown in [Table 54]. The temporally-associated infusion/injection site reaction events occurred exclusively in the isavuconazole group, were uncommon, limited to one event per patient, were of mild intensity, not serious, localized, self-contained and resolved spontaneously and without sequelae. None of these events resulted in study drug discontinuation. One event was due to IV leakage, one event occurred after a > 3-hour infusion of placebo and in one patient, no filter was used.

Table 54 TEAEs of Local Infusion/Injection Site Reactions Occurring During the Study Drug IV Period or no more than 1 Day after IV Infusion (0104)

MedDRA v12.1 High Level Preferred Term	Isavuconazole (n = 257) n (%)	Voriconazole (n = 259) n (%)
Overall	**5 (1.9)**	**0**
Infusion site reactions	**4 (1.6)**	**0**
Infusion site irritation	1 (0.4)	0
Infusion site oedema	1 (0.4)	0
Infusion site pain	2 (0.8)	0
Injection site reactions	**1 (0.4)**	**0**
Injection site reaction	1 (0.4)	0

TEAE(s): treatment-emergent adverse event(s).

9.9.3 Systemic Infusion-related Reaction TEAEs

Three isavuconazole treated patients and one voriconazole treated patient experienced an adverse event of infusion-related reaction. None of these events were serious or led to withdrawal from study drug. None of these events were considered by the investigator to be related to study drug. The 3 isavuconazole treated patients received other IV concurrent medications at the time of the event: one patient received antithymocyte globulin, one received packed red blood cells and platelets and one patient received alemtuzumab.

9.9.4 Anaphylaxis and Severe Cutaneous Adverse Reactions

9.9.4.1 TEAEs in the Anaphylactic Reaction SMQ

A summary of TEAEs associated with anaphylaxis found by a search using an anaphylactic reaction SMQ is presented in [Table 55].

Table 55 TEAEs in Anaphylactic Reaction SMQ by Preferred Term (0104)

MedDRA v12.1 Preferred Term, n (%) of patients	Isavuconazole (n = 257)	Voriconazole (n = 259)
Patients with Patients with ≥ 1 Anaphylaxis TEAE	**2 (0.8)**	**3 (1.2)**
Anaphylactic shock	1 (0.4)	0
Circulatory collapse	1 (0.4)	0
Anaphylactic reaction	0	2 (0.8)
Shock	0	1 (0.4)

SMQ: standard MedDRA query; TEAE(s): treatment-emergent adverse event(s).

There were 2 (0.8%) isavuconazole treated patients and 3 (1.2%) voriconazole treated patients in Study 0104 who had TEAEs in the anaphylactic reaction SMQ. One of the anaphylaxis events (anaphylactic shock) in an isavuconazole treated patient was attributed to concomitant treatment (human immunoglobulin administration) and not to isavuconazole. The event was considered serious, but resolved on the same day and the patient remained in the study with no interruption in administration of isavuconazole. The second isavuconazole treated patient had a medical history of cardiac failure, hypertensive heart disease, left bundle branch bock and anemia and experienced an adverse event of circulatory collapse on day 39, the last day of study drug dosing. The event resolved, was not serious, and was not

considered by the investigator to be related to isavuconazole. This patient died on day 80 due to cardiac failure.

In Study 0104, no patient with an anaphylaxis TEAE permanently discontinued study drug or died due to the event. There were no anaphylactic events in Study 0103.

9.9.4.2 TEAEs in the Severe Cutaneous Adverse Reactions SMQ

A summary of TEAEs found by a search using the severe cutaneous acute reactions SMQ is presented in [Table 56]. This SMQ is broad and will identify severe and non-severe cases. Details of the individual cases and their degree of severity are defined in the mini-narratives that follow the table.

Table 56 TEAEs in the Severe Cutaneous Adverse Reactions SMQ (0104)

MedDRA v12.1 Preferred Term, n (%) of patients	Isavuconazole (n = 257)	Voriconazole (n = 259)
Patients with ≥ 1 TEAE in the SCAR SMQ	**3 (1.2)**	**2 (0.8)**
Dermatitis exfoliative	1 (0.4)	1 (0.4)
Erythema multiforme	2 (0.8)	0
Toxic skin eruption	0	1 (0.4)

SCAR: severe cutaneous adverse reactions; SMQ: standard MedDRA query; TEAE(s): treatment-emergent adverse event(s).

No patient discontinued study drug due to these events. Brief summaries of these patients are provided below:

Isavuconazole Treatment Group:

- Patient > 50 years of age with mild erythema multiforme: This patient had a history of myelodysplasia and AML and was on chemotherapy. The patient received isavuconazole for 85 days. The patient had a serious event of vasculitis on day 24. On day 31, the patient developed mild erythema multiforme, which resolved on day 115 (30 days after the last dose of isavuconazole). Treatment was methylprednisolone. The investigator did not consider the erythema multiforme to be related to study drug (vasculitis possibly related) and gave another etiology for the vasculitis as treatment with cytarabine on days 19 to 23.
- Patient > 50 years of age with mild exfoliative dermatitis: This patient had a history of active toxiderma at baseline. The patient received isavuconazole for 84 days. Mild exfoliative dermatitis was reported on day 109, 25 days after the last dose of isavuconazole. The investigator did not consider the exfoliative dermatitis to be related to isavuconazole.
- Patient > 50 years of age with moderate erythema multiforme: This patient had a history of AML. The patient was discontinued from the study on day 21 due to non-compliance. Mild erythema was reported on day 9. On day 31 (10 days after the last dose of isavuconazole), moderate erythema multiforme was reported. The investigator did not consider this event to be related to isavuconazole.

Voriconazole Treatment Group:

- Patient > 50 years of age with mild toxic skin eruption: This patient had a history of AML and began receiving chemotherapy on day 37. Voriconazole was received for 68 days. Events of mild contact dermatitis were reported on days 44 to 49 and mild toxic skin eruption on days 50 to 53. On day 58, the patient was reported to have mild urticaria and severe *Acinetobacter* bacteremia. Serious septic shock and multi-organ failure were reported on day 67 and the patient died on day 69.
- Patient < 50 years of age with mild exfoliative dermatitis: This patient had a history of chronic myeloid leukemia. Voriconazole was received for 59 days. This patient had a mild rash on days 12 to15. Voriconazole treatment was interrupted and the rash resolved. On day 29 the patient had mild exfoliative dermatitis that resolved without treatment on day 43. The patient also had mild erythema on days 30 to 60, which resolved 1 day after the last dose of voriconazole. The voriconazole dose was not changed or interrupted for the exfoliative dermatitis or erythema and the patient completed the study.

No events of severe cutaneous acute reactions or anaphylaxis were reported in the phase 1 studies.

9.9.5 Effects on Cardiac Repolarization and Clinical Significance

9.9.5.1 Thorough QT Study

Studies were conducted to assess the association of isavuconazole administration with changes in QTc interval. Results from a clinical thorough QTc study, conducted to examine the effects of therapeutic (200 mg/day maintenance) and supratherapeutic doses (600 mg/day maintenance) on QT interval, demonstrated that isavuconazole caused dose-dependent QTc shortening of up to 13 msec at the proposed maintenance dose (200 mg qd). Inhibition of the L-type calcium channel, hCav1.2, in an in vitro ion channel study was considered to possibly contribute to the isavuconazole associated QT shortening.

A summary of the proportion of subjects with extreme QTcF values at any time on day 13 in the thorough QT study is presented in [Table 57]. Further details regarding the thorough QT study are provided in [Section 6.3.1.1].

Table 57 Number and Percentage of Subjects with Extreme QTcF Values at any Time Point on Day 13

Parameter	Placebo (n = 39)†	Isavuconazole 200 mg (n = 37)†	Isavuconazole 600 mg (n = 32)†	Moxifloxacin (n = 40)†
Extreme Values‡, n (%)				
< 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

Table continued on next page

Parameter	Placebo (n = 39)†	Isavuconazole 200 mg (n = 37)†	Isavuconazole 600 mg (n = 32)†	Moxifloxacin (n = 40)†
Change from Baseline§, n (%)				
> 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

Safety analysis set: All enrolled subjects who received at least 1 dose of study drug.

Placebo: placebo on days 1 through 13; isavuconazole 200 mg: isavuconazole 200 mg tid on days 1 and 2, isavuconazole 200 mg qd on days 3 through 13; isavuconazole 600 mg: isavuconazole 200 mg tid on days 1 and 2, isavuconazole 600 mg qd on days 3 through 13; moxifloxacin 400 mg: placebo on days 1 through 12, moxifloxacin 400 mg single dose on day 13.

QTcF: QT interval corrected for heart rate by Fridericia's formula.

† Number of subjects with a non-missing value.

‡ Using individual replicates at each time point.

§ Baseline is defined as the average of the replicates at each time point from day -1. Postbaseline is defined as the average of replicates from day 13. Percentages are calculated as the total number of subjects within the change from baseline category divided by the total number of subjects with a non-missing value, at each time point.

SQTS is a rare condition, described as a QTc interval < 330 msec.[62] While familial QT shortening is a well-described clinical syndrome that can result in severe life-threatening ventricular arrhythmias, the clinical significance of drug-induced QTc shortening is unclear.

9.9.5.2 Analysis of QTc in Study 0104: Categorical Analysis of Centrally Read ECGs

The proportion of patients with baseline QTcF values who met the threshold criteria for changes from baseline for QTcF values in Study 0104 are presented in [Table 58].

Table 58 QTcF: Number and Proportion of Patients Meeting Threshold Criteria for Increases and Decreases from Baseline (0104)

QTcF Category, n (%) of patients	Isavuconazole (n = 257)	Voriconazole (n = 259)
n	**227**	**224**
Increases		
> 30 msec	47 (20.7)	91 (40.6)
> 60 msec	10 (4.4)	21 (9.4)
Decreases		
> 30 msec	73 (32.2)	68 (30.4)
> 60 msec	17 (7.5)	10 (4.5)

The n equals the number of patients with both baseline and at least one postbaseline value within 10 days after the last dose of study drug.

Data based on extreme value for 12-lead central ECG. For increases, the highest change from baseline value was used. For decreases, the lowest change from baseline value was used.

Percentages are calculated as the total number of patients within the maximum value category divided by the total number of patients with a non-missing value.

ECG: electrocardiogram; QTcF: QT interval corrected for heart rate by Fridericia's formula.

The proportion of patients in Study 0104 with at least one postbaseline extreme QTcF value who met prolongation and shortening threshold criteria are presented in [Table 59].

Table 59 QTcF: Number and Proportion of Patients with Extreme Outliers (0104)

QTcF Category, n (%) of patients	Isavuconazole (n = 257)	Voriconazole (n = 259)
n	**250**	**252**
Prolongation Thresholds		
> 450 msec	25 (10.0)	46 (18.3)
> 480 msec	3 (1.2)	12 (4.8)
> 500 msec	1 (0.4)	3 (1.2)
Shortening Thresholds		
< 360 msec	51 (20.4)	41 (16.3)
< 330 msec	5 (2.0)	5 (2.0)
< 300 msec	1 (0.4)	0

The n equals the number of patients with at least one postbaseline value within 10 days after the last dose of study drug.

Data based on extreme value for 12-lead central ECG. For increases, the highest change from baseline value was used. For decreases, the lowest change from baseline value was used.

Percentages are calculated as the total number of patients within the maximum value category divided by the total number of patients with a non-missing value.

ECG: electrocardiogram; QTcF: QT interval using Fridericia's correction.

In Study 0104, 5 isavuconazole treated patients (2.0%) experienced postbaseline QTcF < 330 msec. In all of these patients, QTcF < 330 msec was a single, transient finding and none were associated with ventricular arrhythmias or adverse clinical sequelae. No action was taken with regard to isavuconazole treatment as a result of these ECG observations.

In the centrally read qualitative ECG analysis, the frequency of ECG abnormalities were similar between the two groups with no episodes of ventricular fibrillation or ventricular tachycardia observed in any patient on centrally read ECGs. Ventricular rhythm disorders were reported in 5.2% of isavuconazole treated patients and 4.4% of voriconazole treated patients. Of these, 4.8% and 4.4% of patients in the isavuconazole and voriconazole treatment groups, respectively, had isolated ventricular premature beats (monomorphic).

One patient in the isavuconazole group in Study 0104 had a TEAE of QT shortening. No patient in the voriconazole group had a TEAE of QT shortening. A description of this event follows:

- A patient < 50 years of age with a history significant for hyponatremia, hypochloremia, hypomagnesemia and hypokalemia received isavuconazole for 10 days. At baseline, this patient had 2 ECGs with uncorrected QT 310 and 296 msec; heart rate [HR] 123 and 130 bpm; and QTcF 394 and 383 msec. On day 2, ECG showed sinus tachycardia (HR 135 bpm), uncorrected QT 275 msec, QTcF 360 msec (not clinically significant [NCS]). On day 8, the patient experienced non-serious TEAEs of abnormal ECG T wave and ECG QT shortened (QT 301 msec; HR 119 bpm; QTcF 378 msec). On day 10, QT was 287 msec, HR 109 bpm, QTcF 351 msec. The investigator assessed the TEAEs as possibly related to isavuconazole. No treatment was administered. The QT shortened event was reported as resolved on day 9; the abnormal T wave was ongoing. The patient withdrew consent and was discontinued from the study on day 10. It appears that the

TEAE of QT shortened was reported based on the raw QT interval and not the HR corrected QTcF, which was not shortened.

No other TEAEs of QT shortening were reported in the phase 2 and phase 3 studies.

9.9.5.3 TEAEs associated with Potential Torsade de Pointes (SMQ)

To further evaluate the development of any arrhythmia-related event, TEAEs associated with potential torsade de pointes were identified in a wide search using a torsade de pointes SMQ. A numerically lower proportion of isavuconazole treated patients (5.8%) had an event in the torsade de pointes SMQ compared to voriconazole treated patients (7.3%) [Table 60]. More isavuconazole treated patients than voriconazole treated patients experienced loss of consciousness (3 patients vs 0 patients) and syncope (7 patients vs 2 patients), while fewer isavuconazole treated patients than voriconazole treated patients experienced QT prolonged (2 patients vs 8 patients) and cardiac arrest (1 patient vs 6 patients). It should be noted that adverse events related to a possible non-sustained ventricular arrhythmia would not be consistent with the type of arrhythmia observed with familial SQTS.

Table 60 TEAEs in the Torsade de Pointes SMQ (0104)

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

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

SMQ: standard MedDRA query; TEAE(s): treatment-emergent adverse event(s).

A total of 10 isavuconazole treated patients and 2 voriconazole treated patients had loss of consciousness or syncope events. In the 10 isavuconazole treated patients with events of syncope or loss of consciousness:

- 5 patients took concurrent medications (potential alternative etiologies)
- 2 patients had a concurrent clinical conditions (potential alternative etiologies)
- 2 patients experienced the event at least 2 weeks after the last dose of isavuconazole

In the 2 voriconazole treated patients with loss of consciousness or syncope events, the event occurred 25 days after the last dose of voriconazole in one patient and 7 days after the last dose of voriconazole in the second patient (this patient experienced 2 episodes of ventricular tachycardia).

9.9.5.4 Ventricular Arrhythmia-type TEAEs

To complement the broad search using the SMQ of torsade de pointes described above, TEAEs were examined for the high level term of ventricular arrhythmia or cardiac arrest as presented in [Table 61].

Table 61 Important Arrhythmia-type TEAEs (0104)

MedDRA v12.1 HLT Preferred Term, n (%) of patients	Isavuconazole (n = 257)	Voriconazole (n = 259)
Any ventricular arrhythmia or cardiac arrest event in HLT	**5 (1.9)**	**11 (4.2)**
Cardio-respiratory arrest	2 (0.8)	2 (0.8)
Ventricular extrasystoles	2 (0.8)	1 (0.4)
Cardiac arrest	1 (0.4)	6 (2.3)
Ventricular tachycardia	0	2 (0.8)

HLT: high level term; TEAE(s): treatment-emergent adverse event(s).

9.9.6 TEAEs in the Potential Ocular Toxicity Events of Interest

In Study 0104, potential ocular toxicity events of interest were evaluated by review of a group of select MedDRA preferred terms. There was a numerically lower proportion of isavuconazole treated patients (8.2%) compared to voriconazole treated patients (16.6%) who experienced at least one event in the potential ocular toxicity events of interest [Table 62]. The difference between treatment groups was influenced by visual impairment and reduced visual acuity-type events. The most common TEAEs by PT occurring in ≥ 1% of patients in either the respective isavuconazole or voriconazole treatment groups were all lower in isavuconazole treated patients and include visual impairment (1.6% vs 7.3%), blurred vision (1.6% vs 2.3%) and reduced visual acuity (0.4% vs 2.3%).

Table 62 TEAEs in Potential Ocular Toxicity Events of Interest by Preferred Term (0104)

MedDRA v 12.1 Preferred Term, n (%) of patients	Isavuconazole (n = 257)	Voriconazole (n = 259)
Patients with ≥ 1 TEAE in Potential Ocular Toxicity EOI	**21 (8.2)**	**43 (16.6)**
Vision blurred	4 (1.6)	6 (2.3)
Visual impairment	4 (1.6)	19 (7.3)
Eye oedema	2 (0.8)	0
Altered visual depth perception	1 (0.4)	0
Blindness unilateral	1 (0.4)	0
Cataract	1 (0.4)	3 (1.2)
Chorioretinal disorder	1 (0.4)	0
Colour blindness	1 (0.4)	2 (0.8)
Diplopia	1 (0.4)	2 (0.8)
Eye pain	1 (0.4)	4 (1.5)
Opthalmoplegia	1 (0.4)	0
Optic neuropathy	1 (0.4)	0
Periorbital oedema	1 (0.4)	0
Scotoma	1 (0.4)	1 (0.4)
Visual acuity reduced	1 (0.4)	6 (2.3)
Colour blindness acquired	0	1 (0.4)

Table continued on next page

MedDRA v 12.1 Preferred Term, n (%) of patients	Isavuconazole (n = 257)	Voriconazole (n = 259)
Presbyopia	0	1 (0.4)
Pupils unequal	0	1 (0.4)

EOI: event of interest; TEAE(s): treatment-emergent adverse event(s).

This trend was also observed in the Eye Disorders SOC (isavuconazole 15.2%; voriconazole 26.6%). Photophobia (PT), which was not included in the above tabular summary, was reported in 2 (0.8%) isavuconazole and 6 (2.3%) voriconazole treated patients.

9.9.7 TEAEs in the Psychiatric Events of Interest

In Study 0104, psychiatric events of interest were evaluated by review of a group of select MedDRA preferred terms. The overall proportion of patients with events in the psychiatric events of interest was similar between isavuconazole (28.4%) and voriconazole (30.5%) treated patients [Table 63].

While the proportion of isavuconazole and voriconazole treated patients reporting individual events was generally similar, differences were noted for hallucination-type events and agitation. Hallucinations (PT) were reported by 2.3% vs 4.2% of isavuconazole vs voriconazole treated patients, respectively. Visual hallucinations (PT) were reported by 1.2% versus 4.2% of isavuconazole versus voriconazole treated patients, respectively.
Four voriconazole treated patients discontinued study drug due to hallucination or visual hallucination compared to no isavuconazole treated patients and three voriconazole treated patients experienced serious hallucination or visual hallucination compared to no isavuconazole treated patients.

Table 63 TEAEs in Psychiatric Events of Interest by Preferred Term (0104)

MedDRA v12.1 Preferred Term, n (%) of patients	Isavuconazole n = 257	Voriconazole (n = 259)
Patients with ≥ 1 TEAE in the Psychiatric Events of Interest	**73 (28.4)**	**79 (30.5)**
Insomnia	23 (8.9)	24 (9.3)
Anxiety	20 (7.8)	17 (6.6)
Confusional state	16 (6.2)	20 (7.7)
Depression	9 (3.5)	10 (3.9)
Somnolence	7 (2.7)	8 (3.1)
Hallucination	6 (2.3)	11 (4.2)
Delirium	4 (1.6)	1 (0.4)
Hallucination visual	3 (1.2)	11 (4.2)
Aggression	2 (0.8)	1 (0.4)
Agitation	2 (0.8)	7 (2.7)
Mood altered	2 (0.8)	3 (1.2)
Disorientation	1 (0.4)	1 (0.4)
Dysarthria	1 (0.4)	1 (0.4)
Lethargy	1 (0.4)	0
Nervousness	1 (0.4)	1 (0.4)
Panic attack	1 (0.4)	0
Abnormal dreams	0	1 (0.4)
Altered state of consciousness	0	2 (0.8)

Table continued on next page

MedDRA v12.1 Preferred Term, n (%) of patients	Isavuconazole n = 257	Voriconazole (n = 259)
Cognitive disorder	0	1 (0.4)
Dysphoria	0	1 (0.4)
Paranoia	0	1 (0.4)
Stress	0	1 (0.4)

TEAE(s): treatment-emergent adverse event(s).

9.9.8 TEAEs in the Pancreatitis SMQ

There were no events of acute pancreatitis in Study 0104 or in the phase 1 or phase 2 studies.

One patient in Study 0103 with a medical history of pancreatitis experienced several episodes of pancreatitis and relapsing pancreatitis during the course of the study. The investigator considered the events of pancreatitis to be unrelated to isavuconazole.

9.9.9 TEAEs in the Convulsions SMQ

We received a request from the FDA to evaluate cases of convulsions in Study 0104. Convulsions and epilepsy-type events were evaluated by the convulsions SMQ. A summary of TEAEs in the convulsions SMQ is provided in [Table 64].

Table 64 TEAEs in the Convulsions SMQ (0104)

MedDRA v12.1 Preferred Term, n (%) of patients	Isavuconazole n = 257	Voriconazole (n = 259)
Patients with ≥ 1 TEAE in the Convulsions SMQ	**8 (3.1)**	**5 (1.9)**
Convulsion	4 (1.6)	3 (1.2)
Epilepsy	3 (1.2)	1 (0.4)
Febrile convulsion	1 (0.4)	0
Grand mal convulsion	0	1 (0.4)

TEAE(s): treatment-emergent adverse event(s); SMQ: standard MedDRA query.

A detailed examination of individual cases revealed underlying conditions or illnesses contributing to the convulsion events and all were considered by the investigators to have recovered/resolved. A summary for each patient by treatment group is provided below:

Isavuconazole

- A patient with pre-existing right thalamic glioblastoma and a medical history of seizures had an event of epilepsy on day 35 in the setting of hypoglycemia.
- A patient with a medical history of herpes encephalitis, seizures and status epilepticus had an event of epilepsy on day 56.
- A patient with CNS involvement by IFD developed convulsions on day 16.
- A patient with ongoing metabolic encephalopathy developed a convulsion on day 20 in the setting of respiratory decompensation and hypoxia.
- A patient developed febrile convulsions on day 68 in the setting of *Escherichia coli* sepsis.

- A patient with a medical history of intracranial hemorrhage developed convulsions on day 16.
- A patient with a medical history of intracranial clipped aneurysm had an event of epilepsy on day 20.
- A patient developed a convulsion on day 64 while receiving levofloxacin.

Voriconazole

- A patient developed a convulsion on day 7 in the setting of septic shock, hypoxia and hypotension.
- A patient had an event of epilepsy on day 7 in the setting of hypoglycemia.
- A patient with a medical history of convulsions developed convulsions on day 3 in the setting of hypocalcemia.
- A patient developed Grand mal convulsion on day 81 in the setting of meningitis.
- A patient with a medical history of subdural hematoma and seizures developed a convulsion on day 20 in the setting of respiratory depression and transient hypoxia.

As is clear from the above, the vast majority of cases had an identifiable alternative etiology for convulsions.

9.10 Use of Isavuconazole Without an In-line Filter

As discussed in [Section 6.2.1.2], visible translucent to white particulate can be observed when the reconstituted solution of isavuconazonium is diluted into saline or D5W. The particulate is isavuconazole and is expected to rapidly dissolve in human blood and plasma and, therefore, the observed particulate matter is not believed to carry any untoward risk.

However, the infusion solution is recommended to be administered through an in-line filter (0.2 to 1.2 μm pore size), placed between the infusion bag and patient access and is required to produce an infusion solution that is free of visible particulates and meets USP <788> requirements for subvisible particle counts.

In the course of the study, a few sites did not utilize a filter during the IV administration of isavuconazonium. An evaluation was conducted of 21 patients in Study 0104 and 6 patients in Study 0103 who were known to have been administered IV isavuconazole in the absence of an in-line filter. The analysis was conducted to specifically look for embolic events (SMQ for embolic and thrombotic events, arterial). In patients who received at least one IV infusion of isavuconazole without a filter, no single occurrence of an embolic or thrombotic-type event was observed.

9.11 Safety in Subgroups

A more detailed look at whether the observed differences between treatment groups in the overall safety analysis persisted in select subgroup analysis was undertaken. The subgroups examined were age, gender, HSCT status, active malignancy status and baseline neutropenic

status. The pattern of lower frequency of TEAEs for eye, hepatobiliary and skin disorders in isavuconazole versus voriconazole treated patients is evident and persistent across subgroup variables as shown in [Table 65, Table 66 and Table 67, respectively].

Table 65 Proportion of Patients with TEAEs in the Eye Disorders SOC by Subgroup Status at Baseline (0104)

Variable	Isavuconazole n/n (%)	Voriconazole n/n (%)	Variable	Isavuconazole n/n (%)	Voriconazole n/n (%)
Age ≤ 65 y	30/201 (14.9)	48/201 (23.9)	Age > 65 y	9/56 (16.1)	21/58 (36.2)
Male	20/145 (13.8)	43/163 (26.4)	Female	19/112 (17.0)	26/96 (27.1)
Hematologic malignancy	31/211 (14.7)	56/222 (25.2)	No hematologic malignancy	8/46 (17.4)	13/37 (35.1)
HSCT	9/54 (16.7)	16/51 (31.4)	No HSCT	30/203 (14.8)	53/208 (25.5)
Active malignancy	26/173 (15.0)	44/187 (23.5)	Without active malignancy	13/84 (15.5)	25/72 (34.7)
Neutropenic†	27/163 (16.6)	44/175 (25.1)	Non-neutropenic	12/94 (12.8)	25/84 (29.8)

ANC: absolute neutrophil count; HSCT: hematopoietic stem cell transplant; TEAEs: treatment-emergent adverse events.

† Neutropenia was defined as ANC < 0.5 x 10^9/L (< 500/mm^3) and was determined by the investigator.

Table 66 Proportion of Patients with TEAEs in the Hepatobiliary Disorders SOC by Subgroup (0104)

Variable	Isavuconazole n/n (%)	Voriconazole n/n (%)	Variable	Isavuconazole n/n (%)	Voriconazole n/n (%)
Age ≤ 65 y	18/201 (9.0)	33/201 (16.4)	Age > 65 y	5/56 (8.9)	9/58 (15.5)
Male	9/145 (6.2)	25/163 (15.3)	Female	14/112 (12.5)	17/96 (17.7)
Hematologic malignancy	20/211 (9.5)	38/222 (17.1)	No hematologic malignancy	3/46 (6.5)	4/37 (10.8)
HSCT	6/54 (11.1)	13/51 (25.5)	No HSCT	17/203 (8.4)	29/208 (13.9)
Active malignancy	19/173 (11.0)	28/187 (15.0)	Without active malignancy	4/84 (4.8)	14/72 (19.4)
Neutropenic†	15/163 (9.2)	29/175 (16.6)	Non-neutropenic	8/94 (8.5)	13/84 (15.5)

ANC: absolute neutrophil count; HSCT: hematopoietic stem cell transplant; TEAEs: treatment-emergent adverse events.

† Neutropenia was defined as ANC < 0.5 x 10^9/L (< 500/mm^3) and was determined by the investigator.

Table 67 Proportion of Patients with TEAEs in the Skin and Subcutaneous Tissue Disorders SOC by Subgroup (0104)

Variable	Isavuconazole n/n (%)	Voriconazole n/n (%)	Variable	Isavuconazole n/n (%)	Voriconazole n/n (%)
Age ≤ 65 y	62/201 (30.8)	89/201 (44.3)	Age > 65 y	24/56 (42.9)	21/58 (36.2)
Male	47/145 (32.4)	58/163 (35.6)	Female	39/112 (34.8)	52/96 (54.2)
Hematologic malignancy	73/211 (34.6)	104/222 (46.8)	No hematologic malignancy	13/46 (28.3)	6/37 (16.2)
HSCT	18/54 (33.3)	28/51 (54.9)	No HSCT	68/203 (33.5)	82/208 (39.4)
Active malignancy	66/173 (38.2)	82/187 (43.9)	Without active malignancy	20/84 (23.8)	28/72 (38.9)
Neutropenic†	61/163 (37.4)	82/175 (46.9)	Non-neutropenic	25/94 (26.6)	28/84 (33.3)

ANC: absolute neutrophil count; HSCT: hematopoietic stem cell transplant; TEAEs: treatment-emergent adverse events.

† Neutropenia was defined as ANC < 0.5 x 10^9/L (< 500/mm^3) and was determined by the investigator.

9.12 Overdose

During clinical studies, total daily isavuconazole doses higher than the recommended dose regimen were associated with an increased rate of adverse events. In a thorough QT study, there were proportionally more TEAEs at supratherapeutic doses (isavuconazole 600 mg/day maintenance dose) than in the therapeutic dose group (isavuconazole 200 mg/day maintenance dose) for the following: headache, dizziness, paresthesia, somnolence, disturbance in attention, dysgeusia, dry mouth, diarrhea, oral hypoesthesia, vomiting, hot flush, anxiety, restlessness, palpitations, tachycardia, photophobia and arthralgia [Section 6.3.1.1]. TEAEs leading to discontinuation of study drug occurred in 17.9% (7/39) of subjects in the isavuconazole 600 mg treatment group [Table 68].

Table 68 Overview of Treatment-Emergent Adverse Events in the Thorough QT Study

Number and Percentage of Subjects Who	Placebo (n = 40) n (%)	Isavuconazole 200 mg (n = 41) n (%)	Isavuconazole 600 mg (n = 39) n (%)
Number of subjects experiencing a TEAE	18 (45.0)	22 (53.7)	34 (87.2)
Number of subjects experiencing a drug-related TEAE†	15 (37.5)	17 (41.5)	34 (87.2)
Number of subjects experiencing a SAE	0	0	0
Number of subjects experiencing an TEAE leading to permanent discontinuation of study drug	0	0	7 (17.9)
Number of subjects experiencing a drug-related TEAE† leading to permanent discontinuation of study drug	0	0	6 (15.4)

All enrolled subjects who received at least 1 dose of study drug (Safety analysis set).

TEAE: treatment-emergent adverse event; SAE: serious adverse event

Placebo: placebo on days 1 through 13; isavuconazole 200 mg: isavuconazole 200 mg tid on days 1 and 2, isavuconazole 200 mg qd on days 3 through 13; isavuconazole 600 mg: isavuconazole 200 mg tid on days 1 and 2, isavuconazole 600 mg qd on days 3 through 13.

†Possible or probable, as assessed by the investigator or records where relationship was missing

In general, more subjects in the isavuconazole 600 mg treatment group experienced TEAEs compared to the placebo and isavuconazole 200 mg treatment groups. More subjects in the isavuconazole 600 mg treatment group experienced nervous system-type, gastrointestinal-type and vascular-type adverse events compared to subjects in the isavuconazole 200 mg treatment group and the placebo treatment group [Table 69].

The majority of TEAEs were mild in severity, with only 10 TEAEs considered moderate in severity; none were considered severe.

Table 69 Number and Percentage of Subjects Experiencing TEAEs in At Least 5% of Subjects in Select SOCs in the Thorough QT Study

MedDRA v. 12.1 System Organ Class Preferred Term	Placebo (n = 40) n (%)	Isavuconazole 200 mg (n = 41) n (%)	Isavuconazole 600 mg (n = 39) n (%)
Overall	**14 (35.0)**	**17 (41.5)**	**33 (84.6)**
Nervous System Disorders	**12 (30.0)**	**10 (24.4)**	**22 (56.4)**
Headache	7 (17.5)	6 (14.6)	14 (35.9)
Dizziness	4 (10.0)	3 (7.3)	7 (17.9)
Paraesthesia	2 (5.0)	3 (7.3)	6 (15.4)
Somnolence	1 (2.5)	1 (2.4)	3 (7.7)
Disturbance in attention	1 (2.5)	0	4 (10.3)
Dysgeusia	0	1 (2.4)	4 (10.3)
Gastrointestinal Disorders	**5 (12.5)**	**8 (19.5)**	**21 (53.8)**
Nausea	1 (2.5)	3 (7.3)	10 (25.6)
Abdominal pain	2 (5.0)	0	2 (5.1)
Dry mouth	0	1 (2.4)	5 (12.8)
Diarrhoea	0	1 (2.4)	3 (7.7)
Dyspepsia	2 (5.0)	2 (4.9)	0
Hypoaesthesia oral	0	0	4 (10.3)
Lip dry	0	1 (2.4)	2 (5.1)
Paraesthesia oral	0	1 (2.4)	2 (5.1)
Vomiting	0	0	3 (7.7)
Vascular Disorders	**4 (10.0)**	**2 (4.9)**	**20 (51.3)**
Hot flush	4 (10.0)	2 (4.9)	20 (51.3)
Psychiatric Disorders	**2 (5.0)**	**3 (7.3)**	**8 (20.5)**
Anxiety	1 (2.5)	1 (2.4)	5 (12.8)
Euphoric mood	1 (2.5)	1 (2.4)	2 (5.1)
Insomnia	0	1 (2.4)	2 (5.1)
Nightmare	1 (2.5)	0	0
Restlessness	0	0	2 (5.1)
Cardiac Disorders	**1 (2.5)**	**0**	**5 (12.8)**
Palpitations	1 (2.5)	0	4 (10.3)
Tachycardia	0	0	2 (5.1)

All enrolled subjects who received at least 1 dose of study drug (Safety analysis set).

Placebo: placebo on days 1 through 13; isavuconazole 200 mg: isavuconazole 200 mg tid on days 1 and 2, isavuconazole 200 mg qd on days 3 through 13; isavuconazole 600 mg: isavuconazole 200 mg tid on days 1 and 2, isavuconazole 600 mg qd on days 3 through 13.

The conditions for the supratherapeutic dose in the thorough QT study simulate potential overdose of isavuconazole. The findings appear to be predominantly CNS related. Hot flushes were observed more frequently with the 600 mg dose. This finding is reported for other azoles (e.g., itraconazole, ketoconazole and fluconazole). The pathophysiology that underlies the hot flushes is unknown.

9.13 Safety Conclusions

The safety profile of isavuconazole has been well characterized with a large global safety population. In total, more than 1600 subjects received isavuconazole in the clinical development program.

Results of Study 0104 showed that isavuconazole has a safety profile that is broadly similar to that of voriconazole except for the following findings:

- Fewer isavuconazole than voriconazole treated patients had study drug-related adverse events.
- Fewer isavuconazole than voriconazole treated patients had adverse events associated with voriconazole treatment such as skin, eye and hepatic adverse events.
- Isavuconazole shortens QTc while voriconazole lengthens QTc.

Safety findings from other studies in the clinical development program were concordant with the findings of Study 0104. In particular the safety profile in patients with IM was consistent with that observed in Study 0104 taking into account particular organ involvement in the two conditions and the more common rhino-cerebral involvement in patients with IM.

10 BENEFIT-RISK AND RISK MANAGEMENT

10.1 Summary of Benefit-Risk with Isavuconazole

- Isavuconazole has dose-proportional pharmacokinetics, moderate interpatient variability, high oral bioavailability and no food or gastric pH effect, enabling ease of switching from IV to oral routes of administration. There is no cyclodextrin in the IV formulation. Isavuconazole has a manageable drug-drug interaction profile.
- Isavuconazole demonstrated non-inferior efficacy relative to voriconazole for the primary efficacy endpoint of all-cause mortality through day 42 in the study of IA. Comparable results for all-cause mortality were observed across sensitivity analyses, populations, time points and subgroups, further supporting the effectiveness of isavuconazole.
- Isavuconazole demonstrated activity for the treatment of IM. Isavuconazole was shown to have a clear treatment effect for all-cause mortality relative to untreated literature controls and similar mortality rates relative to treatment of IM with amphotericin-based formulations from historical literature and a matched-case control analysis. These findings are also supported by animal models of invasive mucormycosis. Isavuconazole offers an oral option for the treatment of IM.
- The safety profile of isavuconazole has been well characterized and is broadly similar to the triazole class of antifungal agents as represented by voriconazole, except for a few differentiating features such as:
    - Fewer study drug-related events
    - Fewer patients with events related to the azole class of antifungal agents (i.e., skin, eye and hepatobiliary type of events)
    - QTc shortening
- Safety concerns with isavuconazole treatment can be managed through isavuconazole-specific and azole class labeling in the US package insert
- Results from the development program show that isavuconazole has a favorable benefit-risk profile for the treatment of life-threatening IA and IM.

10.2 Benefits of Isavuconazole

Alternative therapies are needed for the treatment of IA and IM. Current therapies for IA and IM are limited by pharmacokinetic characteristics and toxicity, as noted with voriconazole, and by toxicity and lack of efficacy in high-risk patients, as noted with amphotericin B. Mortality remains high in both diseases. Patients whose IA progresses or who are intolerant of voriconazole have few viable options and there are no approved primary treatments for IM other than amphotericin B.

The data from studies of both the oral and IV formulations have shown that isavuconazole had a more predictable pharmacokinetic/pharmacodynamic profile compared to voriconazole. The pharmacokinetics of isavuconazole are linear and dose-proportional following both oral and IV administration. Isavuconazole has a long half-life enabling once daily maintenance dosing. Further, with rapid absorption, oral bioavailability of 98%, bioequivalence of AUC and the absence of a food or gastric pH effect, isavuconazole can be administered via both routes of administration under fed or fasting conditions and in the presence of drugs that increase gastric pH.

Isavuconazole has moderate pharmacokinetic variability, limiting the risk of subtherapeutic or supratherapeutic exposure, while the variability of voriconazole pharmacokinetics is high.

In addition, IV isavuconazole can be used in patients with renal impairment. The IV formulation of the highly soluble prodrug, isavuconazonium, does not include cyclodextrin. Further, < 1% of unchanged isavuconazole is cleared by the kidney, allowing IV administration of isavuconazole in patients with renal impairment and ESRD.

No dose adjustments are recommended in elderly or renally impaired subjects.

A more manageable drug-drug interaction profile was observed with isavuconazole than with other mould-active azoles. Isavuconazole is a sensitive substrate of CYP3A (5-fold increase in isavuconazole AUC with concomitant ketoconazole) and a mild-to-moderate inhibitor of CYP3A4 (2-fold increase in midazolam AUC), while voriconazole is a strong inhibitor of CYP3A4 (10-fold increase in midazolam AUC).[25] Isavuconazole is a mild inducer of CYP2B6 (42% decrease in bupropion). Isavuconazole does not inhibit or induce CYP1A2, CYP2C9 or CYP2C19 and does not inhibit CYP2A6 or CYP2D6. Isavuconazole is a mild inhibitor of P-gp, OCT1/OCT2 and MATE1. Isavuconazole has no inhibitory effects on sensitive substrates of BCRP, OAT1/OAT2, OATP1B1/OATP1B3 or MATE2-K, but does have mild indirect inhibitory effects on substrates of UGT.

Isavuconazole demonstrated efficacy in the studies of patients with IA and IM. Isavuconazole demonstrated non-inferior efficacy compared to voriconazole for the primary endpoint of all-cause mortality through day 42 in IA. Comparable results for all-cause mortality were observed across sensitivity analyses, populations, time points and subgroups, further supporting the effectiveness of isavuconazole.

Isavuconazole demonstrated activity against several species of Mucorales, which are known to mimic *Aspergillus* infection and have been reported as a cause of breakthrough infection.[63]

Isavuconazole was shown to have a similar treatment effect to that of amphotericin B compared to untreated controls from the literature for all-cause mortality. In a matched-case control analysis from a contemporary registry, similar mortality rates were noted in patients treated with isavuconazole and matched control patients treated with amphotericin-based formulations. In addition, isavuconazole activity is supported by data from validated animal models of mucormycosis.

Isavuconazole demonstrated a favorable safety profile compared to voriconazole. Fewer isavuconazole than voriconazole treated patients experienced TEAEs considered by the investigator to be related to study drug. Fewer isavuconazole than voriconazole treated patients had adverse events associated with voriconazole treatment such as skin, eye and hepatic adverse events.

Further, isavuconazole is orally bioavailable and has no signal of nephrotoxic effects as associated with amphotericin B.

10.3 Risks with Isavuconazole

Review of the nonclinical and clinical studies of isavuconazole, as well as the product information from other antifungals in the azole class, revealed the following safety concerns (important identified risks, important potential risks and missing information) for isavuconazole. The safety concerns, proposed pharmacovigilance plan and proposed risk minimization measures are described in [Table 70]. Three important risks for isavuconazole (hepatotoxicity, infusion-related reactions and severe cutaneous adverse reactions) are also considered to be class effects for azole antifungal agents.

Table 70 Summary of Safety Concerns for Isavuconazole

Safety Concern	Proposed Pharmacovigilance Plan	Proposed Risk Minimization
Important Identified Risks		
Hepatotoxicity	Monitoring of spontaneous and clinical trial adverse event reports.	Proposed US PI includes: • *Warning and Precaution* regarding elevated liver transaminases, stating that monitoring of hepatic enzymes should be considered as clinically indicated. • "Elevated liver chemistry tests" is included as a common adverse reaction.† • Relevant laboratory effects described in *Adverse Reactions* Section.
Table continued on next page		

Safety Concern	Proposed Pharmacovigilance Plan	Proposed Risk Minimization
Infusion-related reactions	Use of a Targeted Data Questionnaire to standardize collection of reports of potential infusion related reactions to facilitate further characterization of this identified risk.	Proposed US PI includes: • Directions to infuse over a minimum of 1 hour, use of an inline filter and not give as a bolus injection. • Dosage and Administration regarding infusion related reactions: Isavuconazole for infusion must be administered through an infusion set with an in-line filter with a microporous membrane pore size of 0.2 µm to 1.2 µm. No significant loss in potency has been noted following infusion using an in-line filter. Isavuconazole should be infused over a minimum of 1 hour, at a concentration of approximately 0.8 mg isavuconazole per mL to reduce the risk for infusion related reactions. Do not administer as an IV bolus injection. • *Warning and Precaution* regarding infusion related reactions: During intravenous administration of isavuconazole, infusion related reactions including hypotension, dyspnea, chills, dizziness, paresthesia, hypoesthesia, nausea and headache were reported. Consider stopping the infusion should these reactions occur. • "Infusion related reaction" is included as a less common adverse reaction.†
Important Potential Risks		
Arrhythmia due to QT shortening	Use of a Targeted Data Questionnaire to standardize collection of reports of QT shortening and potentially-related arrhythmias to facilitate further characterization of this potential risk.	Proposed US PI includes: • *Contraindication* for patients with familial short QT syndrome. • *Warning and Precaution* that caution is warranted when prescribing isavuconazole to patients taking drugs known to decrease the QT interval. • "Electrocardiogram QT shortened" is included as a less common adverse reaction.†
Severe cutaneous adverse reactions	Monitoring of spontaneous and clinical trial adverse event report.	Proposed US PI includes: • *Contraindication* in persons with known hypersensitivity to isavuconazole, any component of isavuconazole or other azole antifungal agents. • *Warning and Precaution* specifying that isavuconazole should be discontinued if a patient develops a severe cutaneous adverse reaction. • "Rash" is included as a common adverse reaction; "drug eruption," "dermatitis exfoliative," and "blister" are included as uncommon adverse reactions.†
Embryo-fetal toxicity	Use of a Targeted Data Questionnaire to standardize collection of reports of potential exposure during pregnancy to facilitate further characterization of this potential risk. Evaluation of exposure during pregnancy in periodic reporting.	Proposed US PI includes: • *Use in Special Populations* includes designation as Pregnancy Category C, statement that isavuconazole should be used during pregnancy only if the potential benefit to the patient outweighs the risk to the fetus and statement that women who become pregnant during isavuconazole treatment are encouraged to contact their physician.

Table continued on next page

Safety Concern	Proposed Pharmacovigilance Plan	Proposed Risk Minimization
Effect on children exposed to isavuconazole via breast milk	Monitoring of spontaneous and clinical trial adverse event reports.	Proposed US PI includes: • *Use in Special Populations* includes statement that nursing mothers should not breast-feed children while taking isavuconazole.
Development of resistance	Monitoring of resistance in *Aspergillus* and other common fungal pathogens through routine quantitative susceptibility testing. Analysis of data from strains tested in sentinel reference laboratories will allow for an understanding of the rate and extent of resistant strains and whether additional measures are needed.	Proposed US PI includes: • *Microbiology* includes susceptibility interpretive criteria for *Aspergillus fumigatus*.
Off-label use	Monitoring of spontaneous adverse event reports for off-label use to determine whether additional measures for prevention are needed. Evaluation of off-label use in periodic reporting.	Proposed US PI includes: • *Indication and Usage* includes statement that isavuconazole is indicated for patients 18 years of age and older in treatment of invasive aspergillosis and treatment of invasive mucormycosis. • *Use in Specific Populations* includes statement that the safety and efficacy of isavuconazole in pediatric patients have not been established.
Missing Information		
Use in patients < 18 years-old	Monitoring of spontaneous adverse event reports for off-label use in patients < 18 years-old to determine whether additional measures for prevention are needed. Implementation of an approved Pediatric Investigational Plan.	Proposed US PI includes: • *Indication and Usage* includes statement that isavuconazole is indicated for patients 18 years of age and older in treatment of invasive aspergillosis and treatment of invasive mucormycosis. • *Use in Specific Populations* includes statement that the safety and efficacy of isavuconazole in pediatric patients have not been established.
Use in patients with severe hepatic impairment	Monitoring of spontaneous and clinical trial adverse event reports to characterize risks of use in these patients.	Proposed US PI includes: • *Use in Specific Populations* includes statement that isavuconazole has not been studied in patients with severe hepatic impairment. • *Use in Specific Populations* includes statement that no dose adjustment is necessary in patients with mild and moderate hepatic impairment.

TEAE: treatment-emergent adverse event; US PI: United States package insert.

† Common = TEAE rate ≥ 5%; Less common = TEAE rate < 5%.

10.4 Benefit-Risk Conclusions

IA and IM are rare fungal infections associated with high mortality and limited therapeutic options. Isavuconazole has been demonstrated to have a favorable benefit-risk profile in these infections. The results of Study 0104 demonstrated that isavuconazole is as effective as voriconazole, the current gold standard, for the treatment of IA. In addition, isavuconazole has favorable pharmacokinetic properties including linear dose-proportionality, moderate interindividual pharmacokinetic variability, high oral bioavailability, no food or gastric pH effect and no cyclodextrin in the IV formulation. Isavuconazole treatment of IM was also found to be associated with outcomes similar to historic data and matched controls treated with amphotericin-based formulations.

In Study 0104, isavuconazole was found to have a safety profile generally similar to that of voriconazole, but with a lower incidence of adverse events involving the skin, eye and hepatobiliary systems. The one unique potential risk with isavuconazole was exposure-related QT shortening, which did not have an identified clinical correlate.

The azoles are a well-characterized class of antifungal agents. Safety concerns with isavuconazole treatment can be managed through azole class and isavuconazole-specific labeling in the US package insert.

In summary, results from the development program demonstrate that isavuconazole has a favorable benefit-risk profile and provides a needed alternative treatment of life-threatening IA and IM fungal infections.

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12 SUPPORTING APPENDICES

Appendix 1: Tabular Listing of All Completed Clinical Studies

Table 71 Tabular Listing of All Completed 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 Ad ministration	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 [^{14}C]ISA including routes of excretion and extent of metabolism, identify metabolic profile of ISA in plasma, urine and/or feces, and evaluate safety/tolerability	Phase 1, open-label, single-dose, mass balance study	[cyano-^{14}C]Izs, equivalent to ISA 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 ISA 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, single-dose, mass balance study	[pyridinylmethyl-^{14}C]Izs, equivalent to BAL8728 75 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 periods	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 treatment, 42-day washout between periods	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: 160 mg loading dose plus 80 mg maintenance dose (qd) or 80 mg loading dose plus 40 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 Healthy: 16; Subjects with mild liver cirrhosis: 16; Subjects with moderate liver cirrhosis: 16	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

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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 (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 ISA and BAL8728 relative to subjects with normal renal function, establish if ISA and BAL8728 are dialyzable and safety/tolerability **Part 2**: Evaluate effect of mild, moderate and severe renal impairment on PK of ISA 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 mild renal impairment: 8 Subjects with moderate renal impairment: 8 Subjects with severe renal impairment: 5	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

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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 (Special Populations - Intrinsic Factors) continued								
PK	9766-CL-0038	**Part 1**: Evaluate PK and safety/tolerability of ISA and BAL8728 after single dose administration of IZs in healthy Chinese subjects **Part 2:** Evaluate PK and safety/tolerability of ISA and BAL8728 after 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); oral tablet Rifampin: 600 mg (qd); 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 INR) 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 capsule	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 for 1 day (day 15)	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-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 day 26	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	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 period (days 3 to 13) including co-administration of midazolam and IZs on day 12	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	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, and 200 mg qd on days 18-28; oral capsule	23	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 methadone and IZs on day 20	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	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 (PT and INR) and safety/tolerability of IZs and warfarin	Phase 1, open-label, sequential dosing study	Warfarin: 20 mg on days 1 and 20; oral tablet IZs, equivalent to ISA: 200 mg tid on days 16-17, and 200 mg qd on days 18-28; oral capsule	21	Healthy volunteers	Single dose on day 1, 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	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	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/DDI	9766-CL-0040/US	DDI and safety/tolerability of IZs and ketoconazole	Phase 1, randomized, open-label, two-arm, parallel group study	**Arm 1**: IZs, equivalent to 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	**Arm 1:** IZs: 12 **Arm 2:** IZs + ketoconazole: 12	Healthy volunteers	**Arm 1:** Single dose day 1 **Arm 2:** Treatment for 24 days (days 1-24) including co-administration of IZs and ketoconazole on day 4	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	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 of IZs and bupropion	Phase 1, randomized, open-label, sequential dosing study	Bupropion: 100 mg on days 1 and 15; oral tablet IZs, equivalent to ISA: 200 mg tid on days 8-9, and 200 mg qd on days 10-20; oral capsule	24	Healthy volunteers	Single dose on day 1, 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	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	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 day 8	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	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

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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 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 on days 4, 5 and 6, respectively; 100 mg on days 7-10; 300, 250 and 200 mg on days 12, 13 and 14, respectively; and 150 mg on days 15-18; oral capsule **IZs, equivalent to ISA, or Placebo:** 100 and 150 mg on days 11 and 19, respectively; iv (1 h) **Moxifloxacin:** 400 mg 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 regimens 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

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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 (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	14 to 21 days IZc or fluconazole was administered daily for at least 14 days (days 1 to EOT) in Groups A, C and D; and IZc was administered weekly on (day 1, 7, 14 and 21) in Group B	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 and 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, yeasts or dimorphic fungi	Up to 180 days (additional duration allowed in amendment 4)	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-004 (9766-CL-0104)	Efficacy and safety of IZs (iv and po) vs VRC (iv and po)	Phase 3, randomized, double-blind non-inferiority 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

AML: acute myelogenous/myeloid leukemia; BA: bioavailability; 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; INR: International Normalized Ratio; ISA: isavuconazole; ISA HCL: isavuconazole hydrochloride; IZc: isavuconazonium hydrochloride; IZs: isavuconazonium; LPV: lopinavir; MAD: multiple-ascending dose; MEGX: monoethylglycinexylidide; MMF: mycophenolate mofetil; NE: norethindrone; PD: pharmacodynamics; PK: pharmacokinetics; PT: prothrombin time; QTcF: QT interval corrected for heart rate by Fridericia's formula; QTcI: QT interval corrected for heart rate using an individual-specific correction formula; RTV: ritonavir; SAD: single-ascending dose; SAF: safety population.

Appendix 2: Inclusion/Exclusion Criteria (0104 and 0103)

Inclusion Criteria (0104)

A patient was eligible for the study if all of the following applied:

1. Either patients and/or legally authorized representative(s), if applicable, who had been fully informed and who gave voluntary written informed consent and HIPAA Authorization for US centers or equivalent privacy language as per national regulations or patients unable to write and/or read but who fully understood the oral information given by the investigator (or nominated representative) and who had given oral informed consent and HIPAA Authorization for US centers or equivalent privacy language as per national regulations, witnessed in writing by an independent person.
2. Ability and willingness to comply with the protocol.
3. Male and female patients aged ≥ 18 years, at time of signing the informed consent form.
4. Female patients were to be non-lactating and at no risk for pregnancy for one of the following reasons:
   - Postmenopausal for at least 1 year
   - Posthysterectomy and/or postbilateral ovariectomy
   - If of childbearing potential, patient must have had a negative urine or serum human chorionic gonadotropin (hCG) pregnancy test at the screening visit and be using a highly effective method of birth control throughout the course of the study. Reliable sexual abstinence throughout the course of the study was acceptable as a highly effective method of birth control for purposes of this study.
5. Patients with proven, probable or possible IFD caused by *Aspergillus* species or other filamentous fungi.

Exclusion Criteria (0104)

A patient was excluded from the study if any of the following applied:

1. Women who were pregnant or breastfeeding.
2. Known history of allergy, hypersensitivity to, or any serious reaction to the azole class of antifungals or to any component of the study medication.
3. Patients for whom voriconazole was contra-indicated, including cardiovascular findings.
4. Patients at high risk for QT/QTc prolongation such as:
   - Baseline prolongation of QTcF ≥ 500 msec;
   - Risk factors for Torsade de Pointes (e.g., uncompensated heart failure, abnormal potassium or magnesium levels that could not be corrected, any unstable cardiac condition during the last 30 days or a family history of long QT syndrome);
   - The use of concomitant medications that prolong the QT/QTc interval.
5. Patients with evidence of hepatic dysfunction at the time of randomization, defined as (may be rechecked using local laboratory):
   - Total bilirubin ≥ 3 times the upper limit of normal (ULN)
   - Alanine transaminase (ALT) or aspartate transaminase (AST) ≥ 5 times ULN or
   - Patients with known cirrhosis or chronic hepatic failure.

6. Concomitant use of sirolimus, efavirenz, ritonavir, astemizole, cisapride, rifampin/rifampicin, rifabutin, ergot alkaloids, long acting barbiturates, carbamazepine, pimozide, quinidine, neostigmine, terfenadine, ketoconazole, valproic acid or St. John's Wort in the 5 days prior to first administration of study medication.
7. Patients with any other invasive fungal infection other than *Aspergillus* species or other filamentous fungi and patients with zygomycosis/mucormycosis or *Scedosporium prolificans* infection not expected to respond to voriconazole treatment.
8. Patients with either chronic aspergillosis, aspergilloma or allergic bronchopulmonary aspergillosis (ABPA).
9. Microbiological (e.g., virological) findings or other potential conditions that were temporally related and suggested a different etiology of the clinical features in the absence of evidence of systemic aspergillosis infection.
10. Patients who had been administered more than 4 cumulative days of itraconazole, voriconazole or posaconazole, for any reason, within the 7 days prior to the first administration of study medication.
    - Patients with applicable host factors who developed new evidence of IFD while on prophylactic therapy, for at least 14 days, with either an amphotericin B product or an echinocandin, were eligible for enrollment.
    - Prior use of fluconazole of any duration and for any reason were eligible for enrollment.
11. Advanced HIV infection with CD4 count < 200 or acquired immunodeficiency syndrome-defining condition.
12. Any known or suspected condition of the patient that could jeopardize adherence to the protocol requirements or impede the accurate measurement of efficacy, for example, neutropenia not expected to resolve, patients with fungal endocarditis, fungal osteomyelitis, fungal meningitis, palliative therapy only for underlying condition.
13. Patients with a concomitant medical condition that, in the opinion of the investigator, was an unacceptable additional risk to the patient should he/she participate in the study.
14. Patients previously enrolled in a phase 3 study with isavuconazole.
15. Treatment with any investigational drug in any clinical trial within 30 days prior to the first administration of study medication except open label protocols.
16. Patients who were unlikely to survive 30 days or patients on mechanical ventilation.
17. Patients with a body weight (BW) ≤ 40 kg.
18. Patients with evidence of moderate to severe renal dysfunction with any of the following:
    - Calculated creatinine clearance < 50 mL/minute at screening
    - Currently on dialysis or likely to require dialysis during administration of study medication.

Inclusion Criteria (0103)

A patient was eligible for the study if all of the following applied:

1. Either patients and/or legally authorized representative(s), if applicable, who were fully informed and who gave voluntary written informed consent and HIPAA Authorization for US centers or equivalent privacy language as per national regulations

   Or, patients unable to write and/or read but who fully understood the oral information given by the investigator (or nominated representative) who gave oral informed consent, and HIPAA Authorization for US centers, or equivalent privacy language as per national regulations, witnessed in writing by an independent person.
2. Ability and willingness to comply with the Protocol.
3. Male and female patients aged ≥ 18 years, at the time of signing the informed consent form.
4. Female patients were non-lactating and at no risk for pregnancy for one of the following reasons:
   - Postmenopausal for at least 1 year.
   - Post-hysterectomy and/or post-bilateral ovariectomy.
   - If of childbearing potential, had a negative urine or serum human chorionic gonadotropin (hCG) pregnancy test at screening and was using a highly effective method of birth control throughout the course of the study. Reliable sexual abstinence throughout the course of the study was acceptable as a highly effective method of birth control for the purposes of this study.
5. Patients in one of the following subgroups:
   a) Patients with proven, probable or possible invasive aspergillosis who had renal impairment (including dialysis), defined as calculated CLCr < 50 mL/min at enrollment who required primary therapy.

      Note: Patients fulfilling the criteria for possible invasive aspergillosis who also had renal impairment were eligible for enrollment; however, diagnostic tests to confirm the invasive aspergillosis as probable or proven by culture, histology/cytology or GM antigen were completed within 7 days after the first administration of study drug.

   b) Patients meeting EORTC/MSG definition of proven or culture positive probable IFD caused by rare moulds, yeasts, or dimorphic fungi (i.e., fungal pathogens other than *Aspergillus fumigatus* or *Candida* species) whether RI or not (including dialysis) who required primary therapy for their IFD at the time of enrollment as defined below.

   c) Patients who had proven or probable zygomycosis, whether RI or not (including dialysis), who required primary therapy. Zygomycosis was documented by culture or histology/cytology.

d) Patients meeting EORTC/MSG definition of proven or culture positive probable IFD caused by rare moulds, yeasts, or dimorphic fungi (i.e., fungal pathogens other than *Aspergillus fumigatus* or *Candida* species), whether RI or not (including dialysis), who were refractory to current treatment defined as,

- Clear documentation of progression of disease.

  Note: radiological progression only in association with white blood cell (WBC) count recovery was not acceptable.

- Failure to improve clinically despite receiving at least 7 days of standard antifungal regimen.

Prior to enrolling patients who fell into this category, the Medical Monitor was contacted for approval.

e) Patients meeting EORTC/MSG definition of proven or culture positive probable IFD caused by rare moulds, yeasts, or dimorphic fungi (i.e., fungal pathogens other than *Aspergillus fumigatus* or *Candida* species), whether RI or not (including dialysis), who were intolerant to current treatment for example:

- Doubling of serum creatinine value to higher than the upper limit of normal (ULN) within 48 hours.
- Serum creatinine > 2.0 mg/mL and current treatment with polyene or IV voriconazole.
- Other significant drug-related adverse reaction(s) to the current antifungal agent, resulting in discontinuation of the treatment, e.g., persistence of visual disturbance, allergic reaction, phototoxicity or severe infusion reaction (hypertensive crisis, severe chills or shock).
- Documented inability to achieve adequate blood levels of posaconazole, voriconazole or itraconazole.

Exclusion Criteria (0103)

A patient was excluded from the study if any of the following applied:

1. Women who were pregnant or breastfeeding.
2. Known history of allergy, hypersensitivity, or any serious reaction to the azole class of antifungals or to any component of the study drug.
3. Patients at high risk for QT prolongation such as:
   - Baseline prolongation of QT interval corrected for heart rate - Fridericia's formula (QTcF) ≥ 500 msec.

- Risk factors for Torsade de Pointes (e.g., uncompensated heart failure, abnormal potassium or magnesium levels that could not be corrected, any unstable cardiac condition during the last 30 days, or a family history of long QT or congenital short QT syndrome).
- The use of concomitant drugs that prolong the QT interval.

4. Patients with evidence of hepatic dysfunction with any of the following abnormalities at the time of enrollment (may be rechecked using local laboratory):
   - Total bilirubin ≥ 3 x ULN.
   - ALT or AST ≥ 5 x ULN.
   - Patients with known cirrhosis or chronic hepatic failure.
5. 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.
6. Patients with either chronic invasive aspergillosis, aspergilloma or allergic bronchopulmonary invasive aspergillosis.
7. Microbiological findings (e.g., virological) or other potential conditions that were temporally related and suggested a different etiology for the clinical features in the absence of evidence of systemic fungal infection.
8. Advanced human immunodeficiency virus (HIV) infection with CD4 count < 50 or uncontrolled acquired immunodeficiency syndrome-defining condition.
9. Any known or suspected condition of the patient that may jeopardize adherence to the Protocol requirements or impede the accurate measurement of efficacy (e.g., neutropenia not expected to resolve or patients with fungal endocarditis).
10. Patients with a concomitant medical condition that, in the opinion of the investigator, were an unacceptable additional risk to the patient should he/she participate in the study.
11. Patients previously enrolled in a phase 3 study with isavuconazole.
12. Treatment with any investigational drug in any clinical trial 30 days prior to the first administration of study drug.
13. Patients who were unlikely to survive 30 days.
14. Patients with a BW < 40 kg.

15. Patients who need primary therapy for invasive aspergillosis who have been administered more than 4 cumulative days of itraconazole, voriconazole, or posaconazole, for any reason, within the 7 days prior to the first administration of study drug:

    - Patients with applicable host factors who develop new evidence of IFD while on prophylactic therapy, for at least 14 days, with either an amphotericin B product or an echinocandin, were eligible for enrollment.
    - Prior use of fluconazole of any duration and any reason were eligible for enrollment.

Appendix 3: Diagnostic and Response Criteria Definitions (0104)

Categorization of Fungal Disease at Baseline by the Data Review Committee (DRC) in IA Study 0104

Consenting patients were to have proven, probable or possible invasive fungal disease caused by *Aspergillus* species or other filamentous fungi to be enrolled into Study 0104. The DRC categorized each patient's IFD based on the protocol and DRC charter, which were consistent with and the EORTC/MSG 2008[27] diagnostic criteria and the use of the galactomannan assay to provide evidence of IFD. The diagnostic criteria used by the DRC for patients with LRTD and non-LRTD locations of infection are described in [Table 72].

Table 72 Diagnostic Criteria for DRC Assessment of IFD in Patients with LRTD and Non-LRTD Locations of Infection

LRTD / Non-LRTD	**Host Factor** (Neutropenia or HSCT or T-cell immune-suppressant or severe immune-deficiency)	**Clinical Feature** **LRTD:** (Presence of imaging sign on CT, HRCT or MRI or nonspecific infiltrates on CT, HRCT, or MRI) **Non-LRTD:** (Sino-nasal infection or central nervous system infection)	**Mycological** (Cytology, direct microscopy, culture from a non-sterile site, antigen detection)	**Mycological – Proven only** (Positive microscopy or culture, from a sterile site or with tissue damage)
Possible	X	X	--	--
Probable	X	X	X	--
Proven	--	--	--	X

--: not applicable; ANC: absolute neutrophil count; CT: computed tomography; DRC: Data Review Committee; HRCT: high-resolution computed tomography; HSCT: hematopoietic stem cell transplant; IFD: invasive fungal disease; LRTD: lower respiratory tract disease; MRI: magnetic resonance imaging.

Neutropenia was defined as ANC < 0.5 x 10^9/L (< 500/mm^3) and was determined by the investigator.

The DRC categorized the invasive fungal disease by type and location of infection. The categories for type of infection were *Aspergillus* Species Only, Non-*Aspergillus* Species Only, Mould Species NOS, *Aspergillus* Species Plus Other Mould Species and No Pathogen Identified. The categories for location of infection were LRTD Only, LRTD Plus Other Organ and Non-LRTD Only.

For patients with non-LRTD locations of IFD, the DRC assessed the locations as Disseminated, Brain, Eye, Liver, Sinus, Skin and Other.

DRC Evaluation Criteria for Clinical, Radiological, Mycological and Overall Responses

The DRC evaluated clinical, radiological and mycological response to determine the status of the patient's invasive fungal disease. The criteria for complete, partial, stable and progression of invasive fungal disease are provided in [Table 73].

Table 73 Criteria for DRC Assessment of Clinical, Radiological and Mycological Response

	Clinical	Radiological	Mycological
Complete	Resolution of all clinical symptoms and physical findings associated with IFD	≥ 90% response	Presumed or documented eradication
Partial	Resolution of at least some clinical symptoms and physical findings associated with IFD	At least 25% response at week 6; Al least 50% response at week 12	Presumed or documented eradication
Stable	Minor or no change in clinical symptoms and physical findings	Abnormalities associated with IFD, no evidence of progression	No evidence of progression
Progression	Worsening or new clinical symptoms and physical findings. New antifungal treatment required.	Worsening or new abnormalities associated with IFD	Evidence of progression

DRC: Data Review Committee; IFD: invasive fungal disease.

DRC Evaluation of Attributable Mortality

The DRC assessment was made by review of patient profiles and autopsy reports. The attribution of death to invasive fungal disease was categorized by the DRC as follows:

- Death directly due to consequences of progressive invasive fungal disease (clear evidence that mortality is due to progressive IFD)
- Death associated with evidence of residual or ongoing invasive fungal disease (evidence of residual or ongoing IFD at the time of death, but death may be due to IFD or progression of underlying disease)
- Death associated with no evidence of residual or ongoing invasive fungal disease (death is not due to IFD)
- Indeterminate cause
- No known death

Appendix 4: Prespecified PPS Criteria (0104)

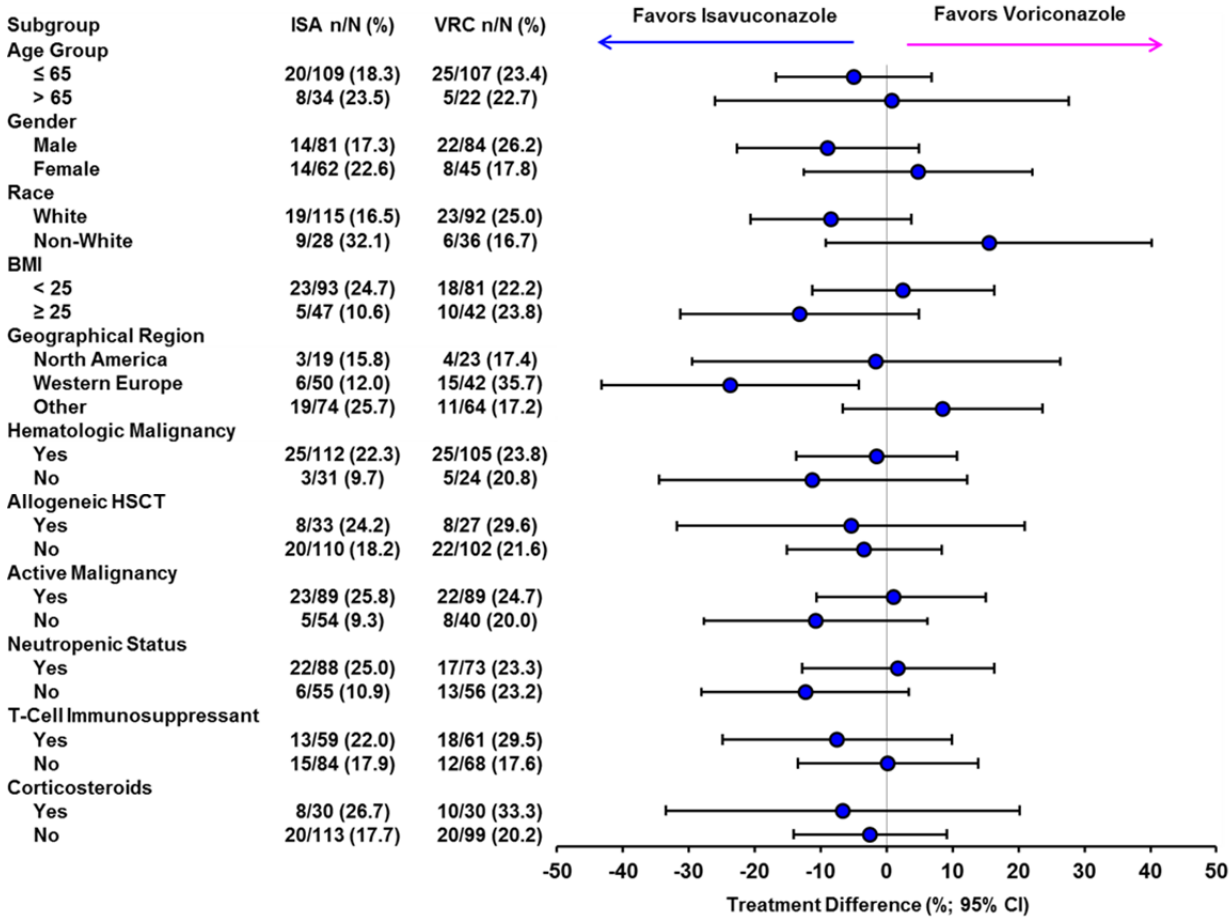
The PPS dataset was constructed per the following prespecified criteria according to the SAP for Study 0104:

- Met Exclusionary #5 (evidence of hepatic dysfunction only)
- Met Exclusionary #6 (use of prohibited medication within 5 days prior to first administration of study drug)
- Met Exclusionary #8 (had chronic aspergillosis, aspergilloma or allergic bronchopulmonary aspergillosis [ABPA])
- Met Exclusionary #10 (received > 4 cumulative days of itraconazole, voriconazole or posaconazole within 7 days of first dose of study drug)
- Met Exclusionary #12 (has a condition that might jeopardize adherence to the protocol)
- Met Exclusionary #14 (was previously enrolled in another phase 3 study with isavuconazole)
- Met Exclusionary #15 (treatment with other investigational drug within prior 30 days)
- Met Exclusionary #16 (unlikely to survive 30 days or on mechanical ventilation)
- Received less than 7 days of study drug
- Withdrew consent or lost-to-follow-up AND last evaluation day prior to day 42
- Took a different study drug during the treatment period
- Took prohibited concomitant medications for at least 3 consecutive days
- Took mould active systemic antifungal therapy for at least 3 consecutive days
- Unblinded patients as documented in the electronic case report form
- Patients that DRC assessed as having no IFD

Appendix 5: All-Cause Mortality through Day 42 in the mITT Population by Subgroup (0104)

Treatment differences and 95% CI for all-cause mortality through day 42 in Study 0104 are presented for the mITT Population by subgroup in [Figure 29].

Figure 29 Treatment Differences and 95% CIs for All-cause Mortality through Day 42 by Subgroup (mITT Population; 0104)



Modified Intent-to-treat (mITT): A subset of ITT patients with proven or probable invasive fungal disease as determined by the DRC.

Neutropenia was defined as ANC < 0.5 x 10^9/L (< 500/mm^3) and was determined by the investigator.

ANC: absolute neutrophil count; BMI: body mass index; DRC: Data Review Committee; HSCT: hematopoietic stem cell transplant; ISA: isavuconazole; VRC: voriconazole.

Appendix 6: Demographics and Baseline Characteristics from Before and After the Enrollment Hold (0104)

The demographics and baseline characteristics of the ITT population before and after the enrollment hold are summarized in [Table 74].

Table 74 Demographics and Baseline Characteristics (ITT Population; 0104)

	Isavuconazole & Voriconazole		Isavuconazole		Voriconazole	
Parameter Statistics	**Pre-Hold (n = 304)**	**Post-Hold (n = 212)**	**Pre-Hold (n = 154)**	**Post-Hold (n = 104)**	**Pre-Hold (n = 150)**	**Post-Hold (n = 108)**
Age (years)						
Mean	50.6	51.9	50.3	52.3	50.8	51.6
Median	52.0	54.0	52.0	56.0	52.5	54.0
Min - Max	17 - 87	18 - 81	17 - 82	20 - 81	18 - 87	18 - 80
Age Category, n (%)						
≤ 45 years	116 (38.2)	79 (37.3)	60 (30.9)	34 (32.7)	56 (37.3)	45 (41.7)
> 45 - ≤ 65 years	126 (41.4)	81 (38.2)	64 (41.6)	44 (42.3)	62 (41.3)	37 (34.3)
> 65 - ≤ 75 years	51 (16.8)	46 (21.7)	23 (14.9)	23 (22.1)	28 (18.7)	23 (21.3)
> 75 years	11 (3.6)	6 (2.8)	7 (4.5)	3 (2.9)	4 (2.7)	3 (2.8)
Sex, n (%)						
Male	178 (58.6)	130 (61.3)	86 (55.8)	59 (56.7)	92 (61.3)	71 (65.7)
Female	126 (41.4)	82 (38.7)	68 (44.2)	45 (43.3)	58 (38.7)	37 (34.3)
Race, n (%)						
White	255 (83.9)	147 (69.7)	134 (87.0)	77 (74.0)	121 (80.7)	70 (65.4)
Black or African American	2 (0.7)	0	1 (0.6)	0	1 (0.7)	0
Asian	46 (15.1)	63 (29.9)	19 (12.3)	26 (25.0)	27 (18.0)	37 (34.6)
Other	1 (0.3)	1 (0.5)	0	1 (1.0)	1 (0.7)	0
Missing	0	1	0	0	0	1
Ethnicity, n (%)						
Hispanic or Latino	23 (7.6)	8 (3.8)	17 (11.0)	5 (4.8)	6 (4.0)	3 (2.8)
Not Hispanic or Latino	281 (92.4)	203 (96.2)	137 (89.0)	99 (95.2)	144 (96.0)	104 (97.2)
Missing	0	1	0	0	0	1
BMI (kg/m^2)						
n	289	211	147	104	142	107
Mean	23.96	23.89	24.33	23.97	23.57	23.82
Median	23.56	23.15	23.55	23.16	23.68	23.15
Min - Max	13.9 - 50.0	14.7 - 38.7	13.9 - 50	14.7 - 38.7	14.5 – 38	15.6 - 36.1
Geographical Region†, n (%)						
North America	33 (10.9)	25 (11.8)	19 (12.3)	11 (10.6)	14 (9.3)	14 (13.0)
Western Europe plus Australia and New Zealand	141 (46.4)	71 (33.5)	70 (45.5)	35 (33.7)	71 (47.3)	36 (33.3)
Other Regions	130 (42.8)	116 (54.7)	65 (42.2)	58 (55.8)	65 (43.3)	58 (53.7)
Proven/Probable, n (%)	153 (50.3)	119 (56.1)	78 (50.6)	65 (62.5)	75 (50.0)	54 (50.0)
Hematologic malignancy, n (%)	253 (83.2)	180 (84.9)	124 (80.5)	87 (83.7)	129 (86.0)	93 (86.1)
Prior allogeneic HSCT, n (%)	60 (19.7)	45 (21.2)	31 (20.1)	23 (22.1)	29 (19.3)	22 (20.4)
Active malignancy at baseline, n (%)	201 (66.1)	159 (75.0)	97 (63.0)	76 (73.1)	104 (69.3)	83 (76.9)
Neutropenic‡, n (%)	196 (64.5)	142 (67.0)	94 (61.0)	69 (66.3)	102 (68.0)	73 (67.6)

Table continued on next page

Parameter Statistics	Isavuconazole & Voriconazole		Isavuconazole		Voriconazole	
	Pre-Hold (n = 304)	Post-Hold (n = 212)	Pre-Hold (n = 154)	Post-Hold (n = 104)	Pre-Hold (n = 150)	Post-Hold (n = 108)
Use of corticosteroids, n (%)	50 (16.4)	37 (17.5)	28 (18.2)	20 (19.2)	22 (14.7)	17 (15.7)
Use of T-Cell immunosuppressant, n (%)	133 (43.8)	87 (41.0)	66 (42.9)	45 (43.3)	67 (44.7)	42 (38.9)
eGFR-MDRD (mL/min/1.73 m^2), n (%)						
< 60	32 (10.8)	21 (10.3)	11 (7.3)	9 (9.0)	21 (14.4)	12 (11.5)
≥ 60	265 (89.2)	183 (89.7)	140 (92.7)	91 (91.0)	125 (85.6)	92 (88.5)
Missing	7	8	3	4	4	4

Intent-to-treat (ITT): All randomized patients who received at least one dose of study medication.

ANC: absolute neutrophil count; BMI: body mass index; eGFR-MDRD: estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula; HSCT: hematopoietic stem cell transplant.

†North America consists of Canada and the US. Western Europe consists of Belgium, France, Germany, Italy, The Netherlands, Spain and Switzerland. Other Regions consists of Argentina, Brazil, Chile, China, Egypt, Hungary, India, Israel, Malaysia, Mexico, Poland, Russia, South Korea, Thailand and Turkey.

‡ Neutropenia was defined as ANC < 0.5 x 10^9/L (< 500/mm^3) and was determined by the investigator.

The demographics and baseline characteristics of the mITT population before the enrollment hold and after the resumption of enrollment are summarized in [Table 75].

Table 75 Demographics and Baseline Characteristics (mITT Population; 0104)

Parameter Statistics	Isavuconazole & Voriconazole		Isavuconazole		Voriconazole	
	Pre-Hold (n = 153)	Post-Hold (n = 119)	Pre-Hold (n = 78)	Post-Hold (n = 65)	Pre-Hold (n = 75)	Post-Hold (n = 54)
Age (years)						
Mean	50.8	51.7	49.6	52.2	52.2	51.2
Median	52.0	54.0	49.5	56.0	54.0	54.0
Min - Max	18 - 81	18 - 81	18 - 81	20 - 81	18 - 77	18 - 75
Age Category, n (%)						
≤ 45 years	56 (36.6)	42 (35.3)	33 (42.3)	21 (32.3)	23 (30.7)	21 (38.9)
> 45 - ≤ 65 years	65 (42.5)	53 (44.5)	27 (34.6)	28 (43.1)	38 (50.7)	25 (46.3)
> 65 - ≤ 75 years	27 (17.6)	23 (19.3)	14 (17.9)	15 (23.1)	13 (17.3)	8 (14.8)
> 75 years	5 (3.3)	1 (0.8)	4 (5.1)	1 (1.5)	1 (1.3)	0
Sex, n (%)						
Male	94 (61.4)	71 (59.7)	45 (57.7)	36 (55.4)	49 (65.3)	35 (64.8)
Female	59 (38.6)	48 (40.3)	33 (42.3)	29 (44.6)	26 (34.7)	19 (35.2)
Race, n (%)						
White	129 (84.3)	78 (66.1)	69 (88.5)	46 (70.8)	60 (80.0)	32 (60.4)
Black or African American	1 (0.7)	0	0	0	1 (1.3)	0
Asian	23 (15.0)	39 (33.1)	9 (11.5)	18 (27.7)	14 (18.7)	21 (39.6)
Other	0	1 (0.8)	0	1 (1.5)	0	0
Missing	0	1	0	0	0	1
Ethnicity, n (%)						
Hispanic or Latino	11 (7.2)	4 (3.4)	8 (10.3)	2 (3.1)	3 (4.0)	2 (3.8)
Not Hispanic or Latino	142 (92.8)	114 (96.6)	70 (89.7)	63 (96.9)	72 (96.0)	51 (96.2)
Missing	0	1	0	0	0	1

Table continued on next page

Parameter Statistics	Isavuconazole & Voriconazole		Isavuconazole		Voriconazole	
	Pre-Hold (n = 153)	Post-Hold (n = 119)	Pre-Hold (n = 78)	Post-Hold (n = 65)	Pre-Hold (n = 75)	Post-Hold (n = 54)
BMI (kg/m^2)						
n	145	118	75	65	70	53
Mean	23.65	23.82	23.81	23.69	23.48	23.98
Median	23.26	22.69	23.03	22.86	23.85	22.52
Min - Max	13.9 - 41.2	15.7 - 38.7	13.9 – 41.2	16.0 - 38.7	14.6 – 38.0	15.7 - 36.1
Geographical Region†, n (%)						
North America	22 (14.4)	20 (16.8)	11 (14.1)	8 (12.3)	11 (14.7)	12 (22.2)
Western Europe plus Australia and New Zealand	58 (37.9)	34 (28.6)	30 (38.5)	20 (30.8)	28 (37.3)	14 (25.9)
Other Regions	73 (47.7)	65 (54.6)	37 (47.4)	37 (56.9)	36 (48.0)	28 (51.9)
Hematologic malignancy, n (%)	121 (79.1)	96 (80.7)	61 (78.2)	51 (78.5)	60 (80.0)	45 (83.3)
Prior allogeneic HSCT, n (%)	34 (22.2)	26 (21.8)	18 (23.1)	15 (23.1)	16 (21.3)	11 (20.4)
Active malignancy at Baseline, n (%)	95 (62.1)	83 (69.7)	46 (59.0)	43 (66.2)	49 (65.3)	40 (74.1)
Neutropenia‡, n (%)	85 (55.6)	76 (63.9)	46 (59.0)	42 (64.6)	39 (52.0)	34 (63.0)
Use of corticosteroids, n (%)	36 (23.5)	24 (20.2)	19 (24.4)	11 (16.9)	17 (22.7)	13 (24.1)
Use of T-Cell immunosuppressant, n (%)	72 (47.1)	48 (40.3)	32 (41.0)	27 (41.5)	40 (53.3)	21 (38.9)
eGFR-MDRD ($mL/min/1.73\ m^2$), n (%)						
< 60	18 (12.2)	12 (10.4)	6 (7.9)	7 (11.1)	12 (16.7)	5 (9.6)
≥ 60	130 (87.8)	103 (89.6)	70 (92.1)	56 (88.9)	60 (83.3)	47 (90.4)
Missing	5	4	2	2	3	2

Modified ITT (mITT): A subset of ITT patients with proven or probable invasive fungal disease as determined by the DRC.

ANC: absolute neutrophil count; BMI: body mass index; DRC: Data Review Committee; eGFR-MDRD: estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula; HSCT: hematopoietic stem cell transplant; ITT: intent-to-treat.

†North America consists of Canada and the US. Western Europe consists of Belgium, France, Germany, Italy, The Netherlands, Spain and Switzerland. Other Regions consists of Argentina, Brazil, Chile, China, Egypt, Hungary, India, Israel, Malaysia, Mexico, Poland, Russia, South Korea, Thailand and Turkey.

‡ Neutropenia was defined as ANC < 0.5 x 10^9/L (< $500/mm^3$) and was determined by the investigator.

Appendix 7: Mucorales Diagnostic and Response Criteria Definitions (0103)

Categorization of Fungal Disease at Baseline by the DRC for IM in Study 0103

Consenting patients were to have proven, probable or possible IFD caused by *Aspergillus* species and renal impairment or proven or probable IFD caused by rare moulds, yeasts or dimorphic fungi to be enrolled into the study. The DRC categorized the patient's IFD based on the protocol and DRC charter, which were consistent with the EORTC/MSG 2008 diagnostic criteria.[27] The diagnostic criteria used by the DRC for patients to be enrolled into the study with Mucorales infections are identified in [Table 76].

The DRC also categorized the IFD by type and location of infection. The categories of type of infection were *Aspergillus* Only, Mucorales Only, Other Filamentous Fungi Only (not *Aspergillus* or Mucorales), Mould Species NOS, Dimorphic Fungi Only, Non-*Candida* Yeast Only, Mixed Infection, and No Pathogen Identified.

The categories for location of IFD were LRTD Only, LRTD Plus Other Organ and Non-LRTD Only.

Table 76 Diagnostic Criteria for DRC Assessment of Mucormycosis

Mucor Category	Definition	
Proven Mucor	A positive diagnostic test obtained within the 7 days after the first administration of study medication	Histopathologic, cytopathologic or wet mount examination of a needle aspiration or biopsy specimen showing hyphal forms with evidence of associated tissue damage (either microscopically or as an infiltrate or lesion by imaging)
		Recovery of a mould by culture from a sample obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, e.g., transbronchial biopsy, open-lung biopsy or brain biopsy
Table continued on next page		

Mucor Category	Definition	
Probable Mucor	At least one host factor	Recently resolved or ongoing neutropenia temporally related to the onset of fungal disease
		Receipt of an allogeneic hematopoietic stem cell transplant
		Treatment with other recognized T-cell immunosuppressants during the past 90 days
		Inherited immunodeficiency
		Prolonged use of steroids at a mean minimum dose 0.3 mg/kg/day of prednisone equivalent for > 3 weeks*
	Plus at least one clinical feature	LRTD: Presence of at least one imaging sign on CT scan (or HRCT) or MRI: - Well defined nodule(s) with or without a halo sign - Wedge-shaped infiltrate - Air crescent sign - Cavity or Presence of new "nonspecific" imaging findings on CT scan (or HRCT) or MRI**
		Sino-nasal: Imaging (CT or MRI) showing sinusitis PLUS at least one of the following: - Acute localized pain (including pain radiating to eye) - Nasal ulcer, black eschar - Extension from the paranasal sinus bony barriers, including into the orbit
		CNS infection: At least one of the following: - Focal lesions on CT or MRI - Meningeal enhancement on CT or MRI
	Plus at least one mycological criterion (cytology, direct microscopy, culture from non-sterile sites)	Sputum, BAL, bronchial brush samples or sinus cavity specimen demonstrating the presence of fungal elements either by recovery by culture of a mould or detection by cytology or direct microscopy of hyphal forms
		Skin ulcers, draining soft tissue lesions or fissures for which both microscopy and (fungal) culture are required

BAL: bronchoalveolar lavage; CNS: central nervous system; CT: computed tomography; DRC: Data Review Committee; EORTC: European Organization for the Research and Treatment of Cancer; HRCT: high-resolution computed tomography; HSCT: hematopoietic stem cell transplant; IFD: invasive fungal disease; LRTD lower respiratory tract disease; MRI: magnetic resonance imaging.

*The protocol was amended during study conduct to disallow steroid use as an eligible host factor. The DRC will use the EORTC 2008 consensus criteria in the categorization of IFD, which include prolonged steroid use as an eligible host factor.

**Only HSCT or neutropenic patients who have nonspecific infiltrates, confirmed by CT scan (or HRCT) or MRI, and have mycological evidence of disease, will be classified as probable.

DRC Evaluation Criteria for Clinical, Radiological, Mycological and Overall Responses

The DRC evaluated clinical, radiological and mycological response to determine the status of the patient's IFD. The criteria for complete, partial, stable and progression of IFD are provided in [Table 77].

Table 77 Criteria for DRC Assessment of Clinical, Radiological and Mycological Response

	Clinical	Radiological	Mycological
Complete	Resolution of all clinical symptoms and physical findings associated with IFD	≥ 90% response	Presumed or documented eradication
Partial	Resolution of at least some clinical symptoms and physical findings associated with IFD	At least 25% response at week 6; Al least 50% response at week 12	Presumed or documented eradication
Stable	Minor or no change in clinical symptoms and physical findings	Abnormalities associated with IFD, no evidence of progression	No evidence of progression
Progression	Worsening or new clinical symptoms and physical findings. New antifungal treatment required.	Worsening or new abnormalities associated with IFD	Evidence of progression

DRC: Data Review Committee; IFD: invasive fungal disease.

Appendix 8: Mortality and Overall Response in Patients with Other Pathogens (0103)

A summary of all-cause mortality through day 42 and day 84 for all other mITT analysis populations is shown in [Table 78].

Table 78 All-cause Crude Mortality through Day 42 and Day 84 (All Other mITT Populations; 0103)

Time Point Outcome	Other Filamentous Fungi (n = 17)	Mould Species NOS (n = 7)	Dimorphic Fungi (n = 29)	Non-*Candida* Yeast (n = 11)	Mixed Infection (n = 15)
Through Day 42					
All-cause Mortality†	2 (11.8%)	0	2 (6.9%)	1 (9.1%)	3 (20.0%)
Deaths	2 (11.8%)	0	2 (6.9%)	1 (9.1%)	2 (13.3%)
Unknown Survival Status	0	0	0	0	1 (6.7%)
Through Day 84					
All-cause Mortality†	3 (17.6%)	1 (14.3%)	2 (6.9%)	1 (9.1%)	5 (33.3%)
Deaths	3 (17.6%)	1 (14.3%)	2 (6.9%)	1 (9.1%)	4 (26.7%)
Unknown Survival Status	0	0	0	0	1 (6.7%)

mITT: modified intent-to-treat; NOS: not otherwise specified.

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

Eight of these patients had a mixed infection that included a Mucorales infection (*Scedosporium prolificans* and *Rhizopus* NOS, *Aspergillus terreus* and *Rhizopus oryzae, Aspergillus flavus* and *Lichtheimia [Absidia] corymbifera, Aspergillus niger* and *Mucormycetes* NOS, *Aspergillus* NOS and *Mucormycetes* NOS, *Mucor circinelloides* and *Fusarium solani, Aspergillus niger* and *Rhizopus oryzae,* and *Aspergillus niger* and *Rhizopus oryzae*). Overall all-cause mortality through day 42 in mITT-Mixed Infection including Mucorales infection patients occurred in 2 patients (25.0%). Overall all-cause mortality through day 84 in patients in the mITT-Mixed Infection population with one infection being a Mucorales infection occurred in 3 patients (37.5%).

A summary of DRC-assessed overall response at EOT for all other mITT analysis populations is shown in [Table 79].

Table 79 DRC-assessed Overall Response at EOT (All Other mITT Populations; 0103)

Outcome Response, n (%)	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)

Patients who were still actively participating in the study at the interim cut of the database are not included in this analysis at the EOT time point.

DRC: Data Review Committee; EOT: end of treatment; mITT: modified intent-to-treat; NOS: not otherwise specified.

Appendix 9 Literature Review References (IM)

In order to interpret isavuconazole efficacy data in the treatment of IM in Study 0103, relevant publications reporting mortality rates with amphotericin-based formulations in patients with IM were reviewed. Thirty-nine publications reporting mortality or clinical outcomes data were identified. The selected publications were reviewed to determine whether they included detailed information on the patients enrolled, including their prognostic factors, mortality and antifungal therapies. Publications not reporting sufficient details on antifungal treatments, including patients treated with combination therapies, or not presenting sufficient details on prognostic factors for outcome (e.g., underlying conditions or site of infection) were excluded from the review.

Eight publications that presented all-cause mortality met the review criteria outlined above. Each publication was reviewed for composition of the study populations with respect to underlying conditions and treatment, thus dividing the publications into two groups:

- Five publications reported mortality in patients with mixed underlying conditions, such as hematological malignancies, solid organ transplant, diabetes, etc. who were treated with amphotericin-based formulations (Herbrecht et al, 2001; Chakrabarti et al, 2009; Shoham et al, 2010; Skiada et al, 2011; Lanternier et al, 2012b).
- Three publications reported mortality in high risk patients with hematological malignancies who were treated with amphotericin-based formulations (Gleissner et al, 2004; Pagano et al, 2004; Kara et al, 2009).

The publications were reviewed for factors that are known to influence prognosis and outcomes in patients with IM. The key factors that may have an adverse effect on outcomes are the presence of hematological malignancy, disseminated infection or CNS involvement and the factors known to be associated with better outcomes are surgery/debridement at the site of fungal infection or diabetes mellitus as the primary underlying condition. The frequencies of these factors, as well as mortality rates reported in the eight publications, are presented in [Table 80 and Table 81]. The Study 0103 data sets could be compared with patients with mixed underlying conditions derived from the literature and the subpopulation of mITT-Mucorales patients with hematological malignancy could be compared with literature reports presenting outcomes for this high risk population.

Despite the inherent limitations with historical reports, the selected publications offer important insights into the outcomes of patients with IM. For those reporting mortality rates in patients with IM (1991 through 2011) who had mixed underlying conditions (e.g., hematological malignancies, SOT, diabetes, etc. – similar to patients in Study 0103) and received amphotericin-based treatment, mortality rates ranged from 35% to 61% and were generally comparable with the mortality rates in Study 0103 (38% and 43% through days 42 and 84, respectively). The literature also reported mortality rates in a high risk patient population with hematological malignancy that ranged from 55% to 80%, compared to rates of 55% to 59% observed through day 42 and day 84 in patients with hematological malignancy in Study 0103.

Table 80 Publications Reporting Mortality in Patients with Mixed Underlying Conditions Treated with Amphotericin-based Formulations

Author[1]	n[2]	Line of treatment*	Proportion of study Population with: HM[3]	Surgery[4]	Dissem-inated[5]	CNS[6]	DM[7]	Mortality	Mortality endpoint definition
Herbrecht et al, 2001 (1991-1994)	21	R, I	48%	59%	29%	5%	29%	**ABCD[15]** 35% (9/20)[8]	Mortality during study (up to 118 days)
Chakrabarti et al, 2009 (2006-2007)	75	N/K	9%	75%	5%	N/K (RC 48%)[10]	33%	**All AmB forms** 45% (24/53)[9] **AmB[16] (plus surgery)** 30% (7/23) **AmB[16] (no surgery)** 100% (10/10) **l-AmB (plus surgery)** 44% (4/9) **l-AmB (no surgery)** 33% (1/3)	All-cause mortality – unspecified time period
Shoham et al, 2010 (1998-2005)	28	P	54%[11]	46%	14%	N/K (RC 17%)[10]	7%	**l-AmB** 61% (17/28)	All-cause mortality during study (duration not specified)
Skiada et al, 2011 (2005-2007)	230	P (87%)[13], R, I	44%	40%	15%	21% (incl. 13% RC)[10]	17%	**All AmB forms** 39% (32/82)[12] **l-AmB** 32% (20/62) **AmB[16]** 50% (6/12) **ABLC[17]** 50% (2/4)	All-cause mortality during course of IM[18]
Lanternier et al, 2012b (2007-2011)	34	P	53%	71%	18%	N/K (RC 26%)[10]	18%	**l-AmB** 42% (13/31)[14]	All-cause mortality at 12 weeks

***** Line of treatment: P = primary, R = refractory to other therapies and I = intolerant to other therapies

N/K = not known

Footnotes continued on next page

1 Dates in parentheses state the period of study.
2 Number of IM patients reported.
3 HM = Patients with hematological malignancies.
4 Surgery = Patients with any surgical procedure/debridement performed to treat IM.
5 Disseminated = Patients with disseminated infection.
6 CNS = Patients with central nervous system infection.
7 DM = Patients with diabetes mellitus.
8 One patient died before response could be assessed (death due to hepatic and renal failure considered not related to infection or therapy).
9 Only 53 out of 75 patients were evaluable. 14 patients were non-evaluable as they were diagnosed only at autopsy and 8 patients died before initiation or completion of adequate therapy or surgical debridement.
10 RC = Patients with rhino-cerebral infection.
11 Shoham 2010 reported patients with hematological disorders rather than hematological malignancies.
12 Data regarding outcome were missing in 30 cases, mortality was calculated for 200 cases. Only 82 out of 200 patients received amphotericin B formulations alone. 30 patients had missing data, 70 received combination therapy, 10 received posaconazole only, 31 received no therapy and 7 received either caspofungin, fluconazole, itraconazole, voriconazole or unknown therapy.
13 87% of patients received antifungal treatment as primary therapy.
14 31 out of 34 patients were evaluable.
15 ABCD = amphotericin B colloidal dispersion.
16 AmB= amphotericin B
17 ABLC = amphotericin B Lipid Complex Injection
18 IM = invasive mucormycosis

Table 81 Publications Reporting Mortality in Patient with Hematological Malignancies Treated with Amphotericin-based Formulations

Author[1]	n[2]	Line of treatment*	Proportion of study Population with:					Mortality	Mortality endpoint definition
			HM[3]	Surgery[4]	Disseminated[5]	CNS[6]	DM[7]		
Gleissner et al, 2004 (1986-2002)	120	N/K	94%	43%	32%	N/K (RC 8%)[8]	10%	**AmB** 61.3% (38/62) **l-AmB** 37.5% (6/16)	All-cause mortality – unspecified time period
Pagano et al, 2004 (1987-2005)	59	P, R, I	100%	12%	7%	19%	17%	**AmB/l-AmB** 80% (47/59)	All-cause mortality within 3 months of diagnosis
Kara et al, 2009 (2001-2005)	20	P, R, I	100%	100%	N/K	N/K	N/K	**AmB/l-AmB** 55% (11/20)	All-cause mortality during course of mucormycosis

* Line of treatment: P = primary, R = refractory to other therapies and I = intolerant to other therapies.

N/K = not known

1 Dates in parentheses state the period of study.

2 Number of IM patients reported.

3 HM = Patients with hematological malignancies.

4 Surgery = Patients with any surgical procedure/debridement performed to treat IM.

5 Disseminated = Patients with disseminated infection.

6 CNS = Patients with central nervous system infection.

7 DM = Patients with diabetes mellitus.

8 RC = Patients with rhino-cerebral infection.