CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207500Orig1s000 / 207501Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 505 (b)(1)
Application Number(s)	207500 and 207501
Priority or Standard	Priority
Submit Date(s)	July 8, 2014
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Division / Office	Division of Anti-Infective Products / Office of Antimicrobial Products
Reviewer Name(s)	Edward Weinstein, MD, PhD Elizabeth O'Shaughnessy, MD
Review Completion Date	December 8, 2014
Established Name	Isavuconazonium sulfate (BAL8557)
(Proposed) Trade Name	Cresemba ®
Therapeutic Class	Azole-class antifungal
Applicant	Astellas Pharma Global Development, Inc.
Formulation(s)	1. Lyophilized powder for intravenous infusion 2. Hard capsules for oral administration
Dosing Regimen	200 mg every 8 hours for the first 48 hours via oral or intravenous administration, then 200 mg per day via oral or intravenous administration.
Indication(s)	Treatment of 1) Invasive aspergillosis and 2) Invasive mucormycosis
Intended Population(s)	Adults, 18 years of age and older.

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommendation is to approve isavuconazonium (CRESEMBA) for the treatment of invasive aspergillosis (IA), and for the treatment of invasive mucomycosis (IM). The data submitted from an adequate and well-controlled clinical trial in invasive aspergillosis indicate that isavuconazonium met the pre-specified non-inferiority margin for the primary endpoint of 42 day mortality with respect to voriconazole, the active control. A second, open-label trial of isavuconazonium for the treatment of invasive mucormycosis provided evidence for a survival benefit relative to no treatment at all. The submitted clinical safety data support the use of isavuconazonium at the recommended dosage for the proposed indications. My recommendation is to approve isavuconazonium for both indications, with modifications to the applicant's proposed label.

1.2 Risk Benefit Assessment

The Applicant conducted two phase 3 trials to demonstrate the safety and efficacy of isavuconazonium for the proposed indications. The primary clinical trial to support isavuconazonium efficacy for the treatment of IA was Study 9766-CL-0104, a randomized, double-blind, non-inferiority, multi-center trial design which compared isavuconazonium to voriconazole.The primary efficacy endpoint was the rate of all-cause mortality through Day 42 in the Intent-to-Treat (ITT) population. Isavuconazonium was considered non-inferior to voriconazole if the upper bound of the 95% confidence interval of the Day 42 mortality rate was less than the justified, pre-specified10% non-inferiority margin. A key secondary efficacy endpoint was the Data Review Committee (DRC) assessment of overall response at end of treatment (EOT).

In Trial 9766-CL-0104, the ITT population of 516 patients contained 258 patients in each treatment group, defined as patients who received at least one dose of study drug. Eligible patients had proven, probable, or possible invasive fungal infections per the European Organisation for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) 2008 criteria. Patients with renal impairment (creatinine clearance less than 50 mL/minute) were excluded. Patients were stratified by history of allogeneic bone marrow transplant, uncontrolled malignancy at baseline, and by geographic region. The mean age of patients was 51years (range 17-87 years) and the majority were Caucasian (78%), male (60%), with fungal disease involving the lungs (95%). An independent, blinded DRC determined the modified ITT (mITT) population of 143 isavuconazonium-treated patients and 129 voriconazole-treated patients with proven or probable invasive fungal disease. Of these, a further 123 isavuconazonium-treated

patients and 108 voriconazole-treated patients had confirmed IA by culture, histology, or galactomannan assay and were included in the mycological ITT (myITT) population. At least one *Aspergillus* species was identified in 30% of the subjects; *A.fumigatus* and *A. flavus* were the most common pathogens identified. There were less than 7 patients with other *Aspergillus* species (*A. niger*, *A. sydowi*, *A. terreus,* and *A. westerdijkiae*).

Patients randomized to receive isavuconazonium were administered a loading dose of 200 mg intravenously every 8 hours for the first 48 hours. Beginning on Day 3, patients received intravenous or oral therapy at 200 mg once daily. Patients randomized to receive voriconazole treatment were administered a loading dose of 6 mg/kg intravenously every 12 hours for the first 24 hours followed by 4 mg/kg intravenously every 12 hours for the following 24 hours. Therapy could then be switched to an oral formulation at a dose of 200 mg every 12 hours. In this trial, the protocol-defined maximum treatment duration was 84 days. Mean treatment duration was 47 days for both treatment groups, of which 8 to 9 days was by an intravenous route of administration.

All-cause-mortality through Day 42 in the overall population (ITT) was 18.6% in the isavuconazonium treatment group and 20.2% in the voriconazole treatment group (treatment difference -1.0% with 95% confidence interval (-7.8%, 5.7%). Non-inferiority of isavuconazonium compared to voriconazole was demonstrated with respect to all-cause mortality through Day 42 since the upper bound of the 95% confidence interval was less than 10%. The results were robust across the mITT and myITT populations. Overall success at End of Treatment (EOT) as judged by the DRC in patients with proven or probable invasive aspergillosis was based on clinical, mycological, and radiological factors (DRC treatment outcome criteria are listed in Appendix 9.5). In this subgroup of patients with proven or probable IA, overall success at EOT was seen in 35% of isavuconazonium-treated patients compared to 38.9% of voriconazole-treated patients.

Additional supportive data for the IA indication was from Trial 9766-CL-0103, an open label, multi-center, non-comparative trial that included patients with renal impairment. Twenty four (24) patients were assessed by the DRC as having IA and 20 patients in this group were renally impaired. The all-cause mortality rate through Day 42 was 12.5% for all patients and 15% for those that were renally impaired. The DRC-assessed overall response at EOT was 34.8% for patients with IA and 30.0% for those who were renally impaired. The results are consistent with those of Trial 9766-CL-0104.

Trial 9766-CL-0103 also contained the primary data for the proposed indication of IM. Due to the single arm, open-label design, historical natural history data were used as a basis of comparison. The Sponsor also presented a comparative analysis of matched, amphotericin B-treated controls from the Fungiscope Registry[1] as supportive evidence.

[1] http://www.fungiscope net

The population considered for the proposed indication consisted of 37 mITT-Mucorales patients from the ITT population (n=146) whom the DRC classified as having Mucorales per the the EORTC/MSG 2008 guidelines. The Mucorales mITT population was further stratified by treatment status. The primary treatment group (n=21) was defined as those patients who received isavuconazonium as initial antifungal therapy, the remaining two groups received salvage therapy. The refractory treatment group (n=11) was identified by the progression of disease while on therapy at enrollment, and the intolerant treatment group (n=5) either failed to achieve therapeutic drug levels or experienced significant drug related adverse reaction(s). The patients were Caucasian (68%), male (81%), had a mean age of 49 years (22-79 years), and had pulmonary (59%), or sinus (43%) involvement. *Rhizopus oryzae* and Mucormycetes were the most common pathogens identified. There were less than 6 patients with other Mucorales that include *Lichtheimia corymbifera, Mucor amphibiorum, Mucor circinelloides, Rhizomucor pusillus, Rhizopus azygosporus,* and *Rhizopus microsporus.*

Patients were treated with isavuconazonium intravenously or via oral administration at a loading dose of 200 mg every eight hours for the first 48 hours; and a maintenance dose of 200 mg daily thereafter. Median treatment duration was 102 days for patients classified as primary, 33 days for refractory, and 85 days for intolerant.

Overall mortality was 37.8% [22.5, 55.2] at Day 42 and 43.2% [27.1, 60.5] at Day 84. The primary treatment group mortality was similar to the overall rate, with 33% 42-day mortality and 43% 84-day mortality rates. The closest publication[2] approximating a natural history study in a modern population was a single study of 70 consecutive patients with hematologic malignancy and mucormycosis using diagnostic criteria similar to Trial 9766-CL-0103. A delay of 6 days in initiating amphotericin B-based therapy resulted in an 84 Day mortality rate of 82.9% [68.9, 96.8]. In the isavuconazole-treated population, 9 of 22 or 40.9% [20.4, 61.5] subjects with IM and hematologic malignancy died by Day 84. The upper limit of the 95% confidence interval for mortality in the isavuconazonium treatment group is below the lower limit of the 95% confidence interval for no treatment at all. The existing scientific literature and Fungiscope database offered a combined estimate of 96.2% [94.0, 98.4] mortality without treatment, but this estimate is confounded because a significant number of diagnoses of IA were made at autopsy.

The DRC assessed overall response rate 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. Approximately one third, 28.6% of patients, was assessed as stable. For primary therapy patients, 31.6% of patients were assessed to be a success,

[2] Chamilos G., Lewis, R.E., Kontoyiannis, D.P. "Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis." Clin Infect Dis. 2008;47(4):503-9.

with 15.8% of patients assessed to be a complete and 15.8% a partial success. Successful salvage therapy occured in 4 of 11 (36.4%) of patients with refractory IM.

The safety population of 1692 isavuconazonium exposed individuals included 1145 healthy subjects dosed in 40 phase 1 studies,144 subjects in the phase 2 trial population, and 403 subjects in the phase 3 trials. The phase 1 population included subjects with mild to moderate hepatic impairment as well as subjects with end-stage renal disease.

Isavuconazonium demonstrated an overall favorable safety profile with similar rates of mortality and non-fatal adverse events as the comparator, voriconazole. The proportion of all known patient deaths was similar between treatment groups (ISA: 31.5%, 81/257; VRC: 33.6%, 87/259). More than half of the subjects experienced a treatment emergent serious adverse event (SAE) in either treatment group. The overall incidence of treatment emergent SAEs was lower in isavuconazonium-treated subjects, 134/257 (52.1%), than in voriconazole-treated subjects 149/259 (57.5%). There were fewer adverse events leading to discontinuation of therapy in the isavuconazonium treatment arm 37/257 (14.4%) than in the voriconazole treatment arm 59/259 (22.8%).

The incidence of treatment emergent adverse events (TEAE) in isavuconazonium-treated subjects was significantly lower than voriconazole-treated subjects for the hepatobiliary, eye, and skin system organ classes (SOC).

Hepatotoxicity is a safety concern for the azole antifungal class, and in the controlled phase 3 trial, there were a total of 24 hepatobiliary adverse events in the isavuconazonium treatment group. Of these events, 12 (50%) resolved, 2 (8%) were improving, 9 (38%) were not resolved, and 1 (4%) event proved fatal (acute hepatitis). This is in comparison to voriconazole, in which there were 44 events: 21 (48%) resolved, 21(48%) were not resolved, and 2 (4%) were recovering. Isavuconazonium therapy was discontinued in the one patient (Subject 9709-12) with fatal hepatitis. Hy's Law criteria were met in 3 isavuconazonium-treated patients and 7 voriconazole-treated patients. One of the isavuconazonium treated patients who satisfied Hy's Law had a severe adverse reaction of acute hepatic failure with a fatal outcome.

A safety concern unique to the submission is the formation of drug particulate in the IV formulation. Following reconstitution, water soluble isavuconazonium sulfate may spontaneously hydrolyze in aqueous solution and a trace amount may precipitate as insoluble isavuconazonium. As a result, the study drug was administered through an inline filter to remove particulate. There were 27 reported instances of isavuconazonium administration without an-line filter and there were no embolic, thromboembolic, or significant infusion site AEs observed within this patient subpopulation.

One unique safety finding different from other azole class antifungals is exposure-related shortening of the QT interval, the clinical significance of which is uncertain Two

Thorough QT studies were conducted in healthy volunteers, neither of which showed QT prolongation, and both showed QT shortening. In study 9766-CL-0017, isavuconazonium 200 mg TID followed by 200 mg QD was administered for 11 days, or 600 mg TID followed by 600 mg QD for 11 days. For the isavuconazonium 200mg and 600mg treatment groups, the mean change from placebo baseline-adjusted in QTcF decreased by 9 to 13 msec and by 19 to 25 msec, respectively, within 1 hour and 24 hours post dose. No QTcF < 330 msec was observed. No QTcF prolongation was observed in the isavuconazonium treatment groups. The frequency of QT shortening TEAEs among isavuconazonium-treated patients in Trial 9766-CL-0104 was 0.4% (1 patient) with a QTcF of 378 msec, compared to none in the voriconazole treatment group. The adverse effect resolved the following day without treatment, and the patient withdrew consent. No events of ventricular tachycardia or ventricular fibrillation were observed on any of the centrally read ECGs for either treatment group. Familial QT shortening is a well-described clinical syndrome that can result in severe life-threatening ventricular arrhythmias, but there is no consensus in the scientific literature regarding thresholds of concern for drug induced QT shortening[3]. Drug induced QT shortening due to isavuconazonium presents a risk in patients with familial short QT syndrome, but it is difficult to estimate risk for the general patient population.

The other safety findings are consistent with the known adverse effects characteristic of azole-class antifungal drugs, namely hypersensitivity reactions, and infusion related reactions.

In summary, the data submitted by the applicant demonstrate an acceptable safety profile for isavuconazonium and provide adequate evidence for approval of isavuconazonium for the treatment of invasive aspergillosis and invasive mucormycosis.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None. Adverse reactions associated with isavuconazonium can be adequately addressed in labeling.

1.4 Recommendations for Postmarket Requirements and Commitments

Dr. Bala, the Clinical Microbiology Reviewer, DAIP has proposed the following PMR:

Conduct surveillance studies for five years from the date of marketing CRESEMBA to determine if there is a shift in wild-type population and epidemiological cut-off values in organisms relevant to the indication in the package insert for invasive aspergillosis and

[3] Shah RR. Drug-induced QT interval shortening: potential harbinger of proarrhythmia and regulatory perspectives. *Br J Pharmacol*. Jan 2010; 159(1): 58–69.

mucormycosis.

MO Comment: I concur that surveillance studies would be useful to judge the efficacy of isavuconazonium over time, and perhaps to contribute to the determination of breakpoints.The feasibility of the study will be further discussed with the Applicant.

2 Introduction and Regulatory Background

This new drug application (NDA) is submitted by Astellas Pharma US Inc. in accordance with Section 505 (b)(1) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 314.50) to seek marketing clearance for isavuconazonium sulfate. NDA 207500 relates to the hard capsules for oral administration, and NDA 207501 to the lyophilized powder for intravenous administration.

2.1 Product Information

Isavuconazonium sulfate (BAL8557-002, also referred to as ASP9766) with the proposed trade name, CRESEMBA, is a new molecular entity in the azole class. Following intravenous administration, the isavuconazonium prodrug is hydrolyzed to the active moiety, isavuconazonium (BAL4815) and an inactive cleavage product (BAL8728). Orally administered isavuconazonium is converted to the active product, Isavuconazole, within the gut. Isavuconazonium acts by inhibiting sterol 14-alpha-demethylase, a microsomal P450 enzyme essential for ergosterol biosynthesis in fungi.

2.2 Tables of Currently Available Treatments for Proposed Indications

The following table (Table 1) shows the list of antifungal agents that are currently approved and available in the United States for the treatment of infections caused by invasive aspergillosis (IA) and invasive mucormycosis (IM). Some of these products are indicated for second line use, with the labels specifying use for “Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy”. Given the rarity of invasive mucormycosis, no randomized, well-controlled, comparative antifungal treatment studies have been conducted to support regulatory approval. Therefore, the table separately includes drugs used off-label for the proposed indication.

Table 1: Antifungal agents used for the treatment of Invasive Aspergillosis (IA) and/or Invasive Mucormycosis (IM)

Drugs approved for the proposed indication:

Generic/ Chemical Name	Brand Name(s)	Dosage form	Indication
Liposomal Amphotericin B (LAmB)	Ambisome, Abelcet, Amphotec	IV	IA

Amphotericin B deoxycholate	Generic Amphotericin B	IV	Both IA and IM
Voriconazole	Vfend	IV and Oral	IA
Itraconazole	Sporanox	Oral	IA*
Caspofungin	Cancidas	IV	IA*

Drugs used off-label for proposed indication:

Generic/ Chemical Name	Brand Name	Dosage form	Indication
Micafungin	Mycamine	IV	Both IA and IM
Anidulafungin	Eraxis	IV	Both IA and IM
Caspofungin	Cancidas	IV	IM
Posaconazole	Noxafil	IV and Oral	IM and IA[#]
Liposomal Amphotericin B (LAmB)	Ambisome, Abelcet, Amphotec	IV	IM

*Second line IA treatment
[#]Indicated for IA prophylaxis

2.3 Availability of Proposed Active Ingredient in the United States

Isavuconazonium is not available as a marketed product in the United States or in any other country.

2.4 Important Safety Issues with Consideration to Related Drugs

Isavuconazonium is a member of the azole class of antifungal agents, which includes drugs such as voriconazole, posaconazole, fluconazole and itraconazole. Drug-drug interactions, elevated liver transaminases, QT prolongation/torsades de pointes and are important azole class effects. Additional class effects include severe cutaneous adverse reactions, anaphylaxis, and visual disturbances or hallucinations. A table of the precautions and warnings appearing on the package inserts is presented below.

Table 2: Package Insert Warnings and Precautions listed for Selected Azole Class Antifungal Drugs

Drug (Commercial Name) Date of Approval	Voriconazole (Vfend) 5/24/2002	Posaconazole (Noxafil) 9/15/2006	Fluconazole (Diflucan) 1/29/1990	Itraconazole (Sporanox) 9/11/1992
Drug Interactions (CYP3A4 Inhibition)	X	X	X	☒
Hepatic Toxicity	X	X	X	X
Visual Disturbances	X			
Fetal Harm	X		X	
Arrhythmias and QT Prolongation	X	X	X	X
Infusion Reactions	X			
Laboratory Abnormalities (K, Mg, Ca, Cr, LFTs)	X			
Hepatic Impairment (Precaution)	X			
Renal Impairment (Precaution)	X	X	X	
Acute Renal Failure	X			
Acute Pancreatitis	X			
Exfoliative Cutaneous Reactions	X			
Fluorosis and Periostitis	X			
Anaphylaxis			X	
Dizziness and Seizures			X	
Congestive Heart Failure				☒
Neuropathy				X
Hydroxypropyl-β-cyclodextrin				X
Hearing Loss				X

☒ = Boxed Warning

2.5 Summary of Presubmission Regulatory Activity Related to Submission

December 20, 2005 – End of Phase 2 Type B meeting held between Basilea Pharmaceuticals and FDA's Division of Special Pathogen and Transplant Products

June 5, 2006 – [redacted] (b) (4) WSA-CS-004. FDA advised that efficacy can be demonstrated for additional fungal pathogens in a minimum of 20 well-documented cases for each rare pathogen where isavuconazonium sulfate is used as

the initial therapy or in refractory disease in patients who received prior antifungal treatment. Additional comments (b) (4) provided.

November 16, 2006 – Basilea and FDA agreement that any deaths and lost to follow-up patients will be designated as failures.

March 11, 2010 – FDA notified of IND transfer from Basilea to Astellas effective close of business March 12, 2010.

April 13, 2010 – Type B meeting to discuss (b) (4) WSA-CS-004 (Invasive Aspergillosis) and other clinical development issues associated with change in Sponsorship

- The Applicant proposes to change primary endpoint in trial WSA-CS-004 to all-cause mortality
- FDA indicates that they are in general agreement with the proposed endpoint
- FDA requests additional support including confirmation that the Applicant remain blinded to the trial outcomes due to the conduct of an interim (futility) analysis
- The Applicant provides confirmation that the Applicant remain blinded to outcomes and commits to provide further details regarding the conduct of the interim analysis
- FDA requests a detailed non-inferiority margin justification in support of proposed endpoint
- Performance characteristics of Bio-Rad Platelia Aspergillus EIA, for galactomannan in specimens other than serum will be reviewed at time of NDA submission

October 6, 2010 – Teleconference regarding further discussion of the primary endpoint for WSA-CS-004, Invasive Aspergillosis

- The Applicant provides supporting information regarding the interim analysis to support that the Applicant remain blinded to outcomes
- FDA indicates that the additional information adequately addresses their questions regarding the interim analysis
- FDA agrees with the proposed change in primary endpoint but requests additional information to justify the proposed non-inferiority margin. Specifically, FDA requests historical literature to support the superiority of amphotericin B to placebo in order to establish the non-inferiority margin

August 31, 2011 – Type C meeting (teleconference) to discuss justification for 10% noninferiority margin proposed for trial WSA-CS-004 (Invasive Aspergillosis)

- The Applicant provides details of a meta-analysis conducted to support the efficacy of amphotericin B over placebo.
- FDA indicates that the information appears to be adequate and they agree to move forward with the change in primary endpoint. FDA requests copies of all cited literature in the meta-analysis in order to confirm the proposed margin.

September 17, 2012 – Comments from FDA

FDA provides feedback on Applicant proposed galactomannan cut-off, timing of samples, modifications to EORTC criteria, and use of piperacillin/tazobactam.

October 4, 2012 – Confirmation of 10% non-inferiority margin for 6 week all-cause mortality endpoint request submitted on May 17, 2012 (N0146)

May 6, 2013 – Orphan Drug Designation granted for Invasive Aspergillosis (submitted March 14, 2013)

June 14, 2013 –FDA provides feedback on IA trial statistical analysis plan (SAP)

October 25, 2013 – Orphan Drug Designation granted for Zygomycosis (submitted March 14, 2013)

October 29, 2013 – Pre-NDA CMC Type B Meeting on drug substance impurities, drug substance and drug product specifications, justification for specifications for potentially genotoxic impurities BAL19714 and 2-butenal, oral drug product dissolution test method, and IV drug product infusion solution.

November 5, 2013 - Pre-NDA meeting held to review planned submission and to present top-line results from the Phase 3 IA trial

November 8, 2013 – QIDP designation granted for Invasive Aspergillosis (N224, submitted September 23, 2013)

February 7, 2014 – QIDP designation granted for Invasive Mucormycosis (N227, submitted December 17, 2013)

June 6, 2014 –Type C meeting to discuss the management of the Phase 3 clinical program and to present top line results for patients with invasive mucormycosis

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was well organized in electronic Common Technical Document (eCTD) format as described in the CDER guidance entitled Guidance for Industry: Providing Regulatory Submissions in Electronic Format—Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications; June 2008.

A Reviewer's Guide located in the module 1.2 folder was of good quality and utility. There were no missing datasets and overall the quantity and quality of the submission was adequate to start the review. There were no invalid MedDRA codings in the clinical datasets submitted. Selected clinical narratives were submitted for patient deaths, discontinuations, severe adverse reactions and adverse events of interest. Narratives for all of the subjects with the diagnosis of mucormycosis were supplied by the Applicant upon request by the review team.

3.2 Compliance with Good Clinical Practices

All studies were conducted in accordance with International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) consolidated guidelines and the ethical principles of the Declaration of Helsinki. The sponsor has submitted a statement of compliance for the two pivotal studies supporting the IA and IM indications. Each site signed either the Statement of Investigator Form (Food and Drug Administration [FDA 1572]) or the Non-United States (US) Investigator Form (CL-FRM-035).

Documentation of laboratory quality assurance certificates were provided in the submission.

Patient informed consent forms presented in Appendices 13.1.3.2 for Studies 9766-CL-0104 and 9766-CL-0103 adequately expressed the risks and benefits of study participation. Lists of IRBs were provided for both trials.

Protocol Violations

9766-CL-0104: The protocol deviations summarized in Table 3 are based on the ICH E3 definition of deviations and were assessed by the Sponsor.

Table 3: Protocol Deviations (ITT Population)

Deviations for All Sites	ISA (n = 258)	VRC (n = 258)	Total (n = 516)
Any Deviation	80 (31.0%)	89 (34.5%)	169 (32.8%)
PD1	39 (15.1%)	46 (17.8%)	85 (16.5%)
PD2	3 (1.2%)	4 (1.6%)	7 (1.4%)
PD3	18 (7.0%)	26 (10.1%)	44 (8.5%)
PD4	26 (10.1%)	32 (12.4%)	58 (11.2%)

PD1: Entered into the trial even though they did not satisfy entry criteria
PD2: Developed withdrawal criteria during the trial and was not withdrawn
PD3: Received wrong treatment or incorrect dose
PD4: Received excluded concomitant treatment
ISA: isavuconazonium; ITT: intent-to-treat population; VRC: voriconazole.
Source: Trial 9766-CL-0104 Table 12.1.1.5

Four entry criteria accounted for the majority of the deviations identified as PD1. Details on the top 4 criteria and the incidence between treatment arms are provided in Table 4.

Table 4: Incidence of Protocol Deviations between Treatment Arms

Entry Criteria	ISA (n = 258) n (%)	VRC (n = 258) n (%)	Total (n=516) n (%)
Inclusion 5 – IFD†	10 (3.9)	10 (3.9)	20 (3.9)
Exclusion 8 –Chronic aspergillosis, aspergilloma or ABPA	9 (3.5)	7 (2.7)	16 (3.1)
Exclusion 18 – Renal Dysfunction‡	6 (2.3)	11 (4.3)	17 (3.3)
Exclusion 10 – Prior cumulative AFT for > 4 days within 7 days prior to first dose	4 (1.5)	11 (4.3)	15 (2.9)
Amphotericin	0	4 (1.5)	4 (0.8)
Amphotericin/Itraconazole	0	1 (0.4)	1 (0.2)
Caspofungin	0	2 (0.8)	2 (0.4)
Itraconazole	1 (0.4)	1 (0.4)	2 (0.4)
Posaconazole	2 (0.8)	1 (0.4)	3 (0.6)
Voriconazole	0	2 (0.8)	2 (0.4)
Micafungin	1 (0.4)	0	1 (0.2)

ABPA: allergic bronchopulmonary aspergillosis; AFT: antifungal therapy; ISA: isavuconazonium; VRC: voriconazole.
† Per investigator assessment. To ensure consistent evaluation regarding the definition of IFD, the DRC had the option of classifying patients as proven, probable, possible or no IFD.
‡ Exclusion criterion 18 was originally exclusion criterion 5.
Source: Trial 9766-CL-0104 Appendices 13.2.2.2 and 13.2.4.3.2

Developed Withdrawal Criteria but Not Withdrawn

Seven patients met a treatment discontinuation criterion as established in the protocol, but were not discontinued from treatment. Four of these patients enrolled under Amendment 1 and did not have probable or proven IFD confirmed within 7 days of starting treatment. Two patients (320460 and 320624) had an increase in QTcF > 40 msec from baseline but were not discontinued. QT interval associated adverse events are discussed in this review in section 7.3.4.

Received Wrong Treatment or Incorrect Dose

Patients identified as receiving the wrong treatment or incorrect dose were categorized as PD3 (Table 5). This group included non-protocol drug administration (i.e. IV infusion completed in < 30 minutes), but also six patients who received one or more doses of the incorrect trial drug during the treatment period. A summary of patients with incorrect trial drug administration is provided in (Table 5). Due to the blinded nature of the trial, the blinded site staff was unaware of the error until the infusion or kit dispensation had already occurred.

Table 5: Patient with Incorrect Drug Administration, Trial 9766-CL-0104

Patient No.	Randomized Treatment	No. of Doses of Incorrect Treatment	Trial Day Incorrect Treatment Administered
012903	ISA	8 oral doses of VRC	Kit dispensed to patient on day 40

320441	ISA	1 infusion of VRC	Day 28
320458	VRC	1 infusion of ISA	Day 4
320630	VRC	8 oral doses of ISA	Days 25 to 32
860201	ISA (included in VRC treatment arm for SAF)	16 infusions of VRC	Days 1 to 7
970102	VRC	5 oral doses of ISA	Days 6 to 10

ISA: isavuconazonium; VRC: voriconazole.
Source: Trial 9766-CL-0104 Appendices 13.1.7.1, 13.2.5.1.1 and 13.2.5.4

Received an Excluded Concomitant Treatment

The protocol prohibited a substantial number of concomitant medications that have drug-drug interaction as well as medications with systemic anti-fungal activity. A summary of the patients who received an excluded concomitant treatment is provided in Table 6.

Table 6: Patients Who Received an Excluded Concomitant Medication

	Isavuconazonium (n=258)	**Voriconazole (n= 258) n (%)**	**Total (n=516) n (%)**
Took a prohibited medication during study treatment and follow-up (including potentially mould active systemic AFT)†	26 (10.1)	32 (12.4)	58 (11.2)
Received a prohibited medication only during study treatment (including potentially mould active systemic AFT)‡	22 (8.5)	30 (11.6)	52 (10.1)
Received concomitant potentially mould active systemic AFT during study treatment‡	3 (1.2)	5 (1.9)	8 (1.6)

† Any patient that took a prohibited medication including potentially mould active systemic AFTs per the protocol [Appendix 13.1.1, Final Protocol Section 7].
‡ Does not include patients that started prohibited medication after EOT
Source: Trial 9766-CL-0104 Table 12.1.1.5 and Appendices 13.2.2.2 and 13.2.4.3.2

MO Comment: Protocol violations appear to be reasonably balanced between the trial arms. A single patient, 860201 in Trial 9766-CL-0104 received 16 infusions over 7 days of the wrong drug, and is addressed in each of the safety and efficacy sections.

Trial 9766-CL-0103

The 37 case reports in the invasive mucormycosis trial were manually reviewed. There were two subjects who received voriconazole treatment, but as discussed in section 6.1.4, voriconazole is not expected to have any significant activity against Mucorales.

Use of Non-Protocol-specified In-line Filters

During the course of the trial 14 sites were identified as not using the correct filters as required and outlined in the Investigational Drug Handling Guide when administering the

study drug. A communication was also sent to clinical sites by Basilea reminding the Investigators of this requirement and suspending further enrollment at sites that did not have the correct supplies. Both Sponsors (Basilea and Astellas) provided infusion supplies to sites who could not procure them on their own.

A total of 42 patients were identified as having been administered the study drug with incorrect filter, of which 27 patients had no filter. An analysis specifically looking for embolic events or infusion related adverse events was conducted in Safety Section 7.3.5.

Site Inspections

Six sites were jointly selected for inspection by the Office of Scientific Investigations (OSI, CDER) and DAIP. Government travel to Israel was not permitted during the time of this review, therefore the selection focused on European and Latin American sites with high enrollment and/or high treatment effect favoring the active study drug. Preliminary findings as of the date of this review do not indicate concerns that would affect the outcome of the review. Information on the selected sites is summarized in Table 7.

Table 7: Sites Selected for GCP Inspections

Name of Investigator Investigator Address	Site # Protocol #Subjects	Inspection Dates	Final Classification
Heinz, Werner Oberduerrbacher Strasse 6,Studienambulanz Haematologie/Onkologie Wuerzburg, BY 97080 DEU Western Europe	Site 4910 9766-CL-0104 23 Subjects		Pending
Maertens, Johan UZ Gasthuisberg - Hematology,Herestraat 49 Leuven, 3000 BEL Western Europe	Site 3204 9766-CL-0104 59 Subjects	10/27/2014 – 10/31/2014	Pending

Marty, Francisco 75 Francis Street Boston, MA 2115 USA United States	Site 115 9766-CL-0104 9 Subjects 9766-CL0103 14 Subjects		Pending
Raad, Issam 1515 Holcombe Blvd, Unit 1460 Houston, TX 77030 USA United States phone:1 713	Site 118 9766-CL0104 24 Subjects 9766-CL0103 4 Subjects	10/07/2014 - 10/27/2014	Pending
Selleslag, Dominik Ruddershove 10 Brugge, 8000 BEL Western Europe	Site 3206 9766-CL0104 35 Subjects		Pending
Telles Filho, Flavio de Queiroz Rua General Carneiro 181 Curitiba, PR 80060-150 BRA Latin America	Site 5503 9766-CL0104 8 Subjects 9766-CL0103 8 Subjects	11/03/2014 – 11/7/2014	Pending

MO Comment: Inspections were ongoing at the time of the submission of this report. Significant findings will be addressed in a follow-up addendum.

3.3 Financial Disclosures

The Applicant submitted form 3454 certification of financial interest in accordance with 21 CFR part 54 for each of the phase 3 clinical studies. The applicant identified a participating investigator in both studies, (b) (6) who was reimbursed $30,000 for his participation on the DRC for Study WSA-CS-003 and $1,000 for consulting fees. In addition, for assistance with the Fungiscope database, an additional $94,000 is expected to be paid to (b) (6)

(b) (6) was the investigator for site (b) (6) in (b) (6). The site randomized (b) (6) subjects for trial 9766-CL-0104, with an enrollment of (b) (6) subjects to the isavuconazoleIsavuconazonium arm, and (b) (6) subjects to the voriconazole arm. The 42 day all-cause mortality at this site was 60% ((b) (6) enrolled) for isavuconzole, and 50% (b) (6) enrolled) for voriconazole. The site efficacy for the primary end point appeared to be balanced between the study arms. A single subject was enrolled for study 9766-CL-0103 who did not survive to Day 42.

MO Comment: A limited number of patients were enrolled by (b) (6) in the phase 3 studies and the Fungiscope database existed before Astellas contracted with (b) (6) The results of the site do not appear to be irregular, and it is unlikely that the Fungiscope arrangement would invalidate the results of these studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See review by Drs. Yichun Sun and Gene Holbert, the Office of New Drug Quality Assessment, ONDQA

4.2 Clinical Microbiology

See review by Shukal Bala, Ph.D., Division of Anti-infective Products, DAIP

4.3 Preclinical Pharmacology/Toxicology

See review by Owen McMaster Ph.D., Division of Anti-infective Products, DAIP

4.4 Clinical Pharmacology

The clinical pharmacology review team review concluded that the information provided by the applicant in support of the application is acceptable and supports the use of the proposed dose regimen for Cresemba for the treatment of IA and IM.

4.4.1 Mechanism of Action

Isavuconazonium inhibits the cytochrome P450 dependent lanosterol-14α-demethylase in yeasts and molds. Isavuconazonium has in vitro antifungal activity against *Aspergillus* spp. with MIC_{90} ranging from 1 to 2 mg/L. In vivo, isavuconazonium reduced tissue fungal burden and/or increased the survival rate in animal models of *Aspergillus* spp., *R. oryzae*, or *Candida* spp. fungal infections. Like other triazoles, the pharmacodynamic parameter AUC/MIC correlated with treatment outcome as demonstrated in in vitro studies and in vivo animal studies. In vivo and in vitro dynamic models utilizing both wild-type and isolates with elevated MICs to triazoles or well-characterized mutations in the target gene demonstrated that efficacy could be optimized by increasing the isavuconazonium concentrations.

4.4.2 Pharmacodynamics

There was no exposure-response (E-R) relationship for efficacy (imputed mortality before Day 42 or mortality by the end of treatment [Day 84]) and safety events (selected adverse events of interest) with isavuconazonium exposures in the pivotal Phase 3 study, and thus, the proposed dosing regimen for isavuconazonium is acceptable for the overall population. The subgroup of patients categorized as Asian (either based on race or countries of origin) had more mortality as compared to non-Asian patients in the isavuconazonium treatment arm, while a similar analysis for the comparator voriconazole arm did not show such mortality differences. The apparent higher mortality in the Asian population is highly influenced by the results in the enrolled population in South Korea (KOR) and removal of this country during sensitivity analysis resulted in resolution of the discrepancy in mortality between Asians vs. Non-Asians for Cresemba (isavuconazonium) treatment arm. Thus, the mortality differences are not attributable to race or region specific differences in disease/drug/background standard-of-care effects and therefore no action is recommended for isavuconazonium treatment for the subgroup of Asian population.

4.4.3 Pharmacokinetics

The clinical pharmacology assessment of isavuconazonium included results from 20 in vitro and ex vivo studies and 40 in vivo studies that evaluated the PK, drug interactions, and PK/PD of isavuconazonium. In vitro studies demonstrated that isavuconazonium is rapidly hydrolyzed in blood to isavuconazonium by esterases, predominately by butyrylcholinesterase. Isavuconazonium exhibited dose-proportional PK in the dose range of 100 to 600 mg.

Isavuconazonium is extensively distributed with a steady state volume of distribution of approximately 450 L after IV administration. Isavuconazonium is highly protein bound (> 99%), predominantly to albumin. Isavuconazonium is a sensitive CYP3A substrate, an

inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 and an inducer of CYP3A4/5, CYP2B6, CYP2C8, and CYP2C9. The population mean half-life of isavuconazonium was approximately 130 hours for both routes of administration across a range of isavuconazonium doses, suggesting that the elimination process of isavuconazonium is not dependent on dose or route of administration. The absolute oral BA of isavuconazonium administered as capsules was 98%.

Based on population PK analysis, race (Asian vs. non-Asian) was a significant covariate on clearance and BMI was a significant covariate on volume of distribution of isavuconazonium. Correspondingly, Asians had ~50% higher exposure compared to non-Asians for the same dosing regimen. None of the covariates of age, gender, weight or race require dose adjustment based on exposure since the overall exposure response relationship for efficacy and safety was flat within the concentration range achieved in the pivotal phase 3 study 9766-CL-0104.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 8: Summary of Phase 3 Trials

	Phase 3 Trials		
	9766-CL-0104 (WSA-CS-004)		**9766-CL-0103 (WSA-CS-003)**
Design	Double-blind, randomized, noninferiority study to evaluate efficacy and safety of ISA vs VRC for the primary treatment of IFD caused by *Aspergillus* spp. or other filamentous fungi		Open-label, non-comparative study to evaluate the safety and efficacy of ISA for the treatment of invasive aspergillosis in patients with renal impairment or in patients with IFD caused by rare moulds, yeasts or dimorphic fungi
No. of Sites	102		34
Countries with Sites that Enrolled Patients	Argentina, Australia, Belgium, Brazil, Canada, Chile, China, Egypt, France, Germany, Hungary, India, Israel, Italy, Malaysia, Mexico, The Netherlands, New Zealand, Poland, Russia, South Korea, Spain, Switzerland, Thailand, Turkey and the United States		Belgium, Brazil, Germany, India, Israel, Lebanon, Mexico, Russia, South Korea, Thailand and the United States
Treatment Groups	ITT: ISA (n = 258) SAF: ISA (n = 257)	ITT: VRC (n = 258) SAF: VRC (n = 259)	ITT/SAF: ISA (n = 146) RI (n = 59) NRI (n = 87)

Loading Dose	ISA 200 mg administered q8h IV for 2 days	VRC 6 mg/kg administered q12h IV for 1 day	ISA 200 mg q8h IV or oral on days 1 and 2
Maintenance Dose	200 mg once per day IV or oral	4 mg/kg q12h IV or 200 mg q12h oral	ISA 200 mg q24h IV or oral from day 3 to EOT
Patient Population	Patients with IFD caused by *Aspergillus* or other filamentous fungi		Renally impaired (creatinine clearance < 50 mL/min) patients with invasive aspergillosis and patients with IFD caused by other rare moulds, yeasts or dimorphic fungi
Primary efficacy endpoint	Crude rate of all-cause mortality through day 42		DRC-assessed overall response at day 42
Secondary efficacy variables	• Key secondary: DRC-assessed overall response at EOT • All-cause mortality through day 84 • DRC-assessed overall response at days 42 and 84 • Clinical, mycological and radiological response at EOT, and days 42 and 84		• DRC-assessed overall response at EOT and day 84 • DRC-assessed clinical, mycological and radiological success at EOT and days 42 and 84 • Survival rate by days 42, 84, 120 and 180

DRC: Data Review Committee; EOT: end-of-treatment; IFD: invasive fungal disease; ITT: intent to treat; ISA: Isavuconazonium; IV: intravenous; PK: pharmacokinetics; SAF: safety analysis dataset; VRC: voriconazole
Source: NDA Aplication 207-500, Module 2.5, Clinical Overview

Table 9: Summary of Phase 2 Trials

Parameter	**Phase 2 Trials**	
	9766-CL-0101 (WSA-CS-001)	**9766-CL-0102 (WSA-CS-002)**
Design	Randomized, double-blind, phase 2, parallel group, noninferiority study to compare the efficacy and safety of 3 oral dosing regimens of ISA to a standard oral FLU regimen for the treatment of patients with uncomplicated esophageal candidiasis	Open-label, multicenter study of the safety and efficacy of escalating intravenous and oral isavuconazonium in the prophylaxis of patients undergoing chemotherapy for AML
No. of Sites	8	3
Countries with Sites that Enrolled Patients	South Africa	Germany

Treatment Groups	ITT: ISA A (n = 40) ISA B (n = 40) ISA C (n = 41) FLU D (n = 38)	Safety Population: Group 1: (n = 11) Group 2: (n = 12)
Loading Dose	ISA A: 200 mg day 1 ISA B: 400 mg day 1 ISA C: 400 mg day 1 FLU D: 200 mg day 1	Group 1: 400/200/200 mg day 1, 200/200 mg day 2 Group 2: 800/400/400 mg day 1, 400/400 mg day 2
Maintenance Dose	ISA A: 50 mg/day ISA B: 400 mg/week ISA C: 100 mg/day FLU D: 100 mg/day	Group 1: 200 mg/day Group 2: 400 mg/day
Patient Population	Patients with uncomplicated esophageal candidiasis	Neutropenic AML patients who were entering first induction treatment or subsequent chemotherapy and had not experienced a prior invasive fungal
Primary efficacy endpoint	Endoscopically confirmed clinical response at EOT	Rate of microbiological success (absence of break-through fungal infections and lack of need for other systemic AFT)
Secondary efficacy variables	• Overall therapeutic response at EOT • Microbial response at EOT • Relapse rate at the follow-up and late follow-up visits in	none

Source: NDA Aplication 207-500, Module 2.5, Clinical Overview

Table 10: Summary of Phase 1 Studies

Study ID	Country	Study Title	Study Design	Dosing Regimen	Planned /Actual Number of Subjects	Duration of Follow-up (After Dosing)	Estimated/ Actual Completion Date
Phase 1 Studies							
9766-CL-0001 (WSA-CP-001)	Switzer-land	Exploratory assessment of the pharmacokinetics and safety of BAL4815 after single ascending oral administrations of its prodrug BAL8557 in healthy male subjects	Single center, double-blind, randomized, placebo-controlled, single ascending dose study with 4 sequential dose levels.	Single dose ISA PO (100mg, 200 mg, 400mg, or 800mg) or placebo	23 subjects (15 ISA and 8 Placebo)	10 (± 2) days	19-Nov-2012 (Last study evaluation: 07-Mar-2003)
9766-CL-0002 (WSA-CP-002)	Germany	Assessment of the pharmacokinetics and safety of BAL4815 after single ascending intravenous infusions of its prodrug BAL8557 in healthy male subjects	Single center, double-blind, randomized, placebo-controlled, single ascending dose study with 3 sequential dose levels.	Single dose ISA IV (40mg, 80 mg, or 160mg) or placebo	24 subjects (18 ISA and 6 Placebo)	10-25 days	02-Jul-2013 (Last study evaluation: 12-May-2003)
9766-CL-0003 (WSA-CP-003)	Germany	Assessment of the pharmacokinetics and safety of BAL4815 after repeated oral and intravenous administrations of its prodrug BAL8557 in healthy male subjects	Single center, double-blind, randomized, placebo-controlled, multiple dose study with 2 dose regimens for each route of administration (PO and IV).	4 cohorts - 2 dose regimens for each route (loading dose on Day 1 / maintenance QD dose from Day 2), each receiving ISA (n=6) or placebo (n=2): • ISA 100mg PO / ISA 50mg PO on Days 2-21 or placebo PO on Days 1-21; • ISA 200mg PO / ISA 100 mg PO on Days 2-21 or placebo PO on Days 1-21; • ISA 80mg IV / ISA 40 mg IV on Days 2-14 or placebo IV on Days 1-14; ‡ • ISA 160mg IV / ISA 80 mg IV on Days 2-14 or placebo IV on Days 1-14. ‡	32 subjects (12 ISA PO, 12 ISA IV, 8 placebo)	20 (+3) days	09-Aug-2013 (Last study evaluation: 18-Nov-2003)
9766-CL-0004 (WSA- CP-004)	NL	QTc measurements and pharmacokinetics of placebo- and active-controlled multiple dose study of two different dosing regimens of BAL8557 in healthy male and female volunteers	Single center, double-blind, randomized, parallel group, multiple dose study, placebo- and active- (single administration) controlled.	2 treatment groups. Moxifloxacin 400mg PO on Day 1, then: ☐ ISA (400/300/200mg PO) on Days 4-6; ISA 100mg PO QD on Days 7-10; ISA 100mg IV on Day 11; ISA PO (300/250/200mg) on Days 12-14; ISA 150mg PO QD on Days 15-18; ISA 150mg IV on Day 19; OR ☐Placebo PO on Days 4-10 & 12-18 and Placebo IV on Days 11 & 19.	82 subjects (41 ISA and 41 Placebo)	7 days	03-Jul-2013 (Last study evaluation: 20-Oct-2005)

9766-CL-0005 (WSA- CP-005)	NL	Assessment of pharmacokinetic interaction between BAL4815 and ketoconazole or rifampicin after repeated oral administration of prodrug BAL8557 and ketoconazole or rifampicin in healthy male subjects	Single center, multiple dose, open-label, crossover DDI study.	ISA 400 mg PO on Day 1 then ISA 100mg PO from Days 2-14; wash-out Days 15-35; PO QD dosing of ketoconazole 200mg or rifampicin 600mg on Days 36-43; concomitant QD PO dosing of ketoconazole 200mg or rifampicin 600 mg plus ISA 400 mg on Day 44 and ISA 100mg on Days 45-57); PO QD dosing of ketoconazole 200mg or rifampicin 600mg alone on Days 58-71.	52 subjects (26 ISA + ketoconazole and 26 ISA + rifampicin)	2 days	05-Aug-2013 (Last study evaluation: 10-Oct-2005)
9766-CL-0006 (WSA- CP-006)	US	Assessment of the pharmacokinetic interaction between BAL4815 and warfarin after oral administration of prodrug BAL8557 in healthy male subjects	Single center, multiple-dose, open-label DDI study.	Single dose of warfarin 10mg PO on Day 1; wash-out from Days 2-8; ISA 400mg PO on Day 9; ISA 100mg PO QD from Day 10-28. On Day 29, ISA 100mg PO was given followed by warfarin 10mg PO 2 hours later. ISA 100mg PO QD from Days 30-36.	12 subjects	10 (± 2) days	18-Jul-2013 (Last study evaluation: 10-Sep-2005)
9766-CL-0007 WSA-CP-007)	Germany	Assessment of pharmacokinetic interactions between BAL4815 and cyclosporine or tacrolimus after repeated oral administration of prodrug BAL8557 and single doses of cyclosporine or tacrolimus in healthy male subjects	Single center, multiple dose, open-label, cross-over DDI study. Group A: single and combined doses of ISA and/or cyclosporine. Group B: single and combined doses of ISA and/or tacrolimus.	Single PO dose of cyclosporine 300mg or tacrolimus 5mg on Day 1; wash-out from Day 2-7; ISA 400 mg PO on Day 8; ISA 100mg PO on Day 9-27. On Day 22, a single PO dose of cyclosporine 300mg or tacrolimus 5mg was given 2 hours after ISA.	52 subjects (26 cyclosporine +/- ISA and 26 tacrolimus +/- ISA)	16 (± 2) days	29-Aug-2013 (Last study evaluation: 03-Oct-2005)
9766-CL-0008 (WSA- CP-008)	Hungary	Assessment of the pharmacokinetics of BAL4815 after intravenous and oral administration of the prodrug BAL8557 to healthy subjects and subjects with mild or moderate hepatic impairment caused by cirrhosis	Single-center, single-dose, open-label, parallel study randomized for route of administration with study groups matched for age, gender, body weight, and BMI.	Single dose of ISA 100mg IV or ISA 100mg PO	48 subjects	20 days	08-Aug-2013 (Last study evaluation: 24-Sep-2007)

9766-CL-0009 (WSA- CP-009)	Germany	Assessment of the potential pharmacokinetic interaction between BAL4815 and ketoconazole or indinavir or cyclosporine A after oral administration of prodrug BAL8557 in healthy male subjects	Single center, single dose, open-label cross-over DDI study. Group A: Two single doses of ISA, one alone and one concomitantly with ketoconazole. Group B: Two single doses of indinavir, one alone and one concomitantly with ISA. Group C: Two single doses of cyclosporine, one alone and one concomitantly with ISA	Three groups: ☐ ISA 400mg PO on Day 1; ISA 400mg PO + ketoconazole 200mg PO on Day 36; ☐Indinavir 800mg PO on Day 1, and Indinavir 800mg PO + ISA 400mg PO on Day 15. ☐Cyclosporine A 300mg on Day 1, and cyclosporine A 300mg + ISA 400mg on Day 15.	36 subjects (12 in each group)	17 (± 3) days	03-Jul-2013 (Last study evaluation: 06-Apr-2004)
9766-CL-0010 (WSA- CP-010)	Germany	Bioavailability of BAL4815 after oral and intravenous administration of pro-drug BAL8557 in healthy male subjects	Single center, open-label, randomized, 2 treatment cross-over study.	Two single doses. ISA 400mg PO or IV on Day 1, followed by the other route of treatment on Day 43.	14 subjects	45 (± 2) days	15-May-2013 (Last study evaluation: 10-Mar-2008)
9766-CL-0011 (WSA- CP-011)	France	Assessment of pharmacokinetic interaction between BAL4815 and omeprazole after oral administration of prodrug BAL8557 in healthy male subjects	Single center, multiple-dose, open-label DDI study.	Single PO dose of omeprazole 40mg on Day 1; washout from Days 2-8. ISA 200mg PO TID on Days 9 & 10, followed by QD dosing on Days 11-22. On Day 23, concomitant dosing of ISA 200mg + omeprazole 40mg.	28 subjects (27 ISA)	12 (± 2) days	24-Jul-2013 (Last study evaluation: 05-Sep-2008)
9766-CL-0012 WSA-CP-012)	Germany	Assessment of the pharmacokinetic interaction between BAL4815 and sirolimus after oral administration of pro-drug BAL8557 in healthy male subjects	Single-center, multiple-dose, open-label, DDI study.	Single PO dose of sirolimus 1mg on Day 1; washout of 3 weeks. ISA 200 mg PO TID on Days 22 & 23, followed by QD dosing of ISA from Days 24-44. On Day 35, subjects co-administered ISA 200mg and sirolimus 1mg.	26 subjects	10 (± 2) days	19-Jul-2013 (Last study evaluation: 31-Mar-2008)

9766-CL-0013	Switzer-land	Assessment of the pharmacokinetics of two formulations of the azole BAL4815 administered alone or concomitantly with food in healthy male volunteers	Single dose, open-label, randomized, parallel group, single center study. Four groups: two ISA formulations, each given under fasted and fed conditions.	Single dose of ISA 400 mg, administered as either hard capsules or liquid concentrate.	24 subjects	35 (± 2) days	11-Jun-2013 (Last study evaluation: 28-Apr-2006)
9766-CL-0014 (WSA- CP-018)	Ukraine	Assessment of the pharmacokinetics of BAL4815 after intravenous and oral administration of the prodrug BAL8557 to healthy subjects and subjects with mild to moderate hepatic impairment due to liver cirrhosis caused by chronic hepatitis B and/or C	Single-center, single-dose, open-label, parallel study randomized for route of administration with study groups matched for age, gender, body weight, and BMI.	Single dose of ISA 100mg IV or ISA 100mg PO.	48 subjects	20 days	30-Sep-2013 (Last study evaluation: 10-Jan-2008)
9766-CL-0015 (WSA- CP-019)	Germany	Influence of food on the oral pharmacokinetics of BAL4815 administered as the prodrug BAL8557 to healthy male volunteers	Single-center, open-label, randomized, 2-treatment cross-over study.	Two single doses. ISA 400mg on Day 1, either under fasted or fed conditions, followed by ISA 400mg under the alternate conditions on Day 43.	25 subjects	45 (± 2) days	31-May-2013 (Last study evaluation: 04-Apr-2008)
9766-CL-0016	US	A phase 1 open-label mass balance study to evaluate the pharmacokinetics of isavuconazonium after a single oral dose of 14C-labeled isavuconazonium sulfate in healthy male subjects	Open-label, one-period, single-dose study with 14C-labeled prodrug BAL8557.	Single dose of ISA 200 mg PO	7 subjects	21-28 days, depending when radio-activity recovery criteria met.	31-Jan-2014 (Last study evaluation: 05-Dec-2012)

9766-CL-0017	US	A phase 1, randomized, double-blind, placebo and active controlled, parallel study to evaluate the effect of repeat doses of isavuconazonium on cardiac repolarization in healthy adult subjects	Single-center, randomized, double-blind, placebo and active controlled, parallel group study.	4 treatment groups: ☐ ISA 200mg TID for 2 days and ISA 200mg QD for 11 days. ☐ ISA 200mg TID for 2 days and ISA 600mg QD for 11 days. ☐Placebo for 13 days. ☐ Placebo for 12 days and moxifloxacin 400mg on 13th day.	160 subjects (80 ISA, 40 placebo, 40 moxifloxa-cin)	1 day	13-Sep-2013 (Last study evaluation 09-Jul-2012)
9766-CL-0018	US	A phase 1 open-label, 2-part, parallel group study to investigate the effect of renal impairment on the pharmacokinetics of isavuconazonium	Open label study of isavuconazonium in subjects with renal impairment. Part 1 (single center): ESRD and matched healthy subjects. Part 2 (multicenter): Mild, moderate, and severe renal impairment and matched healthy subjects.	ISA 200mg IV Single dose. Part 1: ESRD subjects received 2 single doses (Day 1 after dialysis and Day 15 before dialysis); healthy subjects received 1 single dose on Day 1. Part 2: Subjects received a single dose on Day 1.	49 subjects	Part 1: 7 (± 2) days for ESRD subjects, 14 days for healthy subjects Part 2: 14 days	20-Mar-2014 (Last study evaluation: 16-Apr-2013)
9766-CL-0020	US	Effect of multiple doses of isavuconazonium on the pharmacokinetics of a single dose of sirolimus: a phase 1, open label, sequential study in healthy adult subjects	Open-label, sequential dosing DDI study to assess the effect of multiple doses of isavuconazonium on the PK of a single dose of sirolimus.	Single dose of sirolimus 2mg PO on Days 1 and 26. ISA 200mg PO TID on Days 22 & 23, followed by ISA 200mg PO QD on Days 24-34.	22 subjects (21 ISA)	7 (± 2) days	02-Apr-2013 (Last study evaluation: 18-Jan-2012)
9766-CL-0021	US	Effect of multiple doses of isavuconazonium on the pharmacokinetics of a single dose of tacrolimus: a phase 1, open label, sequential study in healthy adult subjects	Single center, open-label, sequential dosing DDI study to assess the effect of multiple doses of isavuconazonium on the PK of tacrolimus after single dose administration.	Single PO dose of tacrolimus 5mg on Days 1 and 20. ISA 200mg PO TID on Days 16 & 17, followed by ISA 200mg PO QD on Days 18-28.	24 subjects (22 ISA)	7 (± 2) days	10-Jun-2013 (Last study evaluation: 18-Jan-2012)

9766-CL-0022	US	Effect of multiple doses of isavuconazonium on the pharmacokinetics of a single dose of cyclosporine: a phase 1, open label, sequential study in healthy adult subjects	Open-label, sequential dosing DDI study to assess the effect of multiple doses of isavuconazonium on the PK of cyclosporine after single dose administration.	Single PO dose of cyclosporine 300mg on Days 1 and 15. ISA 200mg PO TID on Days 11 & 12, followed by ISA 200mg PO QD on Days 13-18.	24 subjects (21 ISA)	7 (± 2) days	25-Apr-2013 (Last study evaluation: 04-Jan-2012)
9766-CL-0023	US	A phase 1, open-label, drug interaction study of the pharmacokinetics of isavuconazonium and midazolam after separate and concomitant administration to healthy adult subjects	Single center, open-label, DDI study to determine the effect of isavuconazonium at steady state on the pharmacokinetics of midazolam.	Single PO dose of midazolam syrup 3mg on Days 1 and 12. ISA 200mg PO TID on Days 3 & 4, followed by ISA 200mg PO QD on Days 5-13.	23 subjects	7 (± 1) days	20-Jun-2013 (Last study evaluation: 19-Jun-2011)
9766-CL-0024	US	Phase 1, open-label, sequential study of the effect of multiple doses of isavuconazonium on the pharmacokinetics of a single dose of prednisone in healthy adult subjects	Single center, open-label, sequential DDI study to assess the effect of multiple doses of isavuconazonium on the PK of prednisone and its active metabolite, prednisolone, after single dose administration.	Single PO dose of prednisone 20mg on Days 1 and 9. ISA 200mg PO TID on Days 5 & 6, followed by ISA 200mg PO QD on Days 7-10.	21 subjects	8 (± 2) days	18-Jul-2013 (Last study evaluation: 15-Mar-2012)
9766-CL-0025	US	Effect of multiple doses of isavuconazonium on the pharmacokinetics of a single dose of digoxin: a phase 1, open-label, sequential study in healthy adult subjects	Single center, open-label, sequential DDI study to assess the effect of multiple doses of isavuconazonium on the PK of digoxin after single dose administration.	Single PO dose of digoxin 0.5mg on Days 1 and 19. ISA 200mg PO TID on Days 15 & 16, followed by ISA 200mg PO QD on Days 17-26.	24 subjects (21 ISA)	8 (± 2) days	14-Aug-2013 (Last study evaluation: 07-May-2012)

9766-CL-0027	US	Phase 1, open-label, sequential study of the effect of multiple doses of isavuconazonium on the pharmacokinetics of a single dose of methadone in healthy adult subjects	Single center, open-label, sequential DDI study to assess the effect of multiple doses of isavuconazonium on the PK of methadone after a single dose administration.	Single PO dose of methadone 10mg on Days 1 and 20. ISA 200mg PO TID on Days 16 & 17, followed by ISA 200mg PO QD on Days 18-28.	23 subjects (22 ISA)	8 (± 2) days	13-Aug-2013 (Last study evaluation: 13-Jun-2012)
9766-CL-0030	US	A phase 1, open-label, sequential study of the effect of multiple doses of isavuconazonium on the pharmacokinetics of a single dose of mycophenolate mofetil in healthy adult subjects	Open-label, sequential DDI study to assess the effect of multiple doses of isavuconazonium on the PK of MMF after single dose administration	Single PO dose of MMF 1g on Days 1 and 13. ISA 200mg PO TID on Days 9 & 10, followed by ISA 200mg PO QD on Days 11-16.	24 subjects (23 ISA)	8 (± 2) days	06-May-2013 (Last study evaluation: 08-Apr-2012)
9766-CL-0031	US	A phase 1, open-label study to evaluate the effect of multiple doses of isavuconazonium on the pharmacokinetics of a single dose oral contraceptive containing ethinyl estradiol and norethindrone	Open-label, sequential DDI study to assess the effects of multiple doses of isavuconazonium on the PK of ethinyl estradiol and norethindrone given as a single dose in healthy post-menopausal females.	Single doses of ethinyl estradiol (35µg) and norethindrone (1mg) combination oral contraceptive on Days 1 and 13. ISA 200 mg PO TID on Days 9 & 10, followed by ISA 200mg PO QD on Days 11-16.	24 subjects (23 ISA)	8 (± 2) days	09-Aug-2013 (Last study evaluation: 12-May-2012)
9766-CL-0033	US	Phase 1, open label, sequential study of the effect of multiple doses of isavuconazonium on the pharmacokinetics of a single dose of warfarin in healthy male subjects	Single center, open-label, sequential dosing DDI study to assess the effect of multiple doses of isavuconazonium on the PK/PD of warfarin after single dose administration.	Single PO doses of warfarin 20 mg on Days 1 and 20. ISA 200 mg PO TID on Days 16 & 17, followed by ISA 200mg PO QD on Days 18-28.	21 subjects (20 ISA)	7 (± 2) days	18-Jul-2013 (Last study evaluation: 30-Jul-2012)

9766-CL-0035	US	A phase 1, open-label, parallel study to evaluate the effect of multiple doses of isavuconazonium on the pharmacokinetics of multiple doses of lopinavir/ritonavir and the effect of lopinavir/ritonavir on the pharmacokinetics of multiple doses of isavuconazonium in healthy adult subjects	Two-part, open-label, multiple-dose, 3-arm, parallel DDI study to evaluate the safety, tolerability and PK interaction between LPV/RTV and isavuconazonium. Part 1: Subjects randomized to either ISA alone or ISA + LPV/RTV. Part 2: Subjects randomized to either: ISA alone, LPV/RTV alone, or ISA + LPV/RVT	Part 1: ☐ ISA 100mg PO TID on Days 1 and 2, followed by ISA 100mg PO QD on Days 3-13. ☐ ISA as above plus LPV/RTV 400/100mg PO BID for Days 1-13. Part 2 ☐ ISA 200 mg PO TID for Days 1 and 2, followed by ISA 200 mg PO QD for Days 1-13. ☐LPV/RTV 400/100 mg PO BID for Days 1-12 and LPV/RTV 400/100 mg PO QD for Day 13. ☐ ISA as above and LPV/RTV 400/100 mg PO BID for Days 1-13	Part 1: 13 subjects (6 ISA and 7 ISA + LPV/RTV) Part 2: 55 subjects (18 ISA, 19 LPV/RTV, and 18 ISA + LPV/RTV)	7 (± 2) days	18-Sep-2013 (Last study evaluation: 26-Oct-2012)
9766-CL-0038	China	A phase 1, open-label, single and multiple dose study to assess the safety and pharmacokinetics of isavuconazonium in healthy Chinese volunteers	Single center, open-label, single and multiple dose study. Part 1: Subjects receive single PO dose and single IV dose in crossover design. Part 2: Subjects receive multiple IV (Group 1) or PO (Group 2) dosing.	Part 1: Single dose of ISA 200mg PO or IV on Day 1, followed by ISA 200mg using alternate route on Day 31. Part 2: ISA 200mg TID for 2 days followed by ISA 200mg QD for 10 days (PO or IV).	12 subjects (Part 1) + 24 subjects (Part 2)	Part 1: 14 days Part 2: 14 days	13-May-2014 (Last study evaluation: 08-Oct-2012)
9766-CL-0040	US	A phase 1, randomized, open-label, two-arm, parallel group study of the effect of ketoconazole at steady state on the pharmacokinetics of a single dose of isavuconazonium in healthy adult subjects	Open-label, 2-arm, randomized, parallel group DDI study to assess the effect of ketoconazole at steady state on the PK of isavuconazonium after single dose administration.	Two treatment arms: ☐Single PO dose of ISA 200mg on Day 1 ☐Ketoconazole 200mg BID on Days 1-24 and single PO dose of ISA 200mg on Day 4.	24 subjects (12 ISA alone and 12 ketoconazole + ISA)	21 days	22-Jul-2013 (Last study evaluation: 04-Jun-2012)
9766-CL-0041	US	A phase 1, open-label, parallel group, single dose study to evaluate the pharmacokinetics of isavuconazonium in healthy non-elderly and elderly male and female subjects	Open-label, parallel group, single-dose study	Single dose of ISA 200mg PO on Day 1.	48 subjects	14 days	27-Nov-2013 (Last study evaluation: 03-Jan-2013)

9766-CL-0042	US	A phase 1, open-label, sequential study of the effect of multiple doses of isavuconazonium on the pharmacokinetics of a single dose of dextromethorphan in healthy adult subjects	Open-label, sequential DDI study to assess the effect of multiple doses of isavuconazonium on the PK of dextromethorphan and its active metabolite, dextrorphan, after single dose administration	Single PO dose of dextromethorphan 30mg on Days 1 and 10. ISA 200mg PO TID on Days 6 & 7, followed by ISA 200mg PO QD on Days 8-12.	24 subjects	9 (± 2) days	22-Aug-2013 (Last study evaluation: 08-Jun-2012)
9766-CL-0043	US	A phase 1, open label study to evaluate the effect of multiple doses of isavuconazonium on the pharmacokinetics of a single dose of atorvastatin	Single center, open-label, sequential dosing DDI study in healthy subjects to assess the effects of multiple doses of isavuconazonium on the pharmacokinetics of a single dose of atorvastatin.	Single PO doses of atorvastatin 20mg on Days 1 and 12. ISA 200mg PO TID on Days 8 & 9, followed by ISA 200mg PO QD on Days 10-15.	24 subjects	9 (± 2) days	31-Jul-2013 (Last study evaluation: 27-Aug-2012)
9766-CL-0044	US	Phase 1, open-label study to evaluate the effect of multiple doses of isavuconazonium on the pharmacokinetics of a single dose of bupropion	Open-label, sequential dosing study in healthy subjects to assess the effects of multiple doses of isavuconazonium on the PK of a single dose of bupropion.	Single PO dose of bupropion HCl 100mg (immediate release) on Days 1 and 15. ISA 200mg PO TID on Days 8 & 9, followed by ISA 200mg PO QD on Days 10-20.	24 subjects	7 (± 2) days	17-Jul-2013 (Last study evaluation: 02-Jul-2012)
9766-CL-0050	US	A phase 1 open-label mass balance study to evaluate the pharmacokinetics of BAL8728 after a single intravenous dose of 14C-labeled isavuconazonium sulfate in healthy male subjects	Single center, open-label, single-dose mass balance study with 14C-labeled prodrug BAL8557.	Single dose of 200mg ISA IV.	6 subjects	3- 8 days, depending when radio-activity recovery criteria met.	05-Feb-2014 (Last study evaluation: 30-Apr-2013)

97)66-CL-0051	US	A phase 1, open-label study to evaluate the effect of multiple doses of isavuconazonium on the pharmacokinetics of metformin	Open-label DDI study to assess effect of multiple doses of ISA on PK of single dose of metformin	Single PO dose of metformin 850mg on Days 1 & 8. ISA 200mg PO TID on Days 4 & 5, followed by ISA 200mg PO QD on Days 6-9.	23 subjects (ISA) and 24 subjects (metformin)	7 (± 2) days	31-Oct-2013 (Last study evaluation: 21-Feb-2013)
9766-CL-0052	US	A phase 1, open-label study to evaluate the effect of multiple doses of isavuconazonium on the pharmacokinetics of methotrexate	Open-label DDI study to assess the effect of multiple doses of ISA on the PK of a single dose of MTX.	Single PO dose of MTX 7.5 mg on Days 1 & 8. ISA 200mg PO TID on Days 4 & 5, followed by ISA 200mg PO QD on Days 6-9.	24 subjects	7 days	28-Oct-2013 (Last study evaluation: 15-Mar-2013)
9766-CL-0053δ	US	A phase 1 open label study to evaluate the effect of multiple doses of isavuconazonium on the pharmacokinetics of repaglinide and caffeine	Open-label sequential dosing DDI study to assess the effect of multiple doses of ISA on the PK of a single dose of repaglinide, and on the PK of a single dose of caffeine.	Single PO dose of repaglinide (0.5mg) on Days 1 & 14. Single PO dose of caffeine (200mg) on Days 3 & 16. ISA 200mg PO TID on Days 5 & 6, followed by ISA 200mg PO QD on Days 7-17.	24 subjects	7 (± 2) days	02-May-2014 (Last study evaluation: 24-Feb-2014)
9766-CL-0054δ	US	A phase 1 randomized, open label, parallel group study to evaluate the effect of multiple doses of esomeprazole on the pharmacokinetics of isavuconazonium	Randomized, open-label, 2-arm, parallel group study to assess the effect of multiple doses of esomeprazole on the PK of ISA.	Two treatment arms: ☐ ISA 200mg TID on Days 1 & 2, followed by QD dosing on Days 3, 4, & 5. ☐Arm 2: Esomeprazole 40mg daily for 10 days (Days 1-10). ISA 200mg TID on Days 6 & 7, followed by ISA 200mg PO QD on Days 8, 9, & 10.	24 subjects	6 (± 2) days	02-Apr-2014 (Last study evaluation: 19-Feb-2014)

BID: twice daily; BMI: body mass index; DDI: drug-drug interaction; EC: esophageal candidiasis; EOT: end of treatment; ESRD: end-stage renal disease; ISA: isavuconazonium; IV: intravenous(ly); LPV/RTV: lopinavir/ritonavir; MMF: mycophenolate mofetil; MTX: methotrexate; NL: The Netherlands; PK: pharmacokinetic(s); PO: oral(ly); q8h: every 8 hours; q12h: every 12 hours; QD: once daily; QTc: QT interval corrected for heart rate; RMP: Risk Management Plan; ROW: rest of world; TID: three times daily; US: United States: VRC: voriconazole.

† As of the data cutoff (30 September 2013), 5 patients in Study 9766-CL-0103 were actively receiving isavuconazonium under country-specific Amendment 4, which allowed treatment beyond 180 days.

‡ In Study 9766-CL-0003, ISA-treated subjects in cohorts 3 & 4 were to receive loading/maintenance dose of 100mg/50mg or 200mg/100mg but actually received 80mg/40mg or ISA 100mg/50mg

δ Studies 9766-CL-0053 and 9766-CL-0054 were completed after the data cutoff (30 September 2013), and therefore were not included in the Phase 1 Population.

Source: NDA Aplication 207-500, Module 5.2

5.2 Review Strategy

The indication of invasive aspergillosis is supported by Study 9766-CL-0104, a randomized, double-blind, noninferiority, comparative group clinical trial, which evaluated the efficacy and safety of isavuconazonium compared to voriconazole for the treatment of invasive aspergillosis. Study 9766-CL-0104 included 516 adult patients with suspected invasive fungal disease (IFD) caused by *Aspergillus* species or other filamentous fungi. The clinical trial design is presented in Section 6.2. Due to the restrictions on the use of intravenous voriconazole in patients with moderate to severe renal impairment, related to the presence of cyclodextrin excipient, the study excluded patients with estimated creatinine clearance < 50 mL/min. Supportive evidence on the efficacy of isavuconazonium in renally impaired patients with invasive aspergillosis is provided by Study 9766-CL-0103, which enrolled a subpopulation of patients with invasive aspergillosis and renal impairment.

The indication of invasive mucormycosis is supported by data from a subpopulation of patients enrolled in the phase 3 Study 9766-CL-0103, who were confirmed to have proven or probable invasive mucormycosis as determined by an independent Data Review Committee (DRC). Determinations by the DRC were taken as final, and no attempt was made by the reviewer to adjudicate individual cases. The trial was an open-label, multicenter, single arm study of isavuconazonium for the treatment of invasive aspergillosis in patients with renal impairment or in patients with IFD caused by rare fungi. The study design is presented in Section 6.1. Because Study 9766-CL-0103 was an open-label study, results from Study 9766-CL-0103 are supported by a literature review as well as a matched-case control analysis.

5.3 Discussion of Individual Studies/Clinical Trials

The isavuconazonium development program included two phase 2 studies. Studies 9766-CL-0101 (WSA-CS-001) and 9766-CL-0102 (WSA-CS-002), evaluated isavuconazonium in patients with esophageal candidiasis and as prophylaxis in patients with acute myeloid leukemia (AML), respectively. These phase 2 studies are not considered directly supportive of the proposed indications since they evaluated isavuconazonium in different patient populations, for different indications, and in different clinical settings. The safety data from these trials are incorporated into the integrated safety analysis.

- Study 9766-CL-0101 was a randomized, double-blind, active-control noninferiority study to evaluate the safety and efficacy of isavuconazonium in 160 adult patients with uncomplicated esophageal candidiasis for up to 21 days

of therapy. Patients received isavuconazonium at 3 different doses: 200 mg (po) on day 1 followed by 50 mg (po) qd; 400 mg (po) on day 1 followed by 100 mg (po) qd; or 400 mg (po) on day 1 followed by 400 mg (po) once a week. Fluconazole was dosed at 200 mg (po) on Day 1 followed by 100 mg (po) qd. Results are summarized in Table 11. Isavuconazonium efficacy, as measured by clinical cure and microbiological response, was similar between the different dosing regimens and comparable to fluconazole.

Table 11: Phase 2 Study 9766-CL-0101/ WSA-CS-001: Results Summary of Treatment of Esophageal Candidiasis

Treatment Arm Number of Patients Enrolled/	Endpoint (Population)	Statistic	Treatment Group†			
			ISA Group A (n = 38)	ISA Group B (n = 40)	ISA Group C (n = 38)	Fluconazole (n = 37)
ISA 122/117 Fluconazole 48/36	Endoscopically Confirmed Clinical Cure At EOT (PP) Primary endpoint	% (n/N)	94.7 (36/38)	97.5 (39/40)	94.7 (36/38)	94.6 (35/37)
		Treatment Difference (95% CI) ‡	-0.5 (-10, 9.4)	3.5 (-5.6, 12.7)	-0.2 (-9.8, 9.4)	-
		P§	0.2011	0.3827	0.3545	-
	Positive¶ clinical response at EOT (PP) Secondary endpoint	% (n/N)	97.4 (37/38)	97.5 (39/40)	94.7 (36/38)	94.6 (35/37)
	Positive¶ clinical response at EOT (MBE/PP) Secondary	% (n/N)	97.3 (36/37)	100 (37/37)	97.1 (34/35)	94.4 (34/36)
	Microbiological eradication†† at EOT (MBE/PP) Secondary endpoint	% (n/N)	94.6 (35/37)	94.6 (35/37)	91.4 (32/35)	100 (36/36)
		Treatment Difference (95% CI) ‡	-5.5 (-13.2, 2.1)	-5.3 (-12.7, 2.1)	-9.4 (-17.2, -1.6)	-

EOT: End-of-therapy; ISA: isavuconazole; PP: Per Protocol (Efficacy-evaluable); MBE/PP: PP patients who had valid baseline and EOT microbiological data.

† Treatment groups: ISA Group A: oral isavuconazonium 200 mg on day 1, 50 mg once daily from day 2 to EOT; ISA Group B: oral isavuconazonium 400 mg on days 1, 7, 14, and 21 (if applicable); ISA Group C: oral isavuconazonium 400 mg on day 1, 100 mg once daily from day 2 to EOT; Fluconazole: oral fluconazole 200 mg on day 1, 100 mg once daily from day 2 to EOT.

‡ Point estimate treatment difference between each ISA Group and fluconazole group. Confidence interval calculated using the Cochran-Mantel-Haenzel method stratified by center.

§ P value calculated using the Breslow-Day Test for homogeneity of odds ratios across centers.

¶ Defined for a patient that has presented with resolution or improvement in both clinical symptoms and endoscopic grades from baseline to EOT.

†† Defined as cytological or histological confirmation that the original causative organism was eradicated.

Source: Adapted from Sponsor Application NDA 207-500, Module 2.7.3, Table 2.1.3

- Study 9766-CL-0102 was an open-label, multicenter, sequential-cohort comparison of 2 dose levels of isavuconazonium administered as prophylaxis therapy in 23 neutropenic adult patients with AML for up to 28 days of therapy. Patients received one of 2 isavuconazonium dose regimens: 400/200/200 mg on Day 1, 200/200 mg on Day 2 and 200 mg/day until end of treatment (EOT) or 800/400/400 mg on day 1, 400/400 mg on Day 2 and 400 mg/day until EOT. Results are summarized in Table 12. Microbiological success (i.e., an absence of breakthrough fungal infections and no requirement for systemic antifungal treatment prior to EOT) was observed in 90% to100% of patients. No significant differences in microbiological success were observed between dosage groups at any evaluation time point.

Table 12: Phase 2 Study 9766-CL-0102/WSA-CS-002: Results Summary of Prophylaxis in Neutropenic AML Patients

Treatment Arm Number of Patients Enrolled/ Completed	Endpoint (Population)	Timepoint	Treatment Group‡			
			Low		High	
			n	%	n	%
ISA Low dose 12/11 ISA High dose 12/12	Microbiological Success†	Day -5 to day -1	11	11 (100%)	12	12 (100%)
		Day 3	8§	8 (100%)	11¶	11 (100%)
		Day 5	8	8 (100%)	11	11 (100%)
		Day 7	8	8 (100%)	10	10 (100%)
		Day 14	6††	5 (83.3%)	8‡‡	8 (100%)
		Day 21	5	5 (100%)	6	6 (100%)
		EOT	8	6 (75.0%)	12	12 (100%)
		Follow-up§§	10	8 (80.0%)	12	12 (100%)
		Late follow-up§§	10	9 (90.0%)	12	12 (100%)

EOT: End of therapy: ISA: Isavuconazonium;

† Microbiological success was defined as absence of breakthrough fungal infections and no requirement for systemic antifungal treatment prior to EOT. Percentages were based on available observations.

‡ Treatment groups: Low dose group: 400/200/200 mg day 1, 200/200 mg day 2 and 200 mg once daily from day three to EOT; High dose group: 800/400/400 mg day 1, 400/400 mg day 2 and 400 mg once daily from day three to EOT.

§ By this time, 2 patients had discontinued treatment due to AEs.
¶ By this time, 1 patient had discontinued treatment due to an AE.
†† By this time, 3 patients had discontinued treatment due to AEs.
‡‡ By this time, 2 patients had discontinued treatment due to AEs.

§§ Follow-up: 14 days after EOT; Late follow-up: 35 days after EOT.

Source: Adapted from Sponsor Application, NDA 207-500, Module 2.7.3, Table 2.1.4

6 Review of Efficacy

The efficacy of isavuconazonium was assessed as a treatment for two indications: invasive aspergillosis (IA) discussed in Section 6.1, and invasive mucormycosis (IM), discussed in Section 6.2.

Efficacy Summary:

The applicant provided adequate evidence of efficacy for approval of isavuconazonium for the treatment of invasive aspergillosis and invasive mucormycosis.

In Trial 9766-CL-0104, non-inferiority of isavuconazonium compared to voriconazole was demonstrated with respect to all-cause mortality through Day 42, the primary endpoint. In the overall population (ITT) all-cause-mortality through Day 42 was 18.6% in the isavuconazonium treatment group and 20.2% in the voriconazole group (treatment difference -1.0% with 95% confidence interval (-7.8%, 5.7%). The results were robust across the mITT and myITT populations.

The key secondary endpoint was overall success at End of Treatment (EOT) as judged by the Data Review Committee (DRC) in patients with proven or probable invasive aspergillosis was based on clinical, mycological, and radiological factors. In this subgroup of patients with proven or probable IA, overall success at EOT was seen in 35% of isavuconazonium -treated patients compared to 38.9% of voriconazole- treated patients.

Additional supportive data for the IA indication was from Trial 9766-CL-0103, an open label, multi-center, non-comparative trial that included patients with renal impairment. Twenty four (24) patients were assessed by the DRC as having IAIA, of whom 20 were renally impaired. The all-cause mortality rate through Day 42 was 12.5% for all patients and 15% for those that were renally impaired. The DRC-assessed overall response at EOT was 34.8% for patients IAwith IAand 30.0% for those that were renally impaired. The results are consistent with those of Trial 9766-CL-0104.

In Trial 9766-CL-0103, 37 mITT-Mucorales patients from the ITT population (n=146) were classified by the DRC as having invasive mucormycosis. Overall mortality was 37.8% [22.5, 55.2] at Day 42 and 43.2% [27.1, 60.5] at Day 84. The primary treatment group mortality was similar to the overall rate, with 33% 42-day mortality and 43% 84-day mortality rates. Overall mortality was 37.8% [22.5, 55.2] at Day 42 and 43.2% [27.1, 60.5] at Day 84. The primary treatment group mortality was similar to the overall rate, with 33% 42-day mortality and 43% 84-day mortality rates. From the scientific literature, a delay of 6 days in initiating therapy resulted in an 84 Day mortality rate of 82.9% [68.9, 96.8]. In the isavuconazole-treated population, 9 of 22 or 40.9% [20.4, 61.5] subjects with hematologic malignancy died by 12 weeks. The upper limit of the 95% confidence interval for mortality in the isavuconazonium treatment group is below

the lower limit of the 95% confidence interval for no treatment at all. The existing scientific literature and Fungiscope database offered a combined estimate of 96.2% [94.0, 98.4] mortality without treatment, but this estimate is confounded because a significant number of diagnoses of IA were made at autopsy.

The key secondary efficacy outcome of DRC assessed overall response rate at EOT in the mITT-Mucorales population was 31.4%. Complete success was judged in 14.3% of patients and partial success in 17.1% of patients. Approximately one third, 28.6% of patients, was assessed as stable. For primary therapy patients, 31.6% of patients were assessed to be a success, with 15.8% of patients assessed to be a complete and 15.8% a partial success. Successful salvage therapy occured in 4 of 11 (36.4%) of patients with refractory IM.

6.1 Indication: Treatment of Invasive Aspergillosis

The indication of invasive aspergillosis is primarily supported by data from a phase 3 trial, 9766-CL-0104. This was a randomized, prospective, double-blind, active comparative group study, compared the efficacy isavuconazonium to voriconazole with a 10% non-inferiority margin. Study 9766-CL-0104 comprised 516 adult patients with suspected invasive fungal disease (IFD) with diagnosis established by an independent Data Review Committee (DRC). A second, open label study, 9766-CL-0103, provides additional supportive evidence in a patient population with invasive aspergillosis and renal impairment (estimated creatinine clearance < 50 mL/min).

6.1.1 Methods

This multicenter study was conducted at 102 centers globally including sites in the US, European Union (EU), South America, Asia and the Middle East, over a six year study period from March, 2007 to March, 2013. There was a pause between January 2009 and March 2011 during which time there was a change in sponsorship from Basilea to Astellas, and genotoxicity studies were performed. Voriconazole, the FDA approved standard of care for the treatment of IA, was selected as the active comparator. Subjects with renal impairment (creatinine clearance <50 mL/min) were excluded since IV voriconazole contains the solubilizing agent sulfobutyl ether beta-cyclodextrin sodium (SBECD), which may accumulate and exacerbate renal impairment.

Inclusion Criteria (Quoted From Study Report):

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 (Quoted From Study Report):

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 isavuconazonium.
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.

Intervention:
The planned treatment duration was 84 days. Isavuconazonium and voriconazole were administered using IV infusion for loading doses in the first 48 and 24 hours, respectively, and were administered either using IV infusion or oral capsules for maintenance doses from Day 3 or Day 2, respectively, to end of treatment (EOT). Loading doses were administered as 200 mg every 8 hours IV for isavuconazonium and as 6 mg/kg every 12 hours IV for voriconazole. Maintenance doses were administered every 12 hours as 200 mg isavuconazonium or placebo (IV or oral) and 4 mg/kg IV or 200 mg oral voriconazole.

Test Product, Dose and Mode of Administration: Isavuconazonium for IV administration was provided as a lyophilized powder for IV infusion. Each IV vial contained 372.6 mg of isavuconazonium sulfate (BAL8557) corresponding to 200 mg isavuconazonium (BAL4815) and included mannitol and sulfuric acid as excipients. Isavuconazonium (200 mg) was dissolved in 250 mL of a compatible infusion solution. Isavuconazonium for oral administration was provided as capsules, each containing 186.3 mg of isavuconazonium sulfate (BAL8557) corresponding to 100 mg of active isavuconazonium (BAL4815). Voriconazole for IV administration was provided as a lyophilized powder. Each vial contained 200 mg voriconazole and sulfobutyl ether beta-cyclodextrin sodium supplied in single use 30 mL clear glass vials to be dissolved in 250 mL of a compatible infusion solution. VRC for oral administration was provided as capsules, each containing a 200 mg tablet of VRC.

Asessments: Survival status was recorded at Day 42, Day 84 and 4 weeks after the last administration of study drug. A follow-up visit was performed 4 weeks (± 7 days) after the last dose of study drug and was not necessarily the end of study visit for a given patient. The DRC and Investigators evaluated the clinical response to treatment for patients at Day 42, Day 84 and EOT. Baseline mycological assessment (screening through day 7) of the patient's IFD status was performed according to best local practice using local and central laboratories, including samples for fungal culture as well as samples from the infected site for histology and cytology. Baseline radiological assessments of IFD were performed during the screening period. The European Organization for the Research and Treatment of Cancer/Mycoses Study Group

(EORTC/MSG) definitions of IFD were used (**See Appendix 9.4**). Mycological and radiological assessments were also performed at Day 42, Day 84 and EOT. Independent radiologists were responsible for providing a written evaluation of each image and an assessment of radiological response. A DRC, which consisted of experts in the field of fungal infections, was established to conduct a data review for all patients who received at least one dose of study drug. The DRC adjudicated, independently from the Sponsor and the study Investigators, the categorization of the IFD and evaluated clinical, mycological, radiological and overall responses at day 42, day 84 and EOT.

Serum galactomannan (GM) antigen was drawn at screening and on days 1, 2 and EOT for patients with *Aspergillus*. In addition, serum samples obtained at screening, Days 1, 2, 14, 28, 42, 84 and EOT for GM antigen assay (or collected any time while patients with probable, proven or possible Aspergillus were still receiving study drug. A single serum GM value of ≥ 0.7 or two consecutive values each of ≥ 0.5 to < 0.7 (i.e., from two separate blood draws) were considered a positive result except in patients receiving concomitant amoxicillin-clavulanate, piperacillin-tazobactam or Plasma-Lyte™ (Baxter). Patients with BAL GM values of ≥ 1.0 were allowed to enroll as possible IFD.

The Investigator evaluated safety by monitoring treatment-emergent adverse events (TEAEs) and findings from physical examination (including eye exam), vital signs, laboratory tests, 12-lead electrocardiogram (ECG) and concomitant medication/surgery.

Laboratory investigations included hematology, biochemistry, urinalysis and hepatotoxicity tests collected at screening, and at study visits on Days 7, 14, 28, 42, EOT, and at follow-up.

Blood pressure (systolic blood pressure [SBP] and diastolic blood pressure [DBP]; mmHg), pulse rate (PR [beats per minute]), and body temperature (BT, °C or °F) (the most abnormal temperature within this window was recorded) were assessed at screening and on days 1, 2, 3, 7, 14, 28, 42, 84, and every 4 weeks thereafter through EOT and follow-up visit 1. Twelve-lead ECG recordings were obtained at screening, on days 1, 14, 42, and 84, and every 4 weeks thereafter until EOT.

Physical examinations were conducted at screening and on Days 42, 84 and EOT. Vital signs were assessed at screening and on days 1, 2, 3, 7, 42, 84 and EOT. Eye examinations, consisting of visual acuity, confrontational visual field testing and color perception testing, was conducted at screening, day 14, 28, 42 and EOT.

Blood sampling for the analysis of plasma trough concentrations was obtained for all patients. The samples were drawn prior to administration of study drug on Days 7, 14, 28, 42, 84 and every 4 weeks thereafter until day 180/EOT. Plasma samples were collected predose, and 1.5, 3, 4, 6, 12 and 24 hours after the start of infusion or drug intake on day 7 (+ 1 day) or preferably day 14 (± 2 days) for pharmacokinetic profiling of isavuconazonium in patients enrolled in the pharmacokinetic substudy.

Efficacy Endpoints:
The primary objective was to compare all-cause mortality through Day 42 following primary treatment with isavuconazonium versus voriconazole in patients with invasive fungal disease (IFD) caused by *Aspergillus* species. The secondary objectives of the study were to characterize the safety and tolerability as well as DRC adjudicated assessments of efficacy of treatment with isavuconazonium or voriconazole. The exploratory objectives include pharmacokinetic analyses.

Non-inferiority Margin Justification:
In the absence of historical placebo-controlled trials, an estimate of the all-cause mortality rate through Day 42 in 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 conducted by the Applicant. This estimation was further consistent with a mortality rate of 100% in untreated patients reported by Denning[4]. The historical all-cause mortality rate through Day 42 for voriconazole was estimated at 18.8% (95% CI:12.4%, 25.1%) based on the randomized comparative study evaluating voriconazole and amphotericin B[5]. An estimate of effect size (M_1) for voriconazole compared to placebo invasive aspergillosis patients for all-cause mortality through Day 42 is at least 50.0%, so a 10% NIM preserves at least 80% of the estimated voriconazole treatment effect.

6.1.2 Demographics

The baseline characteristics of the ITT population are presented in Table 13. Overall, 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%). A majority, 83.9%, of patients had a hematologic malignancy, 20.3% of patients had prior allogeneic BMT/hematopoietic stem cell transplantation (HSCT), and 65.5% were neutropenic. Approximately half of patients (51.5%) were microbiologically diagnosed as having *Aspergillus* infection based on only serum galactomannan (GM). *Aspergillus sp*. was the only identified causal organism in 32.4% of patients with the most common pathogen being *Aspergillus fumigatus*.

Table 13: Summary of Demographics and Baseline Characteristics (ITT Population - Study 9766-CL-0104)

Parameter Category/Statistics	ISA (n = 258)	VRC (n = 258)	Total (n = 516)
Age (years)			
Mean	51.1	51.2	51.1
Median	54.0	53.5	54.0
Min - Max	17 - 82	18 - 87	17 - 87

[4] Denning DW. "Therapeutic outcome in invasive aspergillosis." Clin Infect Dis. 1996;23:608-15.
[5] Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann J-W, et al. "Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis". N Engl J Med. 2002;347:408-15.

Category	n (%)	n (%)	n (%)
Age Category (years)			
≤ 45	94 (36.4%)	101 (39.1%)	195 (37.8%)
> 45 - ≤ 65	108 (41.9%)	99 (38.4%)	207 (40.1%)
> 65	56 (21.7%)	58 (22.5%)	114 (22.1%)
> 75	10 (3.9%)	7 (2.7%)	17 (3.3%)
Sex			
Male	145 (56.2%)	163 (63.2%)	308 (59.7%)
Female	113 (43.8%)	95 (36.8%)	208 (40.3%)
Race			
White	211 (81.8%)	191 (74.3%)	402 (78.1%)
Black or African American	1 (0.4%)	1 (0.4%)	2 (0.4%)
Asian	45 (17.4%)	64 (24.9%)	109 (21.2%)
Other	1 (0.4%)	1 (0.4%)	2 (0.4%)
Ethnicity			
Hispanic or Latino	22 (8.5%)	9 (3.5%)	31 (6.0%)
Not Hispanic or Latino	236 (91.5%)	248 (96.5%)	484 (94.0%)
Missing	0	1	1
BMI Category (kg/m^2)			
< 25	154 (61.4%)	168 (67.5%)	322 (64.4%)
≥ 25 - 30	70 (27.9%)	59 (23.7%)	129 (25.8%)
≥ 30	27 (10.8%)	22 (8.8%)	49 (9.8%)
Missing	7	9	16
Geographical Region†			
North America	30 (11.6%)	28 (10.9%)	58 (11.2%)
Western Europe, Australia and New Zealand	105 (40.7%)	107 (41.5%)	212 (41.1%)
Other Regions	123 (47.7%)	123 (47.7%)	246 (47.7%)
Hematologic malignancy	211 (81.8%)	222 (86.0%)	433 (83.9%)
Acute myeloid leukaemia	99 (38.4%)	126 (48.8%)	225 (43.6%)
Acute lymphocytic leukaemia	30 (11.6%)	24 (9.3%)	54 (10.5%)
Non-Hodgkin's lymphoma	18 (7.0%)	8 (3.1%)	26 (5.0%)
Chronic lymphocytic leukaemia	10 (3.9%)	13 (5.0%)	23 (4.5%)
Refractory anaemia with an excess of blasts	15 (5.8%)	4 (1.6%)	19 (3.7%)
Aplastic anaemia	9 (3.5%)	7 (2.7%)	16 (3.1%)
Myelodysplastic syndrome	7 (2.7%)	8 (3.1%)	15 (2.9%)
Chronic myeloid leukaemia	5 (1.9%)	8 (3.1%)	13 (2.5%)
Multiple myeloma	5 (1.9%)	7 (2.7%)	12 (2.3%)
B-cell lymphoma	4 (1.6%)	4 (1.6%)	8 (1.6%)
T-cell lymphoma	3 (1.2%)	4 (1.6%)	7 (1.4%)
Acute promyelocytic leukaemia	4 (1.6%)	1 (0.4%)	5 (1.0%)
Hodgkin's disease	2 (0.8%)	3 (1.2%)	5 (1.0%)
Prior Allogeneic BMT/HSCT	54 (20.9%)	51 (19.8%)	105 (20.3%)
Uncontrolled Malignancy at Baseline	173 (67.1%)	187 (72.5%)	360 (69.8%)
Neutropenic‡§	163 (63.2%)	175 (67.8%)	338 (65.5%)
Corticosteroid use	48 (18.6%)	39 (15.1%)	87 (16.9%)
Chronic obstructive pulmonary disease	5 (1.9%)	3 (1.2%)	8 (1.6%)
T-Cell Immunosuppressant use	111 (43.0%)	109 (42.2%)	220 (42.6%)
Diabetes mellitus	4 (1.6%)	0	4 (0.8%)
eGFR-MDRD (mL/min/1.73 m^2)			

< 60	20 (8.0%)	33 (13.2%)	53 (10.6%)
≥ 60	231 (92.0%)	217 (86.8%)	448 (89.4%)

Age was calculated relative to informed consent date.
ITT: all randomized patients who received at least one dose of study drug
ANC: absolute neutrophil count; BMI: body mass index; BMT: bone marrow transplant;
eGFR- MDRD: estimated glomerular filtration rate Modification of Diet in Renal Disease;
HSCT: hematopoietic stem cell transplantation; ISA: isavuconazonium; ITT: intent-to-treat; US: United States; VRC: voriconazole
† 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.
‡ The presence or absence of neutropenia was defined as ANC < 0.5 x 10^9/L (< 500/mm^3) and was determined by the investigator.
Source: Adapted from 9766-CL-0104 Study Report Tables 12.1.2.1.1 , 12.1.2.2.1

MO Comment: For the ITT population, the treatment groups were well balanced for baseline characteristics

The majority of patients in the mITT population had presumed *Aspergillus* based on galactomannan criteria only (isavuconazonium 50.3% and voriconazole 52.7%), as assessed by the DRC (Table 14). The majority of the remaining patients in both treatment groups with proven or probable IFD were reported to have *Aspergillus* species. The most common pathogen at baseline was *Aspergillus fumigatus* in both treatment groups.

Table 14: DRC Assessment of Pathogen Causing IFD at Baseline (mITT Population

Pathogen Causing IFD Pathogen	**ISA (n = 143)**	**VRC (n = 129)**	**Total (n = 272)**
***ASPERGILLUS* species ONLY**	49 (34.3%)	39 (30.2%)	88 (32.4%)
Aspergillus fumigatus	32 (22.4%)	21 (16.3%)	53 (19.5%)
Aspergillus flavus	10 (7.0%)	12 (9.3%)	22 (8.1%)
Aspergillus niger	6 (4.2%)	2 (1.6%)	8 (2.9%)
Aspergillus terreus	4 (2.8%)	2 (1.6%)	6 (2.2%)
Aspergillus NOS	1 (0.7%)	3 (2.3%)	4 (1.5%)
Aspergillus ustus	0	1 (0.8%)	1 (0.4%)
Aspergillus sydowi	1 (0.7%)	0	1 (0.4%)
***ASPERGILLUS* Species PLUS OTHER**	3 (2.1%)	1	4 (1.5%)
Scedosporium NOS	1 (0.7%)	1	2 (0.7%)
Aspergillus fumigatus	0	1	1 (0.4%)
Aspergillus flavus	1 (0.7%)	0	1 (0.4%)
Aspergillus terreus	1 (0.7%)	0	1 (0.4%)
Aspergillus NOS	1 (0.7%)	0	1 (0.4%)
Absidia corymbifera	1 (0.7%)	0	1 (0.4%)
Absidia NOS	1 (0.7%)	0	1 (0.4%)
NON-*ASPERGILLUS* Species ONLY	**5 (3.5%)**	**6**	**11 (4.0%)**
Fusarium NOS	1 (0.7%)	3	4 (1.5%)
Fusarium solani	2 (1.4%)	0	2 (0.7%)
Rhizopus NOS	1 (0.7%)	0	1 (0.4%)
Mucor NOS	0	1	1 (0.4%)
Exserohilum rostratum	0	1	1 (0.4%)

Penicillium marnefii	0	1	1 (0.4%)
Penicillium NOS	0	1	1 (0.4%)
Trichosporon inkin	1 (0.7%)	0	1 (0.4%)
MOLD Species NOS	**14 (9.8%)**	**1**	**29 (10.7%)**
No pathogen identified – Mycology based on GM	**72 (50.3%)**	**68 (52.7%)**	**140 (51.5%)**
Serum Positive GM only	64 (44.8%)	56 (43.4%)	120 (44.1%)
BAL GM Positive only	0	0	0
Serum GM and BAL GM Positive	7 (4.9%)	12 (9.3%)	19 (7.0%)

A patient could have more than one pathogen causing IFD within each category. The incidence for each category is mutually exclusive.

mITT: intent-to-treat patients who had proven or probable IFD as determined by the DRC

DRC: Data Review Committee; GM: galactomannan; IFD: invasive fungal disease; ISA: isavuconazonium; mITT: modified intent-to-treat; NOS: not otherwise specified; VRC:

voriconazole.

Source: 9766-CL-0104 Study Report Table 12.1.5.1

The DRC-assessed location of IFD at baseline for the mITT population showed that most isavuconazonium- and voriconazole-treated patients had lower respiratory tract disease (LRTD) only (81.1%, 116/143; and 82.9%, 107/129, respectively) (Table 15). The most common extrapulmonary site of infection was sinus, followed by disseminated infection.

Table 15: DRC-assessed location of IFD at baseline for the mITT population, Study 9766-CL-0104

IFD Location Categories	ISA (n = 143)	VRC (n = 129)	Total (n = 272)
LRTD Only	116 (81.1%)	107 (82.9%)	223 (82.0%)
LRTD Plus Other Organ	12 (8.4%)	15 (11.6%)	27 (9.9%)
Non-LRTD Only	15 (10.5%)	7 (5.4%)	22 (8.1%)
Non-LRTD Location*	**27 (18.9%)**	**22 (17.1%)**	**49 (18.0%)**
Disseminated	5 (3.5%)	8 (6.2%)	13 (4.8%)
Brain	3 (2.1%)	2 (1.6%)	5 (1.8%)
Eye	4 (2.8%)	1 (0.8%)	5 (1.8%)
Liver	0	3 (2.3%)	3 (1.1%)
Sinus	17 (11.9%)	13 (10.1%)	30 (11.0%)
Skin	3 (2.1%)	5 (3.9%)	8 (2.9%)
Other	8 (5.6%)	5 (3.9%)	13 (4.8%)

*A subject may have more than one Non LRTD Location and hence may be counted in more than one location.
Source: Adapted from 9766-CL-0104 Table 12.1.7.2

Study drug exposure was similar between the arms of the study, as summarized in Table 16. The median duration was 45 days (range 1 to 102) for isavuconazonium and 46.5 days (range 1 to 88) for voriconazole.

Table 16: Study Drug Duration (ITT Population - Study 9766-CL-0104)

Characteristics	ISA (n = 258)	VRC (n = 258)	Total (n = 516)
Total Duration (days)			

n	258	258	516
Mean (SD)	47.0 (32.35)	46.4 (32.06)	46.7 (32.18)
Median	45.0	46.5	45.0
Min - Max	1 - 102	1 - 88	1 - 102

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).

ITT: all randomized patients who received at least one dose of study drug; ISA: isavuconazonium; ITT: intent-to-treat; VRC: voriconazole.

Source: 9766-CL-0104 Table 12.2.1.4

6.1.3 Subject Disposition

Approximately 510 consenting adult patients were planned to be enrolled. A total of 532 patients were consented for the study. Of these, 527 patients were randomized, and 516 patients took at least 1 dose of study drug and were included in the Intent-to-treat (ITT) population. There were 5 screening failures (consented, but not randomized), and 11 subjected randomized, but did not receive study drug (Table 17). Figure 1 depicts the study flow chart.

Figure 1: Flow Chart of the Study Population Disposition, Trial 9766-CL-0104

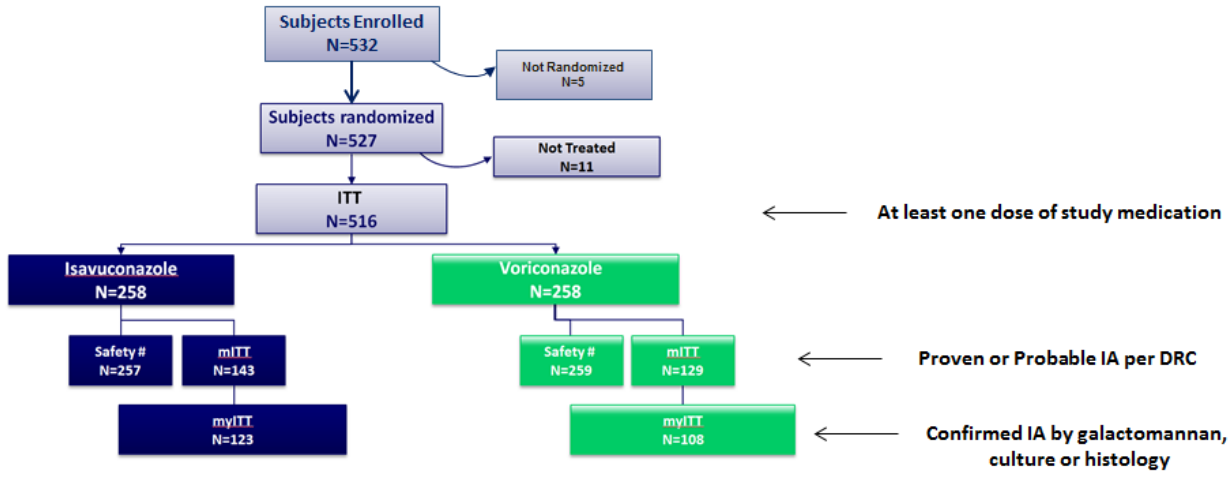


Table 17: Description of Patients Randomized, but Not Treated in Study 9766-CL-0104 (N=11)

Patient No.	Reason Treatment Not Given
11305	Creatinine clearance was less than 30 at Entry
11803	Withdrew consent
320306	Mechanical ventilation at Entry
320426	Withdrew consent
360201	Randomized by mistake.
391301	ALT/AST ≥ 5 X ULN at Entry
660103	Withdrew consent

660104 Death
660708 Violation of Entry criteria
911405 AE/Intercurrent illness
970108 Withdrew consent

MO Comment: Patient 860201 was randomized to the isavuconazonium treatment group, but received voriconazole treatment for the first 7 days and then was switched to isavuconazonium oral study drug. This patient was included in the isavuconazonium treatment group for the ITT population and was included in the voriconazole treatment group for the safety analysis set.

Reasons for drug discontinuation during treatment and follow-up periods for the ITT population are summarized in Table 18. Patients identified as "completed" during the treatment period received the maximum 84 days of treatment or had a successful overall outcome and received a minimum of 7 days of therapy. Patients identified as completed in the Follow-up Period, completed a follow-up visit after the EOT visit.

Table 18: Primary Reasons for Discontinuation Duringduring Treatment and Follow-up Periods (ITT Population), Study 9766-CL-0104

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

ISA: isavuconazonium; ITT: intent-to-treat; VRC: voriconazole.

† This information was collected up to amendment 2.

‡ This information was collected from amendment 3.

Source: Adapted from 9766-CL-0104 Study Report Table 12.1.1.3.1

MO Comment: Overall, the number of patients who prematurely discontinued treatment was similar between the two treatment groups (ISA 54.3%, 140/258; VRC 53.5%, 138/258). The 3 most common reasons for discontinuation of treatment (based on the Investigator's report), were AE/Intercurrent Illness, Insufficient Therapeutic Response and Death.

The different analysis sets used in this study are as follows:

- The intent to treat (ITT) population consisted of all randomized patients who received at least one administration of study drug. For this population, data were analyzed by the treatment group that patients were randomized to even though they might not be compliant with the protocol or assigned treatment.
- The modified ITT (mITT) population consisted of ITT patients who had proven or probable IFD as determined by the DRC. Patients with appropriate host factor and clinical features were considered to have probable IFD based on the GM criteria (GMc) set forth in the protocol: 2 consecutive serum GM values ≥ 0.5 or at least 1 serum GM value ≥ 0.7.
- The modified ITT FDA (mITT-FDA) population consisted of ITT patients who had proven or probable IFD. Patients with an appropriate host factor and clinical features were considered to have probable IFD based on the GM. The FDA GMc used for the mITT-FDA population was 2 consecutive serum GM values ≥ 0.5 or at least 1 serum or BAL GM value ≥ 1.0.
- The mycological ITT (myITT) population is the subset of the mITT population consisting of patients with **confirmation** of proven or probable diagnosis of invasive aspergillosis or other filamentous fungi based on cytology, histology, culture or GM criteria.
- The per protocol analysis sets (PPS) were subsets of the ITT (PPS-ITT) or mITT (PPS-mITT) populations that included patients who did not deviate from prespecified criteria in the statistical analysis plan (described below).
- The safety analysis set (SAF) consisted of all randomized patients who received at least one dose of study drug. For the SAF, data were analyzed according to the study drug that patients received as the first dose even if it was different from the study drug to which they were randomized.

Table 19: Characterization of Analysis Populations, Study 9766-CL-0104

	Isavuconazonium	Voriconazole
ITT	258	258
Proven	29 (11.2)	36 (14.0)
Probable	114 (44.2)	93 (36.0)
Possible	88 (34.1)	108 (41.9)
No IFD	27 (10.5)	21 (8.1)
mITT	143	129
Aspergillus species only	49 (34.3)	39 (30.2)
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)
No pathogen identified*	72 (50.3)	68 (52.7)
myITT	123	108

Probable by serum GM only	71 (57.7)	68 (63.0)
Proven or probable Aspergillosis by culture or histology	52 (42.3)	40 (37.0)
PPS-ITT	172	175
PPS-mITT	108	96
Safety (SAF)	257	259

*Probable based on GM with the exception of 1 isavuconazonium subject who was based on a non-sterile site and had adequate host factors and clinical and radiological factors
Sources: Modified from Cheryl Dixon, PhD, Biometrics Reviewer, and 9766-CL-0104 Study report Tables 12.1.1.2 and 12.3.2.4

The PPS dataset was constructed from prespecified criteria within the SAP. The number and percentage of patients excluded from each criterion are summarized in Table 20. Out of the 516 patients in the ITT analysis, 169 patients (32.8%) were excluded from the PPS-ITT: 86 of 258 isavuconazonium treated patients (33.3%) and 83 of 258 voriconazole treated patients (32.2%).

Table 20: Patients from ITT Population Excluded from Analysis per PPS Criterion, Study 9766-CL-0104

	ISA (n = 258)	**VRC (n = 258)**	**Total (n = 516)**
Overall	**86 (33.3%)**	**83 (32.2%)**	**169 (32.8%)**
Met Exclusionary #5 (evidence of hepatic dysfunction only)†	2 (0.8%)	3 (1.2%)	5 (1.0%)
Met Exclusionary #6 (use of prohibited medication within 5 days prior to first administration of study drug)	1 (0.4%)	2 (0.8%)	3 (0.6%)
Met Exclusionary #8 (had chronic aspergillosis, aspergilloma or ABPA)	6 (2.3%)	2 (0.8%)	8 (1.6%)
Met Exclusionary #10 (received > 4 cumulative days of itraconazole, voriconazole, or posaconazole	4 (1.6%)	10 (3.9%)	14 (2.7%)
Met Exclusionary #12 (has a condition that might jeopardize adherence to the protocol)	1 (0.4%)	0	1 (0.2%)
Met Exclusionary #14 (was previously enrolled in another phase 3 study with ISA)	0	0	0
Met Exclusionary #15 (treatment with other investigational drug within prior 30 days)	0	0	0
Met Exclusionary #16 (unlikely to survive 30 days or on mechanical ventilation)	0	0	0
Received less than 7 days of study drug	29 (11.2%)	30 (11.6%)	59 (11.4%)
Withdrew consent or lost-to-follow-up AND last evaluation day prior to day 42	4 (1.6%)	1 (0.4%)	5 (1.0%)
Took a different study drug during the treatment period	3 (1.2%)	3 (1.2%)	6 (1.2%)
Took prohibited concomitant medications for at least 3 consecutive days	26 (10.1%)	25 (9.7%)	51 (9.9%)
Took mold active systemic AFT for at least 3 consecutive days	3 (1.2%)	1 (0.4%)	4 (0.8%)
Unblinded patients as documented in the eCRF	2 (0.8%)	5 (1.9%)	7 (1.4%)
Patients that DRC assessed as having no IFD	27 (10.5%)	21 (8.1%)	48 (9.3%)

A subject may have more than one reason for being excluded from per protocol analysis set and hence may be counted in more than one category. The exclusion criteria are from protocol amendment 4.
Prohibited concomitant medications and mould active systemic AFT other than the study medication were considered after first dose of study drug through the last dose of study medication for at least 3 consecutive days.
ABPA: allergic bronchopulmonary aspergillosis; AFT: antifungal therapy; DRC: Data Review Committee; eCRF: electronic case report form; IFD: invasive fungal disease; ISA: isavuconazonium; ITT: intent-to-treat; PPS: Per Protocol Set; VRC: voriconazole.
† Patients that the Sponsor confirmed with hepatic dysfunction were counted.
Source: Adapted from Study Report 9766-CL-0104 Table 12.1.1.4.1

MO Comment: The number of patients excluded from the PPS analysis was similar between treatment groups. The most common reason for exclusion was for receiving < 7 days of study drug (ISA 11.2%, 29/258; VRC 11.6%, 30/258).

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint was 42 day all-cause mortality. Both mortality endpoints and overall clinical responses have been used as the basis for determining efficacy of other drug approved for invasive aspergillosis, such as voriconazole (Vfend®) (NDA 21-266), and caspofingin (Cancidas®) (NDA 21-227). The Vfend® Study 307/602 was a randomized, controlled, open-label, initial therapy study of voriconazole versus amphotericin B in 277 patients. The primary efficacy endpoint in Study 307/602 was overall response as assessed by a Data Review Committee (DRC) at Day 84, as well as Day 84 mortality. The caspofungin study used a DRC-adjudicated overall response in 69 patients between the ages of 18 and 80 years with invasive aspergillosis who were enrolled in an open-label, non-comparative study.

MO Comment: In the current trial, a DRC was utilized both for diagnosis of IA and determining outcomes. The charter was adequate in scope and design, and no attempt was made by the reviewer to re-adjudicate the findings of the DRC.
The prospective, randomized, active controlled design satisfies the regulations on adequate and well-controlled trials (21 CFR 314.126). The trial design is robust and provides a reasonable assessment of benefit.

The all-cause mortality rate through Day 42 in the ITT population was 18.6% and 20.2% in the isavuconazonium and voriconazole treatment groups, respectively. This study met the primary objective of demonstrating noninferiority of isavuconazonium relative to voriconazole since the upper bound of the 95% CI (5.9%) (ISA-VRC: -1.0%) is lower than the prespecified NIM of 10%. The NIM of 10% was satisfied in each of the study analysis groups, as summarized in Table 21 in bold face.

Table 21: All-cause Mortality Through Day 42 Primary Endpoint, Study 9766-CL-0104

	Isavuconazonium	Voriconazole	Difference and 95% CI*
ITT**	48/258 (18.6%)	52/ 258 (20.2%)	-1.0 (-8.0, **5.9**)
mITT	28/143 (19.6%)	30/129 (23.3%)	-2.6 (-12.6, **7.3)**
mITT-FDA	28/147 (19.0%)	28/128 (21.9%)	-2.1 (-11.9, **7.7**)

myITT	23/123 (18.7%)	24/108 (22.2%)	-2.7 (-13.6, **8.2**)
PPS-ITT	26/172 (15.1%)	31/175 (17.1%)	−2.6 (-10.3, **5.1**)

*adjusted difference (Isa- Vori) and CI calculated using stratified CMH method with the strata of geographic region, allogeneic BMT status, and uncontrolled malignancy status- CI's are slightly different from those presented in study report but conclusions are the same

**survival status unknown for only 3 isavuconazonium and 2 voriconazole ITT subjects

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

Source: Cheryl Dixon, Ph.D., Biostatistics Reviewer, PPS-ITT from 9766-CL-0104 Tables 12.3.1.1, 12.3.1.4 and 12.3.7.1.3.

All-cause Mortality Through Day 42 for Various Diagnostic Groups

All-cause mortality through day 42 was analyzed by diagnostic group is presented in Table 22.

Table 22: All-cause Mortality through Day 42 by Diagnostic Group, Study 9766-CL-0104

	Isavuconazonium	Voriconazole
Proven	7/29 (24.1)	7/26 (19.4)
Probable	21/114 (18.4)	23/93 (24.7)
Possible	15/88 (17.1)	19/108 (17.6)
No IFD	5/27 (18.5)	3/21 (14.3)
Aspergillus species only	5/49 (10.2)	8/39 (20.5)
Aspergillus species plus other mould species	3/3	0/1
Non-Aspergillus species only	3/5	0/6
Mould species NOS	2/14 (14.3)	6/15 (40.0)
No pathogen identified	15/72 (20.8)	16/68 (23.5)

Source: Cheryl Dixon, Ph.D., Biometrics Reviewer

MO Comment: Mortality appeared to be balanced between arms and was preserved as the certainty of diagnosis increased from possible to probable, and from probable to proven infection. While the numbers are low, one half of the isavuconazonium-treated patients in the Aspergillus only group (5/49) died as compared to voriconazole-treated patients (8/39). The benefit of isavuconazonium treatment in this particular sub-group is meaningful since this patient subset represents a population with positively identified mono-infection with Aspergillus*.*

6.1.5 Analysis of Secondary Endpoints(s)

All-cause Mortality Through Day 84 for Various Populations

All-cause mortality through Day 84 for the ITT population was 29.1% in isavuconazonium-treated patients and 31.0% in voriconazole- treated patients (Table 23). The treatment differences (ISA-VRC) ranged from -5.7% to -1.4% across the various populations, consistent with lower mortality rates in the isavuconazonium treatment group across populations. The upper bound of the 95% CIs around the adjusted treatment differences ranged from 5.4% to 6.4% across the various populations.

Table 23: All-cause Mortality through Day 84, Study 9766-CL-0104

	Isavuconazonium	Voriconazole	Difference and 95%

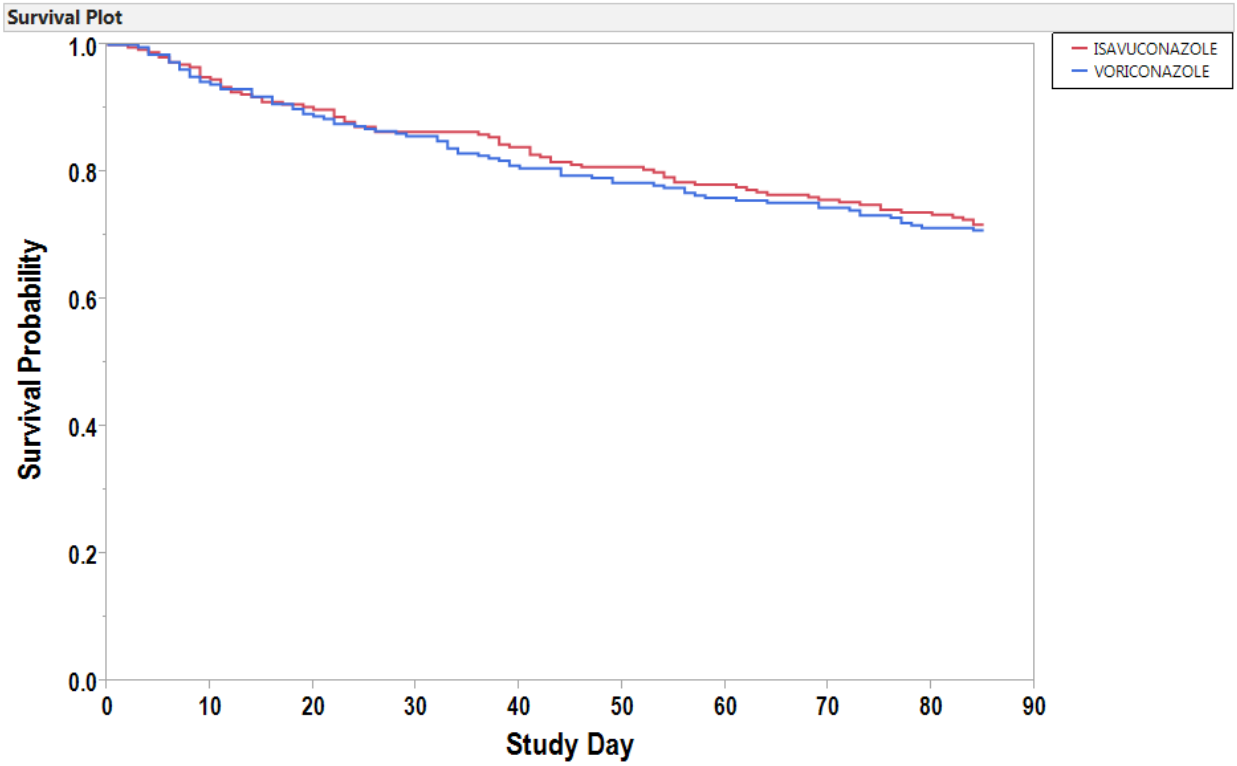
			CI*
ITT**	75/258 (29.1)	80/258 (31.0)	-1.4 (-9.2, 6.4)
mITT	43/143 (30.1)	48/129 (37.2)	-5.5 (-16.3, 5.4)
mITT-FDA	41/147 (27.9)	43/128 (33.6)	-4.7 (-15.4. 6.0)
myITT	35/123 (28.5)	39/108 (36.1)	-5.7 (-17.5, 6.0)
PPS-ITT#	43/172 (25.0)	48/175 (27.4)	-2.8 (-11.9, 6.2)

*adjusted difference (Isa-Vori) and CI calculated using stratified CMH method with the strata of geographic region, allogeneic BMT status, and uncontrolled malignancy status- CI's are slightly different from those presented in study report but conclusions are the same
**survival status unknown for only 3 isavuconazonium and 5 voriconazole ITT subjects
Source: Cheryl Dixon, Ph.D., Biometrics Reviewer, except PPS-ITT Analysis, which was modified from Study Report 9766-CL-0104 Tables 12.3.1.6, 12.3.1.8, 12.3.7.1.4 and 12.3.7.1.6

MO Comment: As expected, mortality rates were numerically higher in both treatment groups through Day 84 than Day 42, but the treatment differences at Day 84 remain similar to that found through Day 42. The point estimate of 84 Day mortality generally favored isavuconazonium, and the largest value of -5.7 was observed in the myITT population (confirmed diagnosis). Nevertheless, the CI intervals pass through 0, indicating that superiority was not achieved. The 10% NIM remained preserved.

The Kaplan-Meier survival curve for 84 Day survival in the ITT populations is presented in Figure 2. The estimate of mortality rate through Day 84 was 28.2% in the isavuconazonium treatment group and 29.3% in the voriconazole treatment group, and the 95% CI around the treatment difference through Day 84 (-1.1%) was (-8.944%, 6.739%). Patients lost to follow up who were counted as dead in the crude mortality rate calculation were censored at the last day of assessment for this K-M survival analysis.

Figure 2: Survival Probability Through Day 84 by Kaplan-Meier Method (ITT Population – Study 9766-CL-0104)



Source: Reviewer generated with JMP11 using the 9766-CL-0104 ADSL Dataset.

MO Comment: I agree that the K-M survival analysis supports the results from the primary analysis in the ITT population, as the survival curves are nearly superimposed.

The key secondary efficacy endpoint of DRC-assessed overall response at EOT was analyzed for the mITT and myITT populations and response rates for success were similar for isavuconazonium- and voriconazole-treated patients (35.0% and 36.4%, respectively). The 95% CI around the adjusted treatment difference (VRC-ISA: 1.6%) was (-9.336%, 12.572%) (Table 24).

Complete success was achieved by 17 (11.9%) and 13 (10.1%) patients in the isavuconazonium and voriconazole treatment groups, respectively. Partial success was achieved by 33 (23.1%) and 34 (26.4%) patients in the isavuconazonium and voriconazole treatment groups, respectively. For this analysis, any visits that the DRC assessed as not done were considered a failure for that visit. A death before Day 42 was also considered a failure, even if the DRC assessed the patient to be a success prior to death.

Table 24: DRC- Assessed Overall Response at EOT- Key Secondary Outcome for Study 9766-CL-0104

	Isavuconazonium	Voriconazole	Difference and 95% CI*

mITT- Success	50/143 (35.0)	47/129 (36.4)	-1.6 (**-12.8**, 9.6)
Complete	17 (11.9)	13 (10.1)	
Partial	33 (23.1)	34 (26.3)	
Stable	42 (29.4)	33 (25.6)	
Progression	51 (35.7)	49 (38.0)	
mylTT- Success	43/123 (35.0)	42/108 (38.9)	-4.0 (**-16.3**, 8.4)
Complete	13 (10.6)	12 (11.1)	
Partial	30 (24.4)	30 (27.8)	
Stable	36 (29.3)	29 (26.9)	
Progression	44 (36.8)	37 (34.4)	

*adjusted difference (Isa-Vori) and CI calculated using stratified CMH method with the strata of geographic region, allogeneic BMT status, and uncontrolled malignancy status- CI's are slightly different from those presented in study report but conclusions are the same also study report presents (Vori-Isa)
Source: Cheryl Dixon, Ph.D., Biometrics Reviewer

DRC-assessed Clinical, Mycological and Radiological Responses at EOT (mITT Population)

The DRC assessments of clinical, mycological and radiological response rates at EOT were similar between treatment groups for the mITT and mylTT populations (Table 25). The difference in DRC adjudicated outcomes for the 42 Day and 84 Day analysis periods are summarized in Table 26.

Table 25: DRC- assessed Clinical, Mycological, and Radiological Response EOT, Study 9766-CL-0104

Population	Response	Isavuconazonium	Voriconazole	Difference and 95% CI*
mITT	Clinical Response	85/143 (59.4)	73/129 (56.6)	0.6 (-10.6, 11.8)
	Complete	61 (42.7)	53 (41.4)	
	Partial	24 (16.8)	20 (15.5)	
	Failure	52 (36.4)	48 (37.2)	
	Not evaluable	6 (4.2)	8 (6.2)	
	Mycological Response	54/143 (37.8)	53/129 (41.1)	-3.8 (-15.3, 7.7)
	Eradication	2 (1.4)	0	
	Presumed	52 (36.4)	53 (41.1)	
	Eradication	12 (8.4)	13 (10.1)	
	Persistence	77 (53.9)	63 (48.8)	
	Presumed Persistence			
	Radiologic Response	41/143 (28.7)	42/129 (32.6)	-5.2 (-16.1, 5.8)
	Success	41 (28.7)	42 (32.6)	
	Failure	69 (48.2)	56 (43.4)	
	No Post-baseline	31 (21.7)	29 (22.5)	
	Not Evaluable	2 (1.4)	2 (1.6)	
mylTT	Clinical Response	74/123 (60.2)	64/108 (59.3)	-1.6 (-14.0, 10.8)
	Complete	50 (40.6)	47 (43.5)	
	Partial	24 (19.5)	17 (15.7)	
	Failure	43 (35.0)	37 (34.3)	
	Not evaluable	6 (4.9)	7 (6.5)	
	Mycological Response	47/123 (38.2)	48/108 (44.4)	-6.9 (-19.5, 5.8)
	Eradication	2 (1.6)	0	
	Presumed	45 (36.6)	48 (44.4)	

Eradication	9 (7.3)	6 (5.6)	
Persistence	67 (54.5)	54 (50.0)	
Presumed Persistence			
Radiologic Response	37/123 (30.1)	39/108 (36.1)	-7.1 (-19.4, 5.1)
Success	37 (30.1)	39 (36.1)	
Failure	61 (49.6)	48 (44.4)	
No Post-baseline	24 (19.5)	20 (18.5)	
Not Evaluable	1 (0.8)	1 (0.9)	

*adjusted difference (Isa-Vori) and CI calculated using stratified CMH method with the strata of geographic region, allogeneic BMT status, and uncontrolled malignancy status. Study report presents (Vori-Isa). Rates are slightly different than those presented in study report since non-evaluable/missing was included in the denominator above but were excluded from those presented in the study report.
Source: Cheryl Dixon, Ph.D., Biometrics Reviewer

Table 26: DRC- assessed Overall, Clinical, Mycological, and Radiological Response at Day 42 and Day 84, Study 9766-CL-0104

Population	Response	Isavuconazonium	Voriconazole	Difference and 95% CI*
mITT		N=143	N=129	
	Overall Response Day 42	51 (35.7)	46 (35.7)	0.5 (-10.6, 11.6)
	Overall Response Day 84	36 (25.2)	42 (32.6)	-8.2 (-18.9, 2.5)
	Clinical Response Day 42	89 (62.2)	69 (53.5)	8.0 (-3.4, 19.5)
	Clinical Response Day 84	65 (45.5)	55 (42.6)	1.5 (-10.0, 13.0)
	Mycological Response Day 42	57 (39.9)	51 (39.5)	0.7 (-10.8, 12.1)
	Mycological Response Day 84	40 (28.0)	47 (36.4)	-9.1 (-20.2, 2.0)
	Radiologic Response Day 42	40 (28.0)	44 (34.1)	-5.5 (-16.4, 5.4)
	Radiologic Response Day 84	31 (21.7)	38 (29.5)	-9.0 (-19.6, 1.5)
myITT		N=123	N=108	
	Overall Response Day 42	44 (35.8)	41 (38.0)	-0.5 (-12.9, 11.8)
	Overall Response Day 84	31 (25.2)	38 (35.2)	-10.5 (-22.4, 1.3)
	Clinical Response Day 42	77 (62.6)	61 (56.5)	5.7 (-6.9, 18.4)
	Clinical Response Day 84	58 (47.2)	50 (46.3)	-0.3 (-13.0, 12.3)
	Mycological Response Day 42	50 (40.7)	46 (42.6)	-0.7 (-13.5, 12.0)
	Mycological Response Day 84	35 (28.5)	43 (39.8)	-11.7 (-24.0, 0.7)
	Radiologic Response Day 42	38 (30.9)	40 (37.0)	-4.7 (-16.9, 7.5)
	Radiologic Response Day 84	28 (22.8)	35 (32.4)	-10.6 (-22.4, 1.3)

*adjusted difference (Isa-Vori) and CI calculated using stratified CMH method with the strata of geographic region, allogeneic BMT status, and uncontrolled malignancy status. Study report presents (Vori-Isa). Rates are slightly different than those presented in study report since non-evaluable/missing was included in the denominator above but were excluded from those presented in the study report.
Source: Cheryl Dixon, Ph.D., Biometrics Reviewer

MO Comment: DRC-assessed overall response including subcomponents was similar between treatment groups at Day 42 for the mITT population. At Day 84,

DRC-assessed overall response rates were numerically lower in isavuconazonium-treated patients (25.2%, 36/143) compared to voriconazole-treated patients (32.6%, 42/129). These results appear to be related to lower partial success rates (15.4% versus 22.5%) and higher rates of patients considered stable (21.0% versus 10.9%) in isavuconazonium-treated patients than in voriconazole-treated patients, respectively (Study 9766-CL-0104 ADSL Database). It is also noted that 25 of 30 isavuconazonium-treated patients and 13 of 14 voriconazole treated patients with stable disease had successful clinical responses DRC-assessed overall response at Day 84 in the myITT population were similar to those of the mITT population (ISA 31/123, 25.2% and VRC 38/108, 35.2%). The rates of success for radiological response were low in both treatment groups mainly due to missing data. The number of patients with no post-baseline radiological assessments at EOT was approximately 22.0% in both treatment groups [9766-CL-0104 ADSL Dataset and Study Table 12.3.3.3]. I agree that the lower rates of success for radiological responses as compared to clinical responses were probably due to the missing radiologic assessments.

6.1.6 Other Endpoints

Pharmacokinetic endpoint and pharmacodynamic analyses were performed by Drs. Dakshina Chilukuri and Dhananjay Marathe. The reader is referred to the Clinical Pharmacology review for more information.

6.1.7 Subpopulations

The primary endpoint was further analyzed by underlying population variables, such as location, BMT status, malignancy status, age, race, renal function and neutropenia status in Table 26B. There were no significant differences between treatment arms for each of the presented variables, as the 95% confidence interval passed through 0 for all categories.

Table 26B: All-cause Mortality Through Day 42 by Strata (ITT Population)

Strata Category	ISA (n = 258)	VRC (n = 258)	Treatment Difference (%) 95% CI (%)†
Geographical Region†			
North America	5/30 (16.7%)	5/28 (17.9%)	-1.2 (-24.459, 22.078)
Western Europe plus Australia and New Zealand	13/105 (12.4%)	25/107 (23.4%)	-11.0 (-22.172, 0.205)
Other Regions	30/123 (24.4%)	22/123 (17.9%)	6.5 (-4.522, 17.530)
Allogeneic BMT Status			
Yes	12/54 (22.2%)	9/51 (17.6%)	4.6 (-12.724, 21.874)
No	36/204 (17.6%)	43/207 (20.8%)	-3.1 (-11.241, 4.989)
Uncontrolled Malignancy Status			
Yes	37/173 (21.4%)	41/187 (21.9%)	-0.5 (-9.633, 8.557)
No	11/85 (12.9%)	11/71 (15.5%)	-2.6 (-14.952, 9.848)
Age			

≤ 45	16/94 (17.0%)	17/101 (16.8%)	0.2 (-11.426, 11.805)
≤ 65	37/202 (18.3%)	39/200 (19.5%)	-1.2 (-9.355, 6.989)
> 65	11/56 (19.6%)	13/58 (22.4%)	-2.8 (-19.607, 14.065)
> 75	2/10 (20.0%)	4/7 (57.1%)	-37.1 (-96.729, 22.443)
Gender			
Male	27/145 (18.6%)	36/163 (22.1%)	-3.5 (-13.130, 6.199)
Female	21/113 (18.6%)	16/95 (16.8%)	1.7 (-9.673, 13.157)
Race			
White	34/211 (16.1%)	36/191 (18.8%)	-2.7 (-10.693, 5.224)
Black§	0	0	NA
Asian	14/45 (31.1%)	14/64 (21.9%)	9.2 (-9.724, 28.197)
Other	0	1/1 (100%)	NA
Ethnicity			
Hispanic or Latino	4/22 (18.2%)	2/9 (22.2%)	-4.0 (-45.066, 36.985)
Not Hispanic or Latino	44/236 (18.6%)	49/248 (19.8%)	-1.1 (-8.560, 6.332)
BMI Category (kg/m^2)			
< 25	34/154 (22.1%)	32/168 (19.0%)	3.0 (-6.461, 12.522)
25 - < 30	11/70 (15.7%)	15/59 (25.4%)	-9.7 (-25.389, 5.970)
≥ 30	1/27 (3.7%)	2/22 (9.1%)	-5.4 (-23.790, 13.016)
eGFR-MDRD Category ($mL/min/1.73\ m^2$)			
< 60	2/20 (10.0%)	9/33 (27.3%)	-17.3 (-41.784, 7.238)
≥ 60	45/231 (19.5%)	42/217 (19.4%)	0.1 (-7.667, 7.918)
Baseline Neutropenic Status (ANC < $500/mm^3$)			
Yes	34/163 (20.9%)	37/175 (21.1%)	-0.3 (-9.592, 9.024)
No	14/95 (14.7%)	15/83 (18.1%)	-3.3 (-15.451, 8.780)

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

ANC: absolute neutrophil count; BMT: bone marrow transplant; eGFR-MDRD: estimated glomerular filtration rate by Modification of Diet in Renal Disease formula; ISA: isavuconazonium; ITT: intent-to-treat; NA: not calculated; VRC: voriconazole.

† North America consists of Canada and the US. Western Europe consists of Belgium, France, Germany, Italy, 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.

‡ The crude treatment difference was calculated by subtracting VRC from ISA (ISA-VRC) and its 95% CI was calculated based on a normal approximation.

§ Black or African American

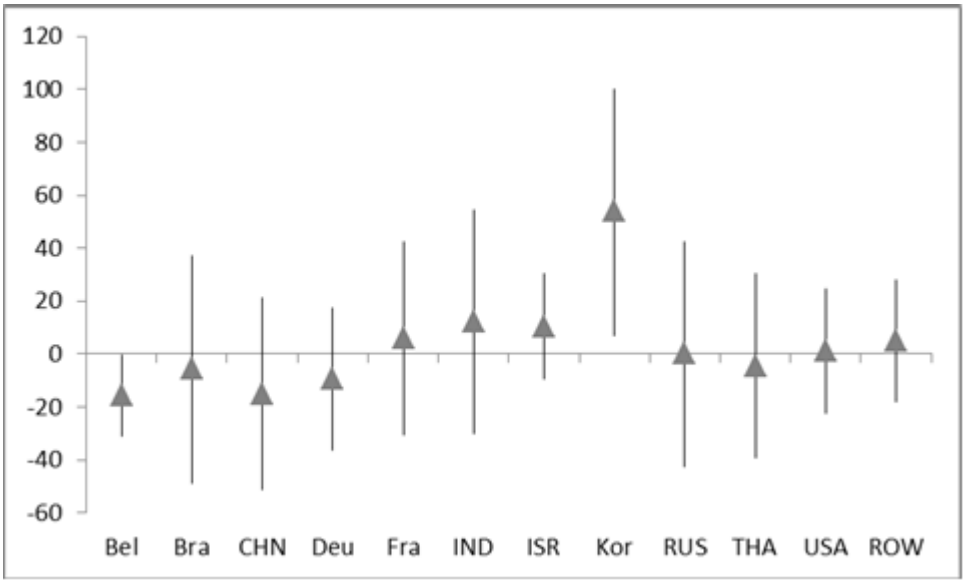
Sources: Modified from Trial 9766-CL-0104 Study Tables 12.3.1.5, 12.3.1.3 and Appendix 13.1.7

MO Comment: Mortality was higher in the Asian popoualtion, apparently as a result of high mortality at a single high enrolling center in South Korea. A further analysis was performed by Cheryl Dixon, the Biometrics Reviewer, who explored this difference. A single Korean site contributed 12 of the 20 Korean patients. The all-cause mortality rate at Day 42 for the Korean sites was 62.5% (5/8) for isavuconazonium and 8.3% (1/12) for voriconazole. Within the Korean sites, there were no identified imbalances in risk factors that might have an impact on outcome, such as uncontrolled malignancy, hematologic malignancy, neutropenia, steroid use, and t-cell immunosuppressant use. Only 1 isavuconazonium patient completed treatment compared to only 1 voriconazole

patient not completing treatment. Therefore, there was a difference in the duration of treatment between arms. The mean duration of treatment was 26.4 days for isavuconazonium compared to 68.8 days for voriconazole. The reasons for treatment discontinuation from isavuconazonium were 2 AE, 2 death, and 3 lack of efficacy. The voriconazole-treated patient discontinued treatment due to lack of efficacy.

Dr. Dixon provided a rough plot of the 95% CI about the difference (isavuconazonium -voriconazole) in All-cause mortality at Day 42 by country (Figure 3). The countries presented had at least 5 patients in each arm and 'ROW' accounts for the remaining countries combined. Below 0 favors isavuconazonium, above 0 favors voriconazole. Korea appears to be an outlier. The remaining Asian countries (China, India, Thailand) fall within the range of the other countries. The CI's are wide due to small sample sizes within each country.

Figure 3: Differential All-Cause Mortality at 42 Days by Country (Isavuconazonium-Voriconazole), Study 9766-CL-0104



I agree with Dr. Dixon's assessment that there is no significant interaction by race with regards to Asians. There may be an issue with the results generated from Korea, but given the small numbers involved it may be due to chance when analyzing a large number of sub-populations.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Pharmacokinetic endpoint and pharmacodynamic analyses were performed by Drs. Dakshina Chilukuri and Dhananjay Marathe. No clear exposure-response relationship was determined, likely due to confounding by numerous underlying host factors. The reader is referred to the Clinical Pharmacology review for more information.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In Study 9766-CL-0104, in the isavuconazonium treatment group, 51 *Aspergillus spp*. collected at baseline were tested. Isavuconazonium demonstrated MIC_{50} and MIC_{90} values against these baseline *Aspergillus spp*. of 1 and 4 mg/L, respectively, using the CLSI method and 1 and 2 mg/L, respectively, using the EUCAST method, with a MIC range of 0.25 to 32 mg/L for both methods. An additional 20 *Aspergillus spp*. isolates collected baseline were tested from Study 9766-CL-0103, with MIC_{50} and MIC_{90} values of 1 and 8 mg/L, respectively, against *Aspergillus spp*. using CLSI methodology. EUCAST values ranged from ≤ 0.12 to 32 mg/L and MIC_{50} and MIC_{90} values of 1 and 4 mg/L, respectively.

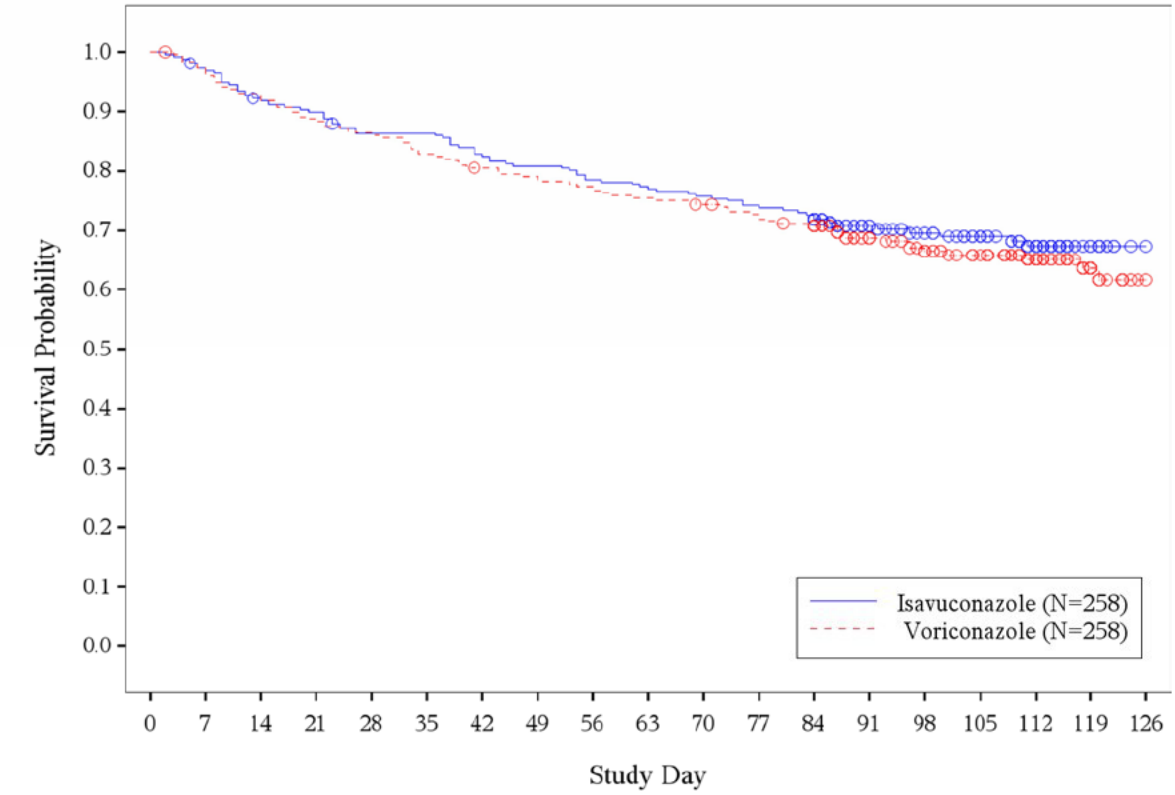
MO Comment: The Clinical Microbiology and Clinical Pharmacology Reviews state that there was no clear relationship between clinical outcome and baseline MIC. For both Aspergillus spp. and Mucorales, successful outcomes were seen in patients with baseline isolate MIC values up to 8 mg/L. However, the number of baseline isolates at each MIC value was small. The actual effect of MIC on clinical outcome may not be clear due to this limitation. Clinical breakpoints are not currently available for mould testing by the National Clinical Laboratory Institute (CLSI) testing methodology mainly due to the low volume of mould infections and the scarcity of isolates with high MICs during clinical trials[6]. A clear relationship between clinical outcome and baseline MIC of other triazoles in invasive mould infections had not been demonstrated.

There is a potential for development or resistance to isavuconazonium. An increase in isavuconazonium MICs, like other triazoles, is likely to be due to multiple mechanisms involving substitutions in the target gene *cyp51*, alterations in sterol profile, and/or efflux pump activity. Per Dr. Shukal Bala, the Clinical Microbiolgy reviewer, increased MICs in *Aspergillus* isolates were associated with elevated activity of efflux pumps. These observations are based on testing of a small number of isolates. The clinical relevance of this finding is not known. For more information, please refer to Dr. Bala's review.

[6] Espinol-Ingroff A. Diekema DJ, Fothergill A. et al. Wild-type MIC distributions and epidemiological cut-off values for the triazoles and six *Aspergillus* species for the CLSI broth microdilution method (M38-A2 Document) J Clin Microiol 2010;48(9):3251-57.

There are limited data available in regards to isavuconazonium efficacy beyond 84 days, as the last possible data point consisted of a follow-up visit 4 weeks after the last dose of study drug (maximum 84 days). The analysis is further complicated by the allowed use of alternative antifungal agents following the end of treatment. Nevertheless, an extended Kaplan Meier survival plot is presented in Figure 4.

Figure 4: Extended 126 Day Survival Probability by Kaplan-Meier Method for ITT Population (Study 9766-CL-0104)



Number of Subjects at Risk

Isavuconazole	258	250	236	230	220	220	211	206	200	197	193	189	185	121	109	99	80	31	20
Voriconazole	258	250	239	228	222	213	206	202	198	193	189	184	179	128	117	103	75	39	22

ITT: all randomized patients who received at least one dose of study drug

ITT: intent-to-treat.

Source: Adapted from Application Material, Module 2.7.2, Summary of Clinical Efficacy, Figure 13

MO Comment: When extended into the follow up period, it appears that the K-M survival curves are not significantly different between the study arms.

6.1.10 Additional Efficacy Issues/Analyses

The use of intravenous voriconazole is discouraged in patients with renal insufficiency due to the potential for accumulation of the solubilizing agent sulfobutyl ether beta-cyclodextrin, and subsequent renal injury. The risks and benefits of IV

voriconazole use in the renally impaired population are carefully considered on a case by case basis. The isavuconazonium pro-drug is water soluble, therefore Study 9766-CL-0103 assessed the efficacy of the drug in patients with renal impairment. A total of 24 patients were assessed by the DRC as having an *Aspergillus* only infection, 20 of whom had renal impairment. Overall all-cause mortality through day 42 in the mITT-*Aspergillus* population occurred in 3 of 20 patients with renal impairment (15.0%). Overall all-cause mortality through Day 84 occurred in 5 of 20 patients (25.0%). The DRC assessed overall response rate at EOT was 30.0%, with 15.0% of patients assessed to be a complete and a partial success.

MO Comment: I agree that the point estimates of all-cause mortality and overall response rates in the renally-impaired mITT-Aspergillus population from Study 9766-CL-0103 were generally similar to those found in non-renally impaired patients in Study 9766-CL-0104. However, this was an uncontrolled, open label study, so the results are descriptive, and non-comparative. Importantly, the numbers of patients treated are too small to stratify by the degree of baseline renal failure.

6.2 Indication: Treatment of Invasive Mucormycosis

The primary trial supporting the proposed indication is ISN 9766-CL-0103/WSA-CS-0103, "Open-Label Study of Isavuconazole in the Treatment of Patients with Aspergillosis and Renal Impairment or of Patients with Invasive Fungal Disease Caused by Rare Moulds, Yeasts or Dimorphic Fungi". Within this trial, a subpopulation of 37 patients with mucormycosis in the modified intent to treat (mITT-Mucorales) population -were confirmed by an independent Data Review Committee (DRC) for an analysis of efficacy. The primary endpoints are 42-day survival and DRC adjudicated overall response at the end of treatment. Secondary endpoints include 84 day survival, and clinical, mycologic and radiologic responses to treatment. Due to the single arm, open- label design, historical natural history data were used as a basis of comparison. The Applicant also presented a comparative analysis of matched, actively treated controls from the Fungiscope Registry as supportive evidence.

6.2.1 Methods

This multicenter study was conducted at 34 centers globally including sites in the US, European Union (EU), South America, Asia and the Middle East, over a six year study period from April, 2008 to January, 2014. An open-label design was selected because the intravenous voriconazole formulation contains the solubilizing agent sulfobutyl ether beta-cyclodextrin sodium (SBECD), which may accumulate in patients with moderate to severe renal impairment (creatinine clearance <50 mL/min). Adult male and female subjects in one of the following subgroups were included in the trial:

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 molds, yeasts, or dimorphic fungi (i.e., fungal pathogens other than *Aspergillus fumigatus* or *Candida* species) whether renal impaired 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.
Patients with advanced HIV disease, hepatic dysfunction (total bilirubin x3 ULN, AST and ALT x5 ULN), ClCr >2 mL/min, QT interval prolongation > 500 ms and/or at risk of torsades de pointes or patients unlikely to survive for 30 days were excluded from the trial.

Intervention:
Isavuconazonium was administered interchangeably via IV or oral formulations, and in the latter case without regard to food intake. An IV isavuconazonium loading regimen was administered during the first 48 hours (200 mg q8h [± 2h]) followed by a maintenance dose from day 3 to end of treatment (EOT) (200 mg q24h [± 2h]). The dose chosen for this study was identical to the dose administered in the randomized, controlled, phase 3 trial for invasive aspergillosis (Study 9766-CL-0104/WSA-CS-004). Patients who were enrolled under Amendment 1 (October 16, 2007; 6 patients) were treated up to a maximum period of 84 days, whereas, most patients who were enrolled from Amendment 3 onwards (November 17, 2010) were treated up to a maximum period of 180 days. An allowance was made to extend isavuconazole dosing beyond 180 days under country-specific Amendment 4 (April 12, 2012 for US, Israel and Belgium), based on Investigator request and Sponsor approval, for patients who demonstrated clinical improvement while on isavuconazole and for whom isavuconazonium was deemed the best therapeutic choice.

Test Product, Dose and Mode of Administration: Isavuconazonium for IV administration was provided as a lyophilized powder for IV infusion. Each IV vial

contained 372.6 mg of isavuconazonium sulfate (BAL8557) corresponding to 200 mg isavuconazole (BAL4815) and included mannitol and sulfuric acid as excipients. Isavuconazole (200 mg) was dissolved in 250 mL of a compatible infusion solution. Isavuconazonium for oral administration was provided as capsules, each containing 186.3 mg of isavuconazonium sulfate (BAL8557) corresponding to 100 mg of active isavuconazole (BAL4815). Ten different lots of capsules and 9 different lots of powder for infusion were used in this study.

Assessments: Survival status was recorded at Day 42, Day 84 and 4 weeks after the final administration of study drug. An additional follow-up visit at 8 weeks after EOT was made if abnormalities (e.g., adverse events [AEs]) were still ongoing at the 4-week follow-up visit. The DRC and Investigators evaluated the clinical response to treatment for patients at Day 42, Day 84 and EOT. Baseline mycological assessment (screening through day 7) of the patient's IFD status was performed according to best local practice using local and central laboratories, including samples for fungal culture as well as samples from the infected site for histology and cytology. Baseline radiological assessments of IFD were performed during the screening period. The European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) definitions of IFD were used (**see Appendix 9.4**). Mycological and radiological assessments were also performed at Day 42, Day 84 and EOT. A DRC, which consisted of 3 experts in the field of fungal infections (b) (4) was established to conduct a data review for all patients who received at least one dose of study drug. The DRC adjudicated, independently from the Applicant and the study Investigators, the categorization of the IFD and evaluated clinical, mycological, radiological and overall responses at Day 42, Day 84 and EOT. The DRC also assessed location of disease, therapy status (i.e., primary, refractory or intolerant) and attributable mortality.

The Investigator evaluated safety by monitoring treatment-emergent adverse events (TEAEs) and findings from physical examination (including eye exam), vital signs, laboratory tests, 12-lead electrocardiogram (ECG) and concomitant medication/surgery.

Laboratory investigations included hematology, biochemistry, urinalysis and hepatic tests collected at screening, and at study visits on Days 7, 14, 28, 42, 84, every 4 weeks thereafter through EOT, and at follow-up visit 1.

Blood pressure (systolic blood pressure [SBP] and diastolic blood pressure [DBP]; mmHg), pulse rate (PR [beats per minute]), and body temperature (BT, °C or °F) (the most abnormal temperature within this window was recorded) were assessed at screening and on Days 1, 2, 3, 7, 14, 28, 42, 84, and every 4 weeks thereafter through EOT, and follow-up visit 1. Twelve-lead ECG recordings were obtained at screening, on Days 1, 14, 42, and 84, and every 4 weeks thereafter until EOT.

Physical examinations were conducted at screening, EOT, and follow-up visit 1.

Blood sampling for the analysis of plasma trough concentrations was obtained for all patients. The samples were drawn prior to administration of study drug on Days 7, 14, 28, 42, 84 and every 4 weeks thereafter until day 180/EOT. Plasma samples were collected pre-dose, and 1.5, 3, 4, 6,12 and 24 hours after the start of infusion or drug intake on Day 7 (+ 1 day) or preferably Day 14 (± 2 days) for pharmacokinetic profiling of isavuconazole in patients enrolled in the pharmacokinetic substudy.

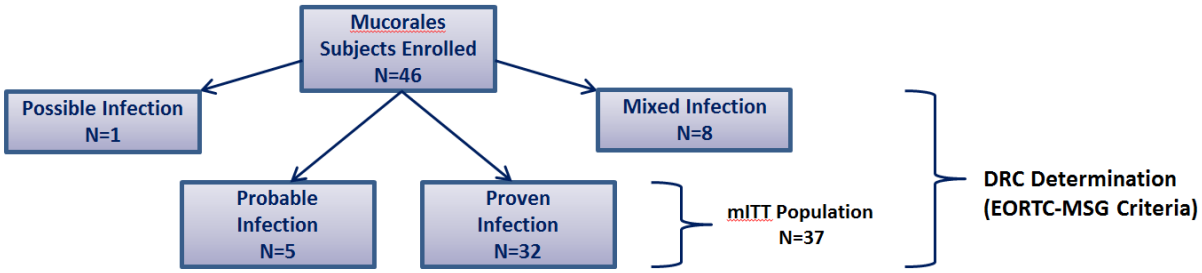
Efficacy Endpoints: The study protocol identified the DRC assessed overall response as the primary endpoint, however, the Applicant believes 42 day mortality is the most relevant endpoint (Module 2.7.3, Section 2.2.2 of study report, 9766-CL-0103). DRC assessed overall response at EOT was therefore analyzed as a secondary efficacy outcome. Additional DRC assessments included clinical, mycological and radiological response at Day 42, Day 84 and EOT.

MO Comment: I agree with the Applicant that survival as a primary outcome allows for a determination of efficacy by comparing the study results to the published scientific literature.

6.2.2 Demographics

This multicenter study was conducted at 34 centers globally including sites in the US, European Union (EU), South America, Asia and the Middle East. A total of 149 patients were enrolled in the study. Of these, 146 patients (98.0%) received at least 1 dose of study drug and were included in the intent-to-treat (ITT) population. The population considered for the proposed indication consists of 37 mITT-Mucorales patients (patients in the ITT whom the DRC classified as having Mucorales only). Figure 5 depicts a flowchart of the study population in study 9766-CL-0103.

Figure 5: Flow Chart of the Mucorales Study Population, Trial 9766-CL-0103



Source: Reviewer Generated from Study Report 9766-CL-0103

The mITT-Mucorales population was further stratified by treatment status. The primary treatment group was defined as initial antifungal therapy, the remaining two groups were considered salvage therapy. The refractory treatment group was identified by the progression of disease while on therapy at enrollment, and the intolerant treatment group either failed to achieve therapeutic drug levels or experienced significant drug

related adverse reaction(s). The categorization of the 37 mITT-Mucorales patients is summarized in Table 27.

Table 27: Distribution of patients by DRC adjudicated infection status and treatment group, mITT-Mucorales Group, Study 9766-CL-0103

	Proven N=32	Probable N=5	Possible N=1
Primary N=22	18 (47.4%)	3 (7.9%)	1 (2.6%)
Refractory N=11	10 (26.3%)	1 (2.6%)	0
Intolerant N=5	4 (10.5%)	1 (2.6%)	0

Source: Reviewer Generated from Study Report 9766-CL-0103

The median age of mITT-Mucorales patients was 50.0 years and the majority of patients were ≤ 65 years (86.5% overall), with 8.1% of patients being over 75 years of age. Overall, the majority of patients were male (81.1%), White (67.6%), with a hematologic malignancy (59.5%). A summary of demographics and baseline characteristics by therapy status is presented in Table 28.

Table 28: Summary of Demographics and Baseline Characteristics by Therapy

Parameter	Primary (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Age (years)				
n	21	11	5	37
Mean (SD)	51.7 (14.72)	46.4 (16.55)	39.6 (15.22)	48.5 (15.51)
Min	25	22	23	22
Median	51.0	50.0	42.0	50.0
Max	77	79	57	79
Category	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Age category (years)				
≤ 45	5 (23.8%)	5 (45.5%)	3 (60.0%)	13 (35.1%)
> 45 - ≤ 65	12 (57.1%)	5 (45.5%)	2 (40.0%)	19 (51.4%)
> 65	4 (19.0%)	1 (9.1%)	0	5 (13.5%)
> 75	2 (9.5%)	1 (9.1%)	0	3 (8.1%)
Gender				
Male	17 (81.0%)	8 (72.7%)	5 (100.0%)	30 (81.1%)
Female	4 (19.0%)	3 (27.3%)	0	7 (18.9%)
Race				
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%)

Other	0	0	0	0
Ethnicity				
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%)
eGFR-MDRD category (mL/min/1.73m^2)				
< 60	6 (28.6%)	3 (27.3%)	2 (40.0%)	11 (29.7%)
≥ 60	15 (71.4%)	8 (72.7%)	3 (60.0%)	26 (70.3%)
Geographic region				
United States	7 (33.3%)	4 (36.4%)	5 (100.0%)	16 (43.2%)
Western Europe (Bel and Ger)	1 (4.8%)	4 (36.4%)	0	5 (13.5%)
Other Regions†	13 (61.9%)	3 (27.3%)	0	16 (43.2%)
Hematologic malignancy	11 (52.4%)	7 (63.6%)	4 (80.0%)	22 (59.5%)
Allogeneic BMT	4 (19.0%)	4 (36.4%)	5 (100.0%)	13 (35.1%)
Uncontrolled malignancy at baseline	11 (52.4%)	6 (54.5%)	1 (20.0%)	18 (48.6%)
Neutropenic‡	4 (19.0%)	5 (45.5%)	1 (20.0%)	10 (27.0%)
Corticosteroid use	5 (23.8%)	3 (27.3%)	2 (40.0%)	10 (27.0%)
T-cell immunosuppressant use	7 (33.3%)	6 (54.5%)	5 (100.0%)	18 (48.6%)
Diabetes	4 (19.0%)	0	0	4 (10.8%)
Disseminated disease	8 (38.1%)	2 (18.2%)	1 (20.0%)	11 (29.7%)
CNS involvement	6 (28.6%)	0	0	6 (16.2%)
Surgery/debridement	9 (42.9%)	1 (9.1%)	0	10 (27.0%)
Underlying Condition				
Acute myeloid leukemia	3 (14.3%)	6 (54.5%)	1	10 (27.0%)
Acute lymphocytic leukemia	2 (9.5%)	0	1	3 (8.1%)
Diabetes mellitus	3 (14.3%)	0	0	3 (8.1%)
Chronic lymphocytic	1 (4.8%)	0	1	2 (5.4%)
Chronic obstructive	0	2 (18.2%)	0	2 (5.4%)
Multiple myeloma	1 (4.8%)	0	1	2 (5.4%)
Aplastic anemia	1 (4.8%)	0	0	1 (2.7%)
B-cell lymphoma	0	1 (9.1%)	0	1 (2.7%)
Colitis ulcerative	0	1 (9.1%)	0	1 (2.7%)
Diabetic ketoacidosis	1 (4.8%)	0	0	1 (2.7%)
Hairy cell leukemia	1 (4.8%)	0	0	1 (2.7%)
Klippel-Trenaunay syndrome	1 (4.8%)	0	0	1 (2.7%)
Lupus nephritis	0	1 (9.1%)	0	1 (2.7%)
Myelodysplastic syndrome	1 (4.8%)	0	0	1 (2.7%)
Non-Hodgkin's lymphoma	1 (4.8%)	0	0	1 (2.7%)
Esophageal adenocarcinoma metastatic	1 (4.8%)	0	0	1 (2.7%)
Renal failure chronic	1 (4.8%)	0	0	1 (2.7%)
Small cell lung cancer	1 (4.8%)	0	0	1 (2.7%)
T-cell prolymphocytic	1 (4.8%)	0	0	1 (2.7%)
Thalassaemia sickle cell	0	0	1	1 (2.7%)

† Other regions includes Russia, Mexico, Brazil, Thailand, South Korea, India, Lebanon, and Israel

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

Source: Reviewer Spreadsheet (Appendix 9.6) and Modified Sponsor Study Report 9766-CL-0103

MO Comment: Underlying host factors in the study population were roughly similar to the population characteristics from two epidemiologic studies (Table 29). It is noted that there were no burn or trauma patients with mucormycosis, and a higher proportion of patients with BMT or hematologic malignancy. The lack of burn patients is expected since the majority of cutaneous infections are considered superficial (Roden et al, 2005).

Table 29: Comparative Underlying Host Factors in mITT Mucorales Population

	Study 9766-CL-0103	Skiada et al (2011)[1]	Roden et al (2005)[2]
Hematologic Malignancy	22/37 (59%)	102/230 (44%)	154/929 (17%)***
Neutropenia at baseline	10/37 (43%)	N/D	N/D
BMT	13/37 (35%)	21/230 (9%)	44/929 (5%)
Diabetes mellitus	4/37 (11%)	39/230 (17%)	337/929 (36%)
Solid Organ Transplant	3/37 (8%)	10/230 (4%)	61/929 (7%)
Solid Organ Malignancy	2/37 (5%)	11/230 (5%)	N/D***
Other#	3/37 (8%)		
Aplastic Anemia	1/37 (3%)	4/230 (2%)	N/D
No Underlying Disease	1/37 (3%)	0/230 (0%)	176/929 (19%)
Burn/Trauma	0/37 (0%)	46/230 (20%)	43/176 (24%)

***Malignancy not differentiated between solid organ and hematologic
Two patients with chronic steroid use (Ulcerative Colitis and COPD), and a third with KLIPPEL-TRENAUNAY-WEBER SYNDROME – A congenital vascular disease involving lymphatics
Table References:
Source: Reviewer Spreadsheet (Appendix 9.6)

[1] Skiada A, Pagano L, Groll A, Zimmerli S, Dupont B, Lagrou K, Lass-Florl C, Bouza E, Klimko N, Gaustad P, Richardson M, Hamal P, Akova M, Meis JF, Rodriguez-Tudela JL, Roilides E, Mitrousia-Ziouva A, Petrikkos G; European Confederation of Medical Mycology Working Group on Zygomycosis. "Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007." Clin Microbiol Infect. 2011 Dec;17(12):1859-67.
[2] Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, et al. "Epidemiology and outcome of zygomycosis: a review of 929 reported cases." Clin Infect Dis. 2005;41:634-53.

MO Comment: The mucormycosis patient population enrolled in Study 9766-CL-0103 reasonably reflects the expected population of patients diagnosed with mucormycosis. The Roden et al study involved a review of 929 cases in the English-language literature since 1885. The work of Skiada and colleagues identified 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007.

The site of infection was adjudicated by the DRC, and is further described in Table 30, below. The reader is also referred to a reviewer generated database in Appendix 9.6.

Table 30: DRC Assessment of IFD Locations at Baseline by Therapy Status

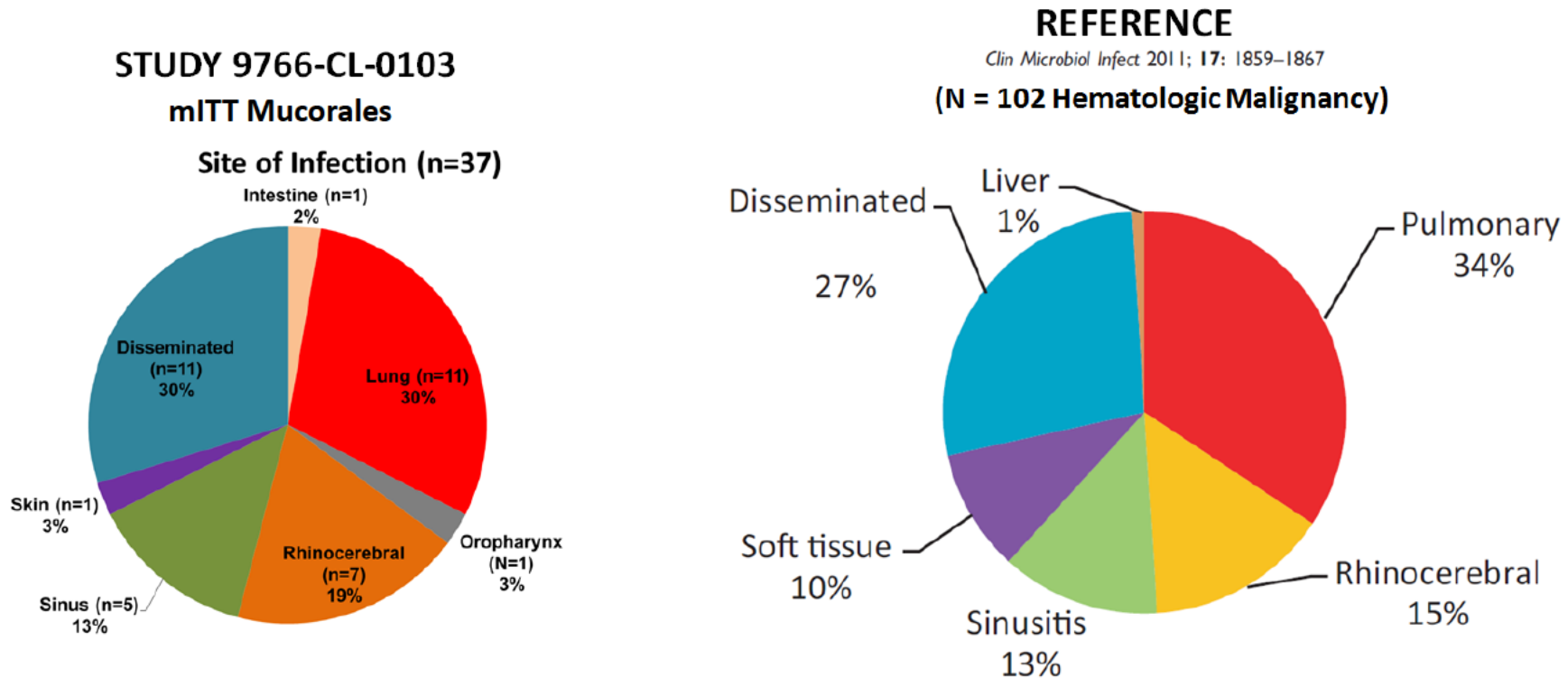
Parameter	Primary (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Disseminated Disease				
Yes	8 (38%)	2 (18%)	1 (20%)	11 (30%)
No	12 (62%)	9 (82%)	4 (80%)	26 (70%)
Location				
LRTD Only*	1 (5%)	5 (46%)	4 (80%)	10 (27%)
LRTD Plus other organ	8 (38%)	3 (27%)	1 (20%)	12 (32%)
Non LRTD Only	12 (57)	3 (27%)	0	15 (41%)
Non-LRTD Location				
Bone	4 (19%)	0	1 (20%)	5 (14%)
CNS	6 (29%)	0	0	6 (16%)
Deep Soft Tissue (e.g. Muscle)	1 (5%)	2 (18%)	0	3 (8%)
Eye	7 (33%)	0	0	7 (19%)
GI Tract	2 (10%)	0	0	2 (5%)
Kidneys	2 (10%)	0	0	2 (5%)
Liver	2 (10%)	0	0	2 (5%)
Sinus	13 (62%)	3 (27%)	0	16 (43%)
Skin	2 (10%)	0	0	2 (5%)
Spleen	1 (5%)	0	0	1 (3%)

*Lower Respiratory Tract Disease

Source: Modified Sponsor Study Report 9766-CL-0103

MO Comment: The frequency and distribution of sites of infection are consistent with the reported literature for mucormycosis, as shown below in Figure 6.

Figure 6: Comparative Location of Primary Infection Site, Study 9766-CL-0103 mITT Mucorales Population to Reference



Source: Reviewer Generated Spreadsheet, Appendix 9.6

The 3 most commonly reported pathogens at baseline, as assessed by the DRC, were Mucormycetes NOS (35.1%) and *Mucor* NOS (not otherwise specified) and *Rhizopus oryzae*, (both reported in 18.9% of patients). 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%). The isolates are summarized in Table 31.

Table 31: DRC Assessment of Pathogen Causing IFD at Baseline in the mITT-Mucorales Study Population

	Primary (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Pathogen				
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	2 (9.5%)	2 (18.2%)	1 (20.0%)	5 (13.5%)
Absidia corymbifera	2 (9.5%)	0	0	2 (5.4%)
Rhizopus NOS	0	1 (9.1%)	1 (20.0%)	2 (5.4%)
Cunninghamella	0	0	1 (20.0%)	1 (2.7%)

Source: Reviewer Spreadsheet (Appendix 9.6) and Modified Sponsor Study Report 9766-CL-0103

Study Drug Exposure: In mITT-Mucorales patients and primary therapy patients, respectively, the median duration of study drug therapy was 84.0 days (range 2 to 882) and 102.0 days (range 2 to 882), with the median duration of intravenous treatment being 10.0 and 9.5 days.

6.2.3 Subject Disposition

In the overall mITT-Mucorales population, 30% of patients completed treatment. The most common reason for discontinuation was patient death (30%). Table 32 summarizes the disposition of the Mucorales study population, and a detailed description follows in Table 33.

Table 32: Primary Reason for Treatment and Study Discontinuation

	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Treatment Discontinuation				
Completed	6 (28.6%)	2 (18.2%)	3 (60.0%)	11 (29.7%)
Discontinued	13 (61.9%)	9 (81.8%)	2 (40.0%)	24 (64.9%)
Primary reason for discontinuation				
Death	6 (28.6%)	3 (27.3%)	2 (40.0%)	11 (29.7%)
Adverse event/intercurrent illness	2 (9.5%)	4 (36.4%)	0	6 (16.2%)
Did not cooperate	3 (14.3%)	1 (9.1%)	0	4 (10.8%)
Insufficient therapeutic response	1 (4.8%)	1 (9.1%)	0	2 (5.4%)
Admin/other	1 (4.8%)	0	0	1 (2.7%)
Discontinuation during follow-up period				
Completed	7 (33.3%)	3 (27.3%)	2 (40.0%)	12 (32.4%)

Discontinued	12 (57.1%)	8 (72.7%)	3 (60.0%)	23 (62.2%)
Primary reason for discontinuation				
Death	10 (47.6%)	6 (54.5%)	2 (40.0%)	18 (48.6%)
Admin/other	0	1 (9.1%)	1 (20.0%)	2 (5.4%)
Withdrew consent	1 (4.8%)	1 (9.1%)	0	2 (5.4%)
Failure to return/lost to follow-up	1 (4.8%)	0	0	1 (2.7%)
Ongoing‡	2 (9.5%)	0	0	2 (5.4%)

‡ Patients who were still actively receiving study treatment as of September 30, 2013.
Source: Reviewer Generated using JMP11 and ADSL Dataset for Study 9766-CL-0103

Table 33: Detailed description of individual subject dispositions

Subject ID	Treatment Group	Disposition / Discontinuation Reason	Cause of Death	Death Day / Last Study Day Alive	Days Alive Since Last Dose
				(b) (6)	
4910-01	Primary Therapy	Investigator Discontinued	Mucormycosis		1
0107-02	Primary Therapy	Death	Respiratory failure		1
9119-05	Primary Therapy	Withdrew Consent	Cerebral infarction		1
9704-02	Primary Therapy	Death	Cardio-respiratory arrest		1
0115-05	Refractory	Death	Pneumonia fungal		1
1105-06	Intolerant	Death	Septic shock		0
9704-01	Primary Therapy	Refused Treatment	Cardio-respiratory arrest		2
9703-02	Refractory	Adverse Event: Malignancy Progression	Malignant neoplasm progression		0
0702-01	Refractory	Adverse Event: Cardiac Failure	Multi-organ failure		5
0115-01	Intolerant	Death	Septic shock		0
0142-02	Primary Therapy	Death	Pneumonia fungal		2
1105-10	Refractory	Lack of Efficacy	Sinusitis fungal		14
0115-08	Primary Therapy	Death	Lung infection pseudomonal		1
1105-09	Refractory	Withdrew Consent			13
0115-14	Primary Therapy	Adverse Event: Malignancy Progression	Renal failure acute		23
9704-12	Primary Therapy	Death	Bacterial sepsis		1
4904-02	Refractory	Death	Pneumonia		0
0141-03	Refractory	Adverse Event: ALT > 5x ULN			58
6603-02	Primary Therapy	Completed			59
9119-02	Primary Therapy	Refused Treatment			1
0148-04	Intolerant	Completed			32

				(b) (6)
1105-01	Primary Therapy	Death	Pneumonia	1
3204-07	Refractory	Adverse Event : Nausea		67
4904-01	Refractory	Completed		98
0105-02	Intolerant	Completed		57
9601-01	Primary Therapy	Completed		52
9119-04	Primary Therapy	Completed		53
6606-05	Primary Therapy	Completed		56
9119-03	Primary Therapy	Completed		57
3204-03	Refractory	Completed		56
9119-01	Primary Therapy	Completed		61
0141-02	Intolerant	Completed		64
5517-09	Primary Therapy	Lack of Efficacy		226
0154-01	Primary Therapy	Ongoing Treatment, Day 84 Presumed Mycologic Eradication per DRC		87
0107-01	Primary Therapy	Adverse Event: Malignancy Progression	Malignant neoplasm progression	8
9704-04	Refractory	Death	Acute myeloid leukaemia	2
9704-03	Primary Therapy	Ongoing Treatment, Day 84 Presumed Mycologic Persistence per DRC		0

Source: Reviewer Generated using JMP11 and ADSL Dataset for Study 9766-CL-0103

6.2.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for this study is the all cause crude mortality rate, determined at Day 42 and Day 84 (Table 34). Overall mortality was 38% at Day 42, and 43% at Day 84. The primary treatment group was similar to the overall rate, with 33% 42-day mortality and 43% 84-day mortality rates. The Kaplan Meier survival analysis is presented in Figure 7.

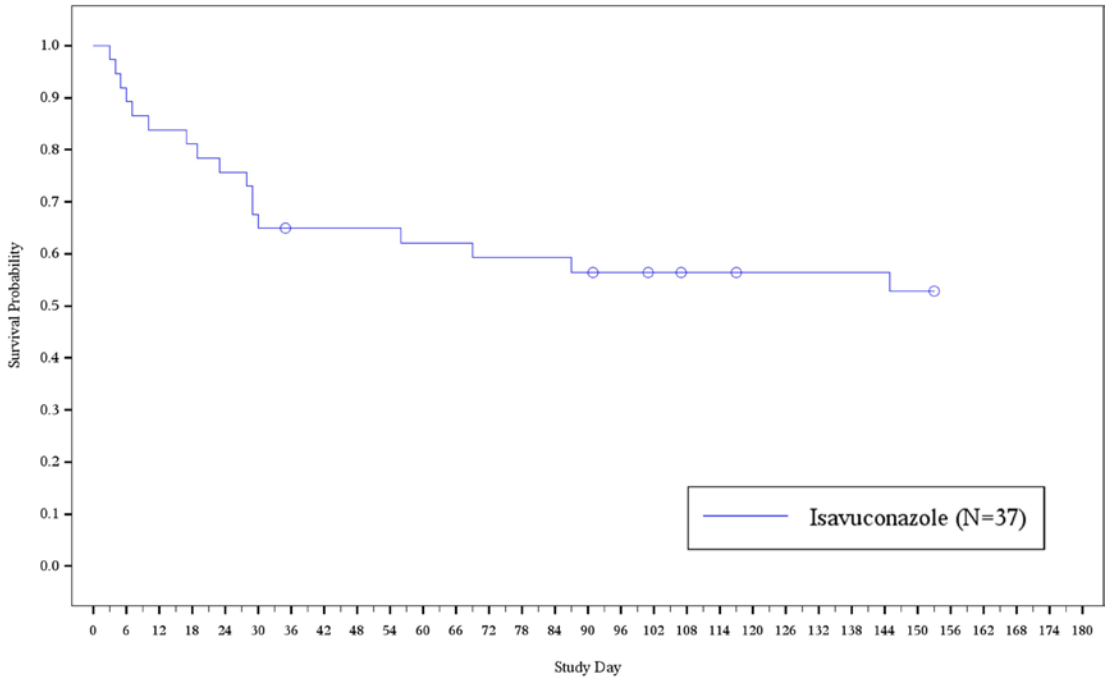
Table 34: All-Cause Crude Mortality through Day 42 and Day 84 in the mITT Mucorales Population

Outcome	Primary (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
By Day 42				
All-Cause Mortality†	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%)
By Day 84				
All-Cause Mortality‡	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%)

Source: Reviewer Spreadsheet (Appendix 9.6) and Modified Sponsor Study Report 9766-CL-0103

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

Figure 7: Survival Probability Through Day 180 by Kaplan-Meier Method



mITT-Mucorales: ITT patients who had proven or probable invasive mucormycosis as determined by the DRC
A patient was censored on the patient's last day known alive or day 181, whichever was earliest
Source: Sponsor 9766-CL-0103 Study Report Figure 12.3.2

MO Comment: Given the open label, single arm design of the study, a contextual, comparative analysis versus historical data and matched controls is discussed in Section 6.1.10

With the exception of a single subject, 0115-14 who succumbed to acute renal failure, mortality was either associated with evidence of IFD or a direct consequence of IFD, as summarized in Table 35.

Table 35: DRC-assessed Attribution of IFD to Death by Therapy Status

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

Source: Reviewer Spreadsheet (Appendix 9.6) and Modified Sponsor Study Report 9766-CL-0103 Study Table 12.3.10.2

The DRC evaluation criteria are attached as Appendix 9.5. DRC assessed overall response rate at EOT in the mITT-Mucorales population (Table 36) was 31.4%, with 14.3% of patients assessed to be a complete success and 17.1% assessed to be a partial success with 28.6% of patients assessed to be stable. For primary therapy patients, 31.6% of patients were assessed to be a success, with 15.8% of patients assessed to be a complete, and 15.8% a partial success.

Table 36: DRC Assessed Overall Response at EOT by Therapy Status

Outcome Response	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Success	6/19 (31.6%)	4/11 (36.4%)	1/5 (20.0%)	11/35 (31.4%)

Complete	3/19 (15.8%)	2/11 (18.2%)	0	5/35 (14.3%)
Partial	3/19 (15.8%)	2/11 (18.2%)	1/5 (20.0%)	6/35 (17.1%)
Failure	13/19 (68.4%)	7/11 (63.6%)	4/5 (80.0%)	24/35 (68.6%)
Stable	6/19 (31.6%)	2/11 (18.2%)	2/5 (40.0%)	10/35 (28.6%)
Progression	7/19 (36.8%)	5/11 (45.5%)	2/5 (40.0%)	14/35 (40.0%)

Source: Reviewer Spreadsheet (Appendix 9.6) and Modified Sponsor Study Report 9766-CL-0103

MO Comment: The DRC determined success of treatment is more conservative than survival alone, since a patient may survive during the study period, but with an indolent, or slowly progressing infection. The partial and complete success rate of 36.4% (4/11 patients) in the refractory group provides support for efficacy, as this represents a salvage regimen. Additionally, 31.6% of primary therapy patients were assessed to be stable (no progression of infection), which is a clinically relevant favorable outcome in this typically immunosuppressed patient population. The study report did not discuss reductions in patient immunosuppression, as increasing host immune response is an important therapeutic approach.

Confounding Systemic Antifungal Therapy During the Study Period:
Six patients (16.2%) were identified who took at least 3 consecutive days of mold active systemic antifungal therapy after the first dose of study drug. These subjects are listed as follows:

Patient 010502 (Intolerant) - voriconazole – days 7 to 19; 132 days on ISV; day (b) (6) last day known alive; DRC considered overall response stable (failure) at EOT

Patient 110506 (Intolerant) – voriconazole – days (-1) to 3; discontinued due to death on day (b) (6) DRC considered overall response progression (failure) at EOT

Patient 011514 (Primary) - posaconazole – day 35 onward; 33 days on ISV discontinued due to malignancy progression, death due to acute renal failure on day (b) (6) DRC considered overall response stable (failure) at EOT

Patient 014103 (Refractory) – posaconazole – day 40 onward; discontinued ISV day 33 due to elevated LFTs, day (b) (6) last known alive; DRC considered overall response stable (failure) at EOT

Patient 070201 (Refractory) – amphotericin B day 19 onward; 18 days on ISV discontinued due to heart failure, death due to multi-organ failure on day (b) (6) DRC considered overall response progression (failure) at EOT

Patient 110510 – (Refractory) – liposomal amphotericin B day 15 onward; 15 days on ISV discontinued due to lack of efficacy, death due to fungal sinusitis on day (b) (6) DRC considered overall response progression (failure) at EOT

MO Comment: Four patients were given either posaconazole or amphotericin B rescue therapy following discontinuation of isavuconazonium. The mortality data is affected by 2 patients surviving beyond 42 days, and 1 beyond 84 days while on alternative therapy. These patients were counted as mortality successes, but failures by the DRC (stable disease). The use of voriconazole was unlikely to affect the outcome for the two patients exposed because voriconazole is not typically active against the Mucorales. It is also noted that the intolerant and refractory patient groups received significant antifungal therapy prior to treatment with isavuconazonium.

6.2.5 Analysis of Secondary Endpoints(s)

The secondary efficacy outcomes included clinical, mycological and radiological response assessed by the DRC at Day 42, Day 84 and EOT. In addition, the DRC assessed the attribution of death to the IFD for death up to Day 42 and for death up to Day 84 as either directly due to consequences of progressive IFD, associated with the evidence of residual or ongoing IFD, associated with no evidence of residual or ongoing IFD, indeterminate cause or no known death.

The DRC assessments of success rates for clinical, mycological and radiological response at EOT (Table 27) were higher for clinical response (45.2%) than mycological (34.3%) and radiological (18.2%), for the mITT-Mucorales population [Table 27]. For primary therapy patients, the DRC assessments of success rates for clinical, mycological and radiological response at EOT were 55.6%, 31.6% and 16.7% respectively.

Table 37: DRC Assessed Success Rates for Clinical, Mycological, and Radiological Response at EOT by Therapy Status (mITT-Mucorales Population - Study 9766-CL-0103)

Outcome Response	Primary Therapy (n = 19*)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 35)
Clinical Response				
Success	10/18 (55.6%)	2/9 (22.2%)	2/4 (50.0%)	14/31 (45.2%)
Failure	8/18 (44.4%)	7/9 (77.8%)	2/4 (50.0%)	17/31 (54.8%)
Not Determined	1	2	1	4
Mycological Response				
Success	6/19 (31.6%)	4/11 (36.4%)	2/5 (40.0%)	12/35 (34.3%)
Failure	13/19 (68.4%)	7/11 (63.6%)	3/5 (60.0%)	23/35 (65.7%)
Radiological Response				
Success	3/18 (16.7%)	2/10 (20.0%)	1/5 (20.0%)	6/33 (18.2%)
Failure	15/18 (83.3%)	8/10 (80.0%)	4/5 (80.0%)	27/33 (81.8%)
Not Determined	1	1	0	2

*Two patients were receiving ongoing therapy at the time of assessment and were excluded.

Source: Reviewer Spreadsheet (Appendix 9.6) and Modified Sponsor Study Report 9766-CL-0103

MO Comment: Additional secondary endpoints include evaluations by the DRC at 42 and 84 days, however these data points provided limited information. At 42 days, 21 of 37 subjects were evaluable because 16 fatalities were excluded. There was 1 success, with 16 patients deemed stable. Similarly, at 84 days, 19 of 37 subjects were alive and evaluable. As such, DRC determinations at the end of therapy were more informative.

6.2.6 Other Endpoints

Exploratory endpoints included an analysis of pharmacokinetic data. The reader is referred to clinical pharmacology review.

6.2.7 Subpopulations

Subgroup analyses were performed on all-cause mortality through Day 42 for the risk factors of hematologic malignancy, diabetes, disseminated disease, CNS involvement and surgery/debridement (Table 38). All-cause mortality through Day 42 was highest in patients with CNS involvement (66.7% of mITT-Mucorales overall, all of whom were primary therapy patients), though these results were based on a small number of patients with this risk factor. Overall mortality in the hematologic malignancy group was 13/22 (59.1%) at 84 days.

Table 38: All-cause Mortality through Day 42 by Risk Factor and Therapy Status

Risk Factor	Primary Therapy (n = 21)	Refractory (n = 11)	Intolerant (n = 5)	Total (n = 37)
Hematologic malignancy	5/11 (45.5%)	5/7 (71.4%)	2/4 (50.0%)	12/22 (54.5%)
Diabetes	1/4 (25.0%)	0	0	1/4 (25.0%)
Disseminated disease	4/8 (50.0%)	1/2 (50.0%)	0/1	5/11 (45.5%)
CNS involvement	4/6 (66.7%)	0	0	4/6 (66.7%)
Surgery/debridement†	4/9 (44.4%)	1/1 (100.0%)	0	5/10 (50.0%)

mITT-Mucorales: ITT patients who had proven or probable invasive mucormycosis as determined by the DRC A patient with a last known survival status before day 42 was counted as dead.
† Surgery was between 7 days before and 7 days after start of study drug.
Source: Reviewer Spreadsheet (Appendix 9.6) and Modified Spons Study Report 9766-CL-0103: SCE Table 3.2.3

MO Comment: It is expected that patients with CNS involvement have the highest mortality rate, as this represents the most serious location for disease, and subjects with hematologic malignancy receive treatments with strong immunosuppressive effects (i.e. neutropenia). This is in contrast to patients with diabetes who have a more benign underlying disease with relatively preserved immune responses.

6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dose for phase 3 studies was selected to ensure achievement of trough exposures above the epidemiologic cut-off values for *Aspergillus spp*. (i.e., 1 to 2 mg/L), and was then extended to the treatment of organisms of the Mucorales order. *In vitro* susceptibility testing of isavuconazonium to *Aspergillus spp.* shows minimum inhibitory concentration (MIC) values at which 90% of the isolates are inhibited at the specified endpoint (MIC_{90} values) ranging from 1 to 2 mg/L. MIC values for organisms of the Mucorales order are variable. The MIC range and MIC_{90} values are as follows: *Rhizomucor spp*., MIC range of 0.12 to 8 mg/L and MIC_{90} of 4 mg/L; *Rhizopus spp*., MIC range of 0.12 to 32 mg/L and MIC_{90} of 8 mg/L; *Absidia spp*., MIC range of 0.12 to 32 mg/L and MIC_{90} of 8 mg/L; *Mucor spp*., MIC range of 0.12 to 32 mg/L and MIC_{90} of 16 mg/L; and *Cunninghamella spp*., MIC range of 0.25 to 32 mg/L and MIC_{90} of 32 mg/L.

Nineteen baseline isolates from the Mucorales order were obtained from Study 9766-CL-0103. Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST)MICs ranged from 0.25 mg/L to 32 mg/L. Successful outcomes were demonstrated in a few patients with MIC values as high as 8 mg/L for these baseline isolates (See Clinical Microbiology Review for more information).

Dosing for the invasive mucormycosis indication was based upon the *in vitro* data and an extension of *in vivo* animal models in mice and rabbits for *Aspergillus spp*. At exposures of approximately 35 µg·h/mL in mice to 140 µg·h/mL in rabbits, [9766-PH-0204; 9766-PH-0207], pharmacodynamic studies demonstrated that AUC/MIC is the pharmacodynamic index that drives efficacy [Lepak et al, 2013[7]; 9766-PH-0204]. The pharmacodynamic target (AUC/MIC total drug) estimated for isavuconazonium against *Aspergillus spp*. is 24.7 (calculated from EUCAST MIC values [EUCAST, 2008]) and 50 (calculated from CLSI MIC values [CLSI, 2008]).

Population pharmacokinetic modeling (see Clinical Pharmacology review) indicated that in the phase 3 population, approximately 95% of patients were predicted to achieve AUC/MIC target exposures at steady state for MIC values of 1 to 2 mg/L.

[7] Lepak AJ, Marchillo K, Vanhecker J, Andes DR. "Isavuconazonium (BAL4815) pharmacodynamic target determination in an *in vivo* murine model of invasive pulmonary aspergillosis against wild-type and *cyp51* mutant isolates of *Aspergillus fumigatus*.".Antimicrob Agents Chemother. 2013 Dec;57(12):6284-9.

MO Comment: The number of isolates from Studies 9766-CL-0104 and 9766-CL-0103 is limited, so no clear MIC threshold was determined for clinical response. In general, there was no correlation between clinical outcome and MICs for invasive molds. A positive response to isavuconazonium therapy was observed with MICs as high as 8 mg/L. This may be explained by the multitude of host factors (i.e. underlying condition, immunosuppression, and location of infection) that play an important part in overcoming the infection. For further information, please refer to the Clinical Microbiology and Clinical Pharmacology reviews.

6.2.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Of the 21 patients who survived beyond Day 84, one patient (Subject ID 490402, infected with *Rhizomucor pusillus* with ISA MIC>16 mg/L (CLSI)) had progressive disease and died on Day (b) (6) One patient (Subject 14103 – *Mucormycetes* NOS- no MIC) discontinued treatment on Day 33 due to elevated liver enzyme tests and posaconazole was initiated. This patient had stable disease at the end of isavuconazonium treatment and was last known alive on Day (b) (6) 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 end of treatment or last DRC assessment.

Complete Overall Response: Of the 5 patients with a complete overall response at the end of treatment:

- Three patients had an underlying hematologic malignancy and disseminated disease including pulmonary involvement. Two of these three patients (Subject 911901- *Mucor* NOS - no MIC, Subject 911903 - *Mucor* NOS - no MIC) received isavuconazonium as primary therapy for 179 and 180 days, respectively. No other Mucorales-active antifungal therapy was administered. Subject 911901 had a laparotomy on Day (b) (6), but neither 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 DRC. Both patients were alive at the last follow-up on Days 241 and 236, respectively.
- Subject 970404 (*Mucormycetes* NOS- no MIC) with underlying hematologic malignancy was classified by the DRC as having disseminated disease involving the ear and lung which was refractory to prior antifungal therapy (amphotericin B, voriconazole, and posaconazole). The patient received isavuconazonium for 735 days, did not receive other antifungal therapy after the start of isavuconazonium and did not have surgical debridement of the

lung. Greater than 90% improvement in the pulmonary infiltrates and complete resolution of clinical symptoms was determined by the DRC. The patient died on day (b) (6) due to AML.

- Subject 010701 (*Actinomucor elegans* - isavuconazonium - MIC 0.25 mg/L (CLSI)) had metastatic small cell lung cancer active at baseline with involvement of the sinuses. Surgical debridement was performed one day prior to the patient starting isavuconazonium as primary therapy. This patient received isavuconazonium therapy for 509 days and the patient died on day (b) (6) due to progression of his underlying malignancy.
- One patient (Subject 320407 - *Rhizopus azygosporus* - isavuconazonium - MIC 1 mg/L.) who had two lung transplants for COPD and pulmonary involvement of disease was refractory to amphotericin B and posaconazole treatment received isavuconazonium for 86 days. A left pneumonectomy was performed (b) (6) days prior initiation of isavuconazonium. 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 end of treatment:

- Subject 014102 (*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 was treated with isavuconazonium for 232 days. The patient was alive at the last follow-up on day 296.
- Two patients two received isavuconazonium for primary therapy. Subject 660302 (*Mucormycetes* NOS- no MIC) did not have an underlying disease documented, but had invasive mucormycosis involvement of the sinuses. Isavuconazonium was administered for 42 days with complete resolution of clinical signs and symptoms and the patient was alive at the last follow-up visit on Day 101. This patient had nasal mass excision (b) (6) days prior to initiation of isavuconazonium. Subject 911904 (*Mucor* NOS - no MIC) had diabetes mellitus with invasive mucormycosis involvement of the eye and sinuses. This patient also had surgical intervention (b) (6) of both involved organs. Isavuconazonium 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.
- Two patients received isavuconazonium who were refractory to amphotericin. Subject 320403 (Mucormycetes NOS- no MIC) had COPD with pulmonary involvement and received isavuconazonium for 182 days and was alive at the last follow-up on day 238, without surgical intervention. Subject 490401 (*Rhizopus oryzae* - ISA MIC 16 mg/L (CLSI)) had ulcerative

colitis with involvement of the sinuses. The patient underwent initial facial resection(b) (6) days prior to initiation of isavuconazonium and had debridement of a muscle graft on (b) (6) Isavuconazonium was administered for 84 days and the patient was alive at the last follow-up on Day 182.

Stable Disease: Of the 9 patients (Subject 960101 - Mucormycetes NOS - no MIC; Subject 010502 -*Cunninghamella spp.* - no MIC; Subject 014804 - *Rhizopus microsporus* ISA MIC 16 mg/L (CLSI); Subject 110501 - Mucormycetes NOS- no MIC; Subject 551709 - *Mucor amphibiorum* - no MIC; Subject 660605 - Mucormycetes NOS- no MIC; Subject 911902 - *Mucor* NOS - no MIC; Subject 015401 - *Rhizopus oryzae* ISA MIC 2 mg/L (CLSI); Subject 970403 - Mucormycetes NOS- no MIC) with stable disease at the end of treatment or last DRC assessment:

- Four patients had hematologic malignancies, 5 had pulmonary involvement including 2 with disseminated disease. Seven patients received isavuconazonium for primary therapy and 2 were intolerant to amphotericin (both due to renal impairment). Treatment duration ranged from 85-882 days. Eight of the 9 patients were known to be alive between 107 and 882 days after the start of isavuconazonium therapy. One patient with metastatic esophageal adenocarcinoma and disseminated disease including pulmonary involvement who received isavuconazonium as primary therapy died on Day (b) (6) It should be noted the 5 of the 9 patients with stable disease, including the individual who died, had complete or partial clinical responses based on the last independent DRC assessment at Day 84.

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MO Comment: It is reasonable to believe that a successful outcome at 84 days therapy is reasonably predictive of a successful outcome for longer periods of follow-up.

6.2.10 Additional Efficacy Issues/Analyses

The Applicant provided a review of the scientific literature and matched controls within the European Fungiscope database to support the efficacy of isavuconazonium relative to amphotericin B deoxycholate. Amphotericin B is the only FDA approved drug for invasive mucormycosis. The Fungiscope matched case analysis provides limited evidence of isavuconazonium efficacy relative to amphotericin B because of the wide confidence margins and the absence of an agreed upon non-inferiority margin. We have therefore concentrated on the benefit of isavuconazonium relative to no treatment.

Natural History of Invasive Mucormycosis:
We identified three epidemiologic reports that provide limited support for assigning a mortality rate of nearly 100% for untreated invasive mucormycosis. A paper by Roden

and colleagues[8] indicated an overall mortality rate of 97% in a broad review of 929 reported cases, but many of the cases were identified post-mortem. We contacted the authors to ascertain the number of patients who were diagnosed with mucormycosis prior to death. There were 241 patients who received no treatment. Of these, 8 (3%) survived. Of the 233 patients who died, 18 (8%) were diagnosed pre-mortem and 215 (92%) were diagnosed post mortem. This gives a mortality rate among those who were diagnosed pre-mortem of 69.2% (18/26, 95% CI [49.6, 88.9])

We next reviewed a study by Skiada and colleagues[9], which indicated that 21 of 22 (95%) untreated patients did not survive. While only 10 cases (4%) were diagnosed post-mortem, information is lacking on how these cases were distributed amongst the treatment groups, the presence of underlying medical conditions, and the duration of the follow up from the time of diagnosis.

The closest publication approximating a natural history study in a modern population was from Dimitrios Kontoyiannis' group (Chamilos et al [10]) at MD Anderson, Houston, TX. A total of 70 consecutive patients with hematologic malignancy and mucormycosis during the period of 1989–2006 were analyzed for 84-day mortality when amphotericin B–based therapy was delayed. The study used diagnostic criteria similar to trial, 9766-CL-0103. A delay of 6 days in initiating amphotericin B–based therapy resulted in a 2-fold increase in mortality rate at 12 weeks after diagnosis (82.9%), compared with early treatment (48.6%). All patients were alive with an active infection at the time of diagnosis. The author's 6-day cutoff was selected based upon a statistical analysis intended to define a meaningful delay of treatment. The study indicated that mortality approached 100% at 84 days if left untreated, but did not present data for the 70 patients individually.

In the isavuconazonium-treated population, 9 of 22 (41%, 95% CI [20.4, 61.5]) subjects with hematologic malignancy died by 12 weeks. Comparing the reported 82.9% 12 week mortality for the 35 patients in the Chamilos *et al* study (95% CI [68.9, 96.8]) suggests a benefit of treatment. As this represents the benefit of Isavuconazonium treatment above a 6 day delay of treatment, it can be considered a conservative assessment of isavuconazonium treatment versus the absence of treatment.

[8] Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, et al. "Epidemiology and outcome of zygomycosis: a review of 929 reported cases." Clin Infect Dis. 2005;41:634-53.

[9] Skiada A, Pagano L, Groll A, Zimmerli S, Dupont B, Lagrou K, Lass-Florl C, Bouza E, Klimko N, Gaustad P, Richardson M, Hamal P, Akova M, Meis JF, Rodriguez-Tudela JL, Roilides E, Mitrousia-Ziouva A, Petrikkos G; European Confederation of Medical Mycology Working Group on Zygomycosis. "Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007." Clin Microbiol Infect. 2011 Dec;17(12):1859-67.

[10] Chamilos G, Lewis RE, Kontoyiannis DP. "Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis." Clin Infect Dis. 2008 Aug 15;47(4):503-9.

MO Comment: We contacted Dr. Kontoyiannis for subject level information, but the data were not readily available. An information request was sent to the Sponsor at the Midcycle Communication (October 20, 2014) for analysis and commentary on these studies, as well as any additional studies, case reports, or expert opinions that would demonstrate a clinical benefit of isavuconazonium in comparison to no treatment at all. A reply was received on November 18, 2014, acknowledging the difficulty of obtaining natural history data. The Applicant performed an audit of the Fungiscope database, an observational registry established in 2003. In this database, there are 136 cases of invasive mucormycosis with available survival data through Day 42, 29 of whom did not receive treatment and all 29 died. In the untreated patients, most were diagnosed post-mortem or shortly before death, similar to the Roden and Skiada papers.

*The diagnosis of invasive mucormycosis is often made at autopsy, therefore, we next explored whether benign colonization is known to occur in immunosuppressed individuals. We queried the PubMed Database with the terms "Mucor, Mucorales, Zygomycosis or Zygmomycetes AND Colonization" in order to determine the incidence of benign Mucorales colonization in immunocompromised individuals. A retrospective study by Silveira and colleagues[11] followed 517 lung transplants performed from March 1996 to March 2006. Eighty-five non-*Aspergillus *molds were isolated from the bronchoalveolar lavages (BAL) of 75 transplant recipients. The incidence rate among the patients who had a positive BAL for Zygomycete was 3.14 per 100 person-years. Of the isolates, 14.1% (12 of 85) were Zygomycetes, including 3* Mucor*, 2* Rhizomucor*, 5* Rhizopus*, 1* Syncephalastrum *and 1* Cunninghamella*. Among the 12 patients with a positive BAL for a Zygomycete, there was 1 probable infection (fatal outcome), representing an attack rate of 8.3%. This contrasted with the overall non-Aspergillus mold attack rate of 1.3% within the study population. From this one study, the presence of Mucorales is rare and associated with a higher risk of invasive disease than other non-Aspergillus fungi.*

We conclude that while the epidemiologic studies are limited, they represent the best available data. It is reasonable to believe that infection with invasive mucormycosis carries a very high risk of mortality, and we agree with the Applicant's position that the mortality rates quoted by the Skiaka, Roden, and Fungiscope database are reflective of the actual mortality rate if the infection is left untreated. There is no serologic biomarker for invasive mucormycosis, and patients with disease may go undiagnosed until autopsy. We agree that post-mortem diagnosis is consistent with the rapid progression of this disease and the difficulty in diagnosis.

[11] Silveira FP, Kwak EJ, Paterson DL, Pilewski JM, McCurry KR, Husain S "Post-transplant colonization with non-Aspergillus molds and risk of development of invasive fungal disease in lung transplant recipients." J Heart Lung Transplant. 2008 Aug;27(8):850-5.

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Table 39 provides a summary of the estimated mortality of untreated patients relative to amphotericin-treated patients.

Table 39: Mortality Rates in Amphotericin-Treated, and Untreated Patients with Invasive Mucormycosis

Study	Amphotericin Treated Patients ACM (%) [95% CI][1]	Untreated Patients ACM (%) [95% CI][1]
Roden	244/648 (37.7%) [33.9, 41.5]	233/241 (96.7%) [93.6, 98.6]
Skiada	58/152 (38.2%) [30.4, 46.4]	21/22 (95.5%) [77.2, 99.9]
Fungiscope[2]	41/107 (38.3%) [29.1, 48.2]	29/29 (100%)[2] [88.1, 100.0]
Meta-Analysis[3]	37.8% [34.7, 41.0]	96.2% [94.0, 98.4]

1) Confidence intervals were calculated by exact binomial method; 95% CI from the meta-analysis was based on the normal approximation.
2) Day 42. 13 with pre-mortem diagnosis, typically within a week of death plus post-mortem diagnosis
3) Based on Roden et al. , Skiada et al., and Fungiscope. Number of Treated patients = 907. Number of Untreated patients = 292.

Source: Adapted from Sponsor's Information Request Response Table 1, November 18, 2014.

The mortality rate and 95% confidence intervals for patients with proven or probable invasive mucormycosis from Study 9766-CL-0103 in comparison to the mortality data from untreated patients are presented in Table 40. In this analysis, the upper limit of the 95% confidence interval for mortality in the isavuconazonium treatment group is below the lower limit of the 95% confidence interval for no treatment.

Table 40: Mortality Rates and 95% CIs in Isavuconazonium-Treated Patients and Untreated Patients

Timepoint	ISA Treated Patients All Mucor ACM[1] (%) [95% CI][2]	ISA Treated Patients Mucor Primary Therapy ACM (%) [95% CI][2]	6-day delay Chamilos et al. ACM (%) [95% CI]	Untreated Patients Mucor Meta-Analysis[3] ACM (%) [95% CI][2]
Day 42	14/37 (37.8%) [22.5, 55.2]	7/21 (33.3%) [14.6, 57.0]	82.9% [68.9, 96.8]	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) 1 patient with unknown survival status at day 42 was assumed to be dead
2) Confidence intervals were calculated using exact binomial method
3) Based on Roden, Skiada, and Fungiscope. Number of Untreated patients = 292

Source: Adapted from Sponsor's Information Request Response Table 2, November 18, 2014.

Applicant Provided Review of the Scientific Literature (module 5.3.5.4):

A literature search was conducted in order to identify clinical trials reporting efficacy of AmB (including its lipid formulations) and posaconazole. The search was restricted to clinical trials in human, published in English without any time limits applied. The query was investigated using the Astellas internal STAR Literature AstellAsk database.

Thirty-nine publications (37 published papers and 2 posters) were identified from review of the literature of which 10 reported mortality data and 23 reported clinical efficacy data. The 10 publications that reported mortality data were analyzed by antifungal treatment and underlying condition.

- Five publications reported mortality in patients with mixed underlying conditions, (i.e. hematologic malignancies, solid organ transplant, diabetes) who were treated with amphotericin B formulations [Herbrecht et al, 2001; Chakrabarti et al, 2009; Shoham et al, 2010; Skiada et al, 2011; Lanternier et al, 2012].
- Two publications reported mortality in patients with mixed underlying conditions, who were treated with posaconazole [Greenberg et al, 2006; van Burik et al, 2006].
- Three publications reported mortality in patients with hematologic malignancies, who were treated with amphotericin B formulations [Gleissner et al, 2004; Pagano et al, 2004; Kara et al, 2009].

The 7 publications reporting mortality in patients with mixed underlying conditions who were treated with either amphotericin B or posaconazole have reported mortality rates in the range of 32% to 61%, with most of the reports showing mortality between 35% and 45% compared to 38% and 43% mortality rates observed through day 42 and day 84, respectively, in Study 9766-CL-0103.

The mortality data from the review are summarized in Table 41.

Table 41: Summary of Publications Reporting Mortality in Patients with Mixed Underlying Conditions Treated with Amphotericin B Formulations or Posaconazole

Author	Number of IM Patients Reported	Line of Therapy	Proportion of Study Population with:					Mortality† (%) (n/N)
			HM (%)	Surg (%)	Diss (%)	CNS (%)	DM (%)	
Herbrecht et al, 2001	21	R, I	48%	59%	29%	5%	29%	ABCD 35% (9/20)‡
Chakrabarti et al, 2009	75	N/K	9%	75%	5%	N/K	33%	All AmB forms 45% (24/53§)
Shoham et al, 2010	28	P	54%¶	46%	14%	N/K	7%	L-AmB 61% (17/28)

Skiada et al, 2011	230	P, R, I	44%	40%	15%	21%	17%	All AmB forms 39% (32/82)†† L-AmB 32% (20/62)
Lanternier et al, 2012a	34	P	53%	71%	18%	N/K	18%	L-AmB 42% (13/31)‡‡
Greenberg et al, 2006	24	P, R, I	58%	71%	17%	58%	21%	Posaconazole 38% (9/24)
van Burik et al, 2006	91	R, I	53%	70%	N/K	12%	33%	Posaconazole 38% (35/91)
Gleissner et al, 2004	120	N/K	94%	43%	32%	N/K	10%	AmB 61.3% (38/62) L-AmB 37.5% (6/16)
Pagano et al, 2004	59	P, R, I	100%	12%	7%	19%	17%	AmB/L-AmB 80% (47/59)
Kara et al, 2009	20	P, R, I	100%	100%	N/K	N/K	N/K	AmB/L-AmB 55% (11/20)

ABCD: amphotericin B coloidal dispersion; AmB: amphotericin B; CNS: patients with central nervous system infections; Diss: patients with disseminated infections; DM: patients with diabetes mellitus; HM: patients with hematologic malignancies; I: intolerant to other therapies' IM: invasive mucormycosis; L-AmB: liposomal amphotericin B; N/K: not known; P: primary; R: refractory to other therapies; Surg: patients with any surgical procedure/debridement performed to treat invasive mucormycosis.

† Timepoint for mortality varies across studies.

‡ One patient died before response could be assessed (death due to hepatic and renal failure considered not related to infection or therapy).

§ 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.

¶ Shoham 2010 reported patients with hematologic disorders rather than hematologic malignancies.

†† Only 82 out of 230 patients received amphotericin B formulations alone.

‡‡ 31 out of 34 patients were evaluable.

Source: Sponsor Module 5 Mucorales Literature Review, Tables 2, 3 and 4.

MO Comment: It is not unexpected that the rates of mortality reported are variable. It is extremely difficult to account for the numerous variables that may have influenced mortality estimates in different populations, including the means of invasive mucormycosis diagnosis, the site of infection, particular species, underlying host factors including the nature and degree of immunosuppression, complicating surgical and antifungal interventions, and the period of observation for determining mortality.

Matched-case Analysis for Study 0103 Primary Therapy of Patients with Invasive Mucormycosis

The Sponsor performed an additional analysis to compare isavuconazonium primary therapy with the current standard of care, amphotericin B. Study subjects with primary, proven, or probable mucormycosis were matched with patients from the Fungiscope Registry Database who received primary therapy with amphotericin B for proven or

probable invasive mucormycosis. The Fungiscope Registry is a global web-based database, coordinated from the Clinical Trials Centre at the University of Cologne, Germany. It contains a large collection of information on rare fungal infections, including more than 150 cases of invasive mucormycosis diagnosed and treated between 2003 and 2013.

Patient matching was independent of theApplicant and was performed at the Clinical Trials Centre at the University of Cologne, Germany by a physician blinded to the outcomes of Study 9766-CL-0103 cases as well as the Fungiscope Registry matched controls.

Eligible patients from Study 9766-CL-0103 were matched with up to 3 controls from the Fungiscope Registry Database for a total of 33 patients in the control group. Case matching used 3 primary criteria:

- Severe disease, defined as CNS involvement or disseminated disease, with the latter defined as a disease involving more than 1 non-contiguous organ.
- Surgery intended as therapeutic intervention for invasive mucormycosis and defined as resection/debridement at the site of infection 7 days prior to or after the start of their primary treatment.
- Underlying condition of hematologic malignancy.

The parameters and demographics of the matched populations are presented in Table 42.

Table 42: Demographic and Baseline Characteristics of the Fungiscope Matched-Case Control Study

Parameter Category/Statistic	**9766-CL-0103 Cases (n = 21)**	**Fungiscope Matched Controls**
Severe Disease		
Yes	12 (57.1%)	13
No	9 (42.9%)	20
Surgery		
Yes	9 (42.9%)	13
No	12 (57.1%)	20
Hematologic Malignancy		
Yes	11 (52.4%)	18
No	10 (47.6%)	15
Parameter	9766-CL-	Fungiscope Matched
Age (years)		
n	21	33
Mean (SD)	51.7 (14.72)	56.5 (12.98)
Min	25	22
Median	51.0	57.0
Max	77	81
Gender		
Male	17 (81.0%)	22 (66.7%)

Female	4 (19.0%)	11 (33.3%)
Race		
White	12 (57.1%)	31 (93.9%)
Black or African American	1 (4.8%)	0
Asian	8 (38.1%)	2 (6.1%)
Weight (kg)		
n	20	32
Mean (SD)	75.9 (19.88)	69.0 (14.60)
Min	48	43
Median	81.3	70.0
Max	112	104
Height (cm)		
n	21	33
Mean (SD)	169.7 (12.26)	170.9 (8.83)
Min	147	156
Median	171.0	173.0
Max	190	189

Source: Adapted from Module 5 Fungiscope Matched-Case Control Study, Tables 2 and 3.

The all-cause Mortality through Day 42 is presented in Table 43:

Table 43: Observed All-Cause Mortality Comparing Study 9766-CL-0103 to the Matched Fungiscope Controls

	All-cause Mortality	95% CI	Width of 95% CI
Observed Mortality - Study 0103 Primary Therapy Cases	33.3% (7/21)	(14.6%, 57.0%)†	42%
Observed Mortality - Fungiscope Matched-Controls	39.4% (13/33)	(22.9%, 57.9%)†	35%

Source: Adapted from from Module 5 Fungiscope Matched-Case Control Study and Sponsor's Information Request Response November 18, 2014.

MO Comment: The point estimates are not significantly different. The small number of subjects and wide confidence intervals do not permit a meaningful analysis of these data. Discussions with the Applicant indicated that it would not be feasible to power the study with greater numbers of patients.

MIC Breakpoint Analysis:
Analyses of clinical fungal isolates from patients in the study with positive culture were tested for antifungal susceptibility according to Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodologies. In the mITT-Mucorales population, the isavuconazonium CLSI MIC values ranged from 0.25 to 32 µg/mL. Pharmacodynamic studies for the assessment of pharmacodynamic targets and indices have not been established for Mucorales organisms, and MIC data from patients in the clinical trials are sparse. In addition, ECVs for Mucorales organisms are not established. Therefore, it is not possible to determine clinical interpretive breakpoints for organisms of the Mucorales order at this time. For more information, please refer to the Clinical Microbiology review.

7 Review of Safety

Safety Summary

The safety population of 1692 isavuconazonium exposed individuals included 1145 healthy subjects dosed in 40 phase 1 studies,144 subjects in the phase 2 trial population, and 403 subjects in the phase 3 trials. The phase 1 population included subjects with mild to moderate hepatic impairment as well as subjects with end-stage renal disease.

Isavuconazonium demonstrated an overall favorable safety profile with similar rates of mortality and non-fatal adverse events as the comparator, voriconazole. The proportion of all known patient deaths was similar between treatment groups (ISA: 31.5%, 81/257; VRC: 33.6%, 87/259). More than half of the subjects experienced a treatment emergent serious adverse event (SAE) in either treatment group. The overall incidence of treatment emergent SAEs was lower in isavuconazonium-treated subjects, 134/257 (52.1%), than in voriconazole-treated subjects 149/259 (57.5%). There were fewer adverse events leading to discontinuation of therapy in the isavuconazonium treatment arm 37/257 (14.4%) than in the voriconazole treatment arm 59/259 (22.8%).

The incidence of treatment emergent adverse events (TEAE) in isavuconazonium-treated subjects was significantly lower than voriconazole-treated subjects for the hepatobiliary, eye, and skin system organ classes (SOC).

Hepatotoxicity is a safety concern for the azole antifungal class, and in the controlled phase 3 trial, there were a total of 24 hepatobiliary adverse events in the isavuconazonium treatment group. Of these events, 12 (50%) resolved, 2 (8%) were improving, 9 (38%) were not resolved, and 1 (4%) event proved fatal (acute hepatitis). This is in comparison to voriconazole, in which there were 44 events: 21 (48%) resolved, 21(48%) were not resolved, and 2 (4%) were recovering. Isavuconazonium therapy was discontinued in the one patient (Subject 9709-12) with fatal hepatitis. Hy's Law criteria were met in 3 isavuconazonium-treated patients and 7 voriconazole-treated patients. One of the isavuconazonium treated patients who satisfied Hy's Law had a severe adverse reaction of acute hepatic failure with a fatal outcome.

A safety concern unique to the submission is the formation of drug particulate in the IV formulation. Following reconstitution, water soluble isavuconazonium sulfate may spontaneously hydrolyze in aqueous solution and a trace amount may precipitate as insoluble isavuconazonium. As a result, the study drug was administered through an

inline filter to remove particulate. There were 27 reported instances of isavuconazonium administration without an-line filter and there were no embolic, thromboembolic, or significant infusion site AEs observed within this patient subpopulation.

One unique safety finding different from other azole class antifungals is exposure-related shortening of the QT interval, the clinical significance of which is uncertain Two Thorough QT studies were conducted in healthy volunteers, neither of which showed QT prolongation, and both showed QT shortening. In study 9766-CL-0017, isavuconazonium 200 mg TID followed by 200 mg QD was administered for 11 days, or 600 mg TID followed by 600 mg QD for 11 days. For the isavuconazonium 200mg and 600mg treatment groups, the mean change from placebo baseline-adjusted in QTcF decreased by 9 to 13 msec and by 19 to 25 msec, respectively, within 1 hour and 24 hours post dose. No QTcF < 330 msec was observed. No QTcF prolongation was observed in the isavuconazonium treatment groups. The frequency of QT shortening TEAEs among isavuconazonium-treated patients in Trial 9766-CL-0104 was 0.4% (1 patient) with a QTcF of 378 msec, compared to none in the voriconazole treatment group. The adverse effect resolved the following day without treatment, and the patient withdrew consent. No events of ventricular tachycardia or ventricular fibrillation were observed on any of the centrally read ECGs for either treatment group. Familial QT shortening is a well-described clinical syndrome that can result in severe life-threatening ventricular arrhythmias, but there is no consensus in the scientific literature regarding thresholds of concern for drug induced QT shortening[12]. Drug induced QT shortening due to isavuconazonium presents a risk in patients with familial short QT syndrome, but it is difficult to estimate risk for the general patient population.

The other safety findings are consistent with the known adverse effects characteristic of azole-class antifungal drugs, namely hypersensitivity reactions, and infusion related reactions.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The most relevant trial population for this safety review is found within Study 9766-CL-0104, as this is the only active controlled, double-blind trial for the intended indication of treatment of invasive aspergillosis. Aggregate safety analyses were conducted of the two phase 3 studies, as well as the combined phase 2 and phase 3 trials. In addition, safety analyses of selected Phase 1 trials (e.g. a thorough QT study) were conducted. Phase 1 safety datasets were searched for adverse events of interest, such as liver function test abnormalities.

[12] Shah RR. Drug-induced QT interval shortening: potential harbinger of proarrhythmia and regulatory perspectives. *Br J Pharmacol*. Jan 2010; 159(1): 58–69.

Safety Population

The integrated safety populations are summarized in Table 44, and described below.

Table 44: Summary of Safety Populations in the Isavuconazonium Clinical Development Program

Category	Design	Isavuconazonium (n)	Comparators/ Controls (n)
Integrated 2 and phase 3 studies		**547**	**297**
Phase 2 studies		**144**	**38**
9766-CL-0101/WSA-CS-001	Double-blind	121	38
9766-CL-0102/WSA-CS-002	Open Label	23	0
Phase 3 studies		**403**	**259**
9766-CL-0103/WSA-CS-003	Open Label	146	0
9766-CL-0104/WSA-CS-004	Double-blind	257	259
Integrated phase 1 studies	Open Label	**1001**	**177**
Phase 1 studies completed after the data cutoff date			
9766-CL-0053	Open Label	24	0
9766-CL-0054	Open Label	24	0
Phase 1 renally-impaired subjects			
9766-CL-0018	Open Label	32	0
Phase 1 hepatically-impaired subjects			
9766-CL-0008	Open Label	32	0
9766-CL-0014	Open Label	32	0
TOTAL		**1692**	**474**

• Phase 3 Controlled Population: All subjects who received at least 1 dose of study medication, isavuconazonium or voriconazole, in active controlled, double-blind Study 9766-CL-0104, conducted globally in subjects with invasive fungal disease (IFD) caused by *Aspergillus* species or other filamentous fungi. Subjects could receive up to 84 days of study medication, and isavuconazonium was administered as an intravenous infusion or oral (hard capsule) therapy.

• Phase 2 and 3 Population: All subjects who received at least 1 dose of isavuconazonium (intravenous solution for infusion or hard capsule oral therapy) in one of the two phase 2 studies (9766-CL-0101 and 9766-CL-0102) or in the completed, controlled phase 3 study 9766-CL-0104 or the open-label phase 3 study 9766-CL-0103. Data from 146 subjects who received at least one dose of isavuconazonium in study 9766-CL-0103 are included in this population, with a data cut-off date of September 30, 2013.

• Phase 1 Population: All healthy subjects pooled from 38 phase 1 studies, including

23 drug-drug interaction (DDI) studies, conducted in North America, Europe, South Africa, and Asia.

A total of 1692 subjects received at least one dose of isavuconazonium in clinical studies. The integrated phase 1 population includes 1049 healthy subjects dosed in 38 phase 1 studies. The phase 2 studies include 144 subjects and the phase 3 studies include 403 subjects. Subjects in the safety population are included based on the treatment they received, irrespective of the treatment to which they were randomized.

Standard safety evaluations were conducted in all studies and included physical examinations, vital signs, and clinical laboratory evaluations, as well as monitoring for AEs and concomitant medication usage. Comprehensive electrocardiogram (ECG) evaluations were conducted in two TQT studies.

MO Comment: The two phase 2 studies (9766-CL-0101 and 9766-CL-0102), the phase 3 study 9766-CL-0104, and the open-label phase 3 study 9766-CL-0103 are of varying durations (up to 21 days, 28 days, 84 days, or 180 days or longer), indications (esophageal candidiasis [EC], fungal prophylaxis in acute myeloid leukemia [AML], IFD caused by Aspergillus in subjects with renal impairment , IFD caused by rare molds, yeasts or dimorphic fungi, or IFD caused by Aspergillus species or other filamentous fungi), study designs (open-label or double-blind parallel) and geographical locations (South Africa, Germany, or global). Therefore, substantial differences in indication, treatment duration, and dosage limit comparisons across study groups. Study 9766-CL-0104 is the only controlled phase 3 study in this application, therefore this population is the main source of data for the analyses of safety.

7.1.2 Categorization of Adverse Events

Treatment-emergent AEs were defined as any adverse experience that occurred during the period of study drug administration, whether or not it was considered study drug-related, extending to 28 days from the time of last exposure to study drug. Adverse events were mapped to Preferred Terms (PTs) using the MedDRA Version 12.1. All AEs are organized by System Organ Class (SOC) and preferred terms (PT). Events that have the potential to be coded into several categories were checked manually as well as analyzed by creating Standardized MedDRA Queries (SMQs).

Safety analyses were conducted by reviewing the sponsor's safety reviews and summaries and querying the submitted SDTM and ADaM datasets. In addition, safety datasets were analyzed with the MedDRA-Based Adverse Event Diagnostics March 10, 2014 release (MAED), an adverse event analysis tool. These analyses were conducted for all levels of the MedDRA hierarchy but preferred terms were included in the review. In addition, Standardized MedDRA Queries (SMQs)—narrow, broad, and algorithm were created to group closely related AEs. Safety analyses were also conducted using Empirica Study 3.1, JMP 11, and JReview 9.2.

The reviewer conducted searches for AEs across relevant SOCs, for instance for evaluation of the incidence of hypersensitivity reactions, adverse events were searched with terms included under the SOC of skin and subcutaneous tissue disorders (e.g. rash), immune system disorders (e.g. anaphylactoid reaction), and blood and lymphatic system disorders (e.g. eosinophilia).

The following groups of adverse events were analyzed in detail: Hepatic disorders and Liver Function Tests Abnormalities, Hypersensitivity Reactions, Visual Disturbances, Cardiac Arrhythmias. These events were selected for additional analyses because they were known to occur with azole class antifungals. Additionally, Thromboembolic AEs were analyzed due to the potential for drug precipitation in the infusion solution.

MO comment: Safety data were adequately reported at 3 levels as per ICH E3, and 21CFR§314.50, including extent of exposure, summary of adverse events and summary of changes in laboratory tests and electrocardiogram (ECG) parameters. MedDRA 12.1 was used to hierarchically encode verbatim terms into preferred terms, group terms, and system organ class.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling of data from the Phase 1, 2 and 3 studies was not done to compare incidence rates of adverse effects due to significant differences in study design, and drug exposure among the studies.

7.2 Adequacy of Safety Assessments

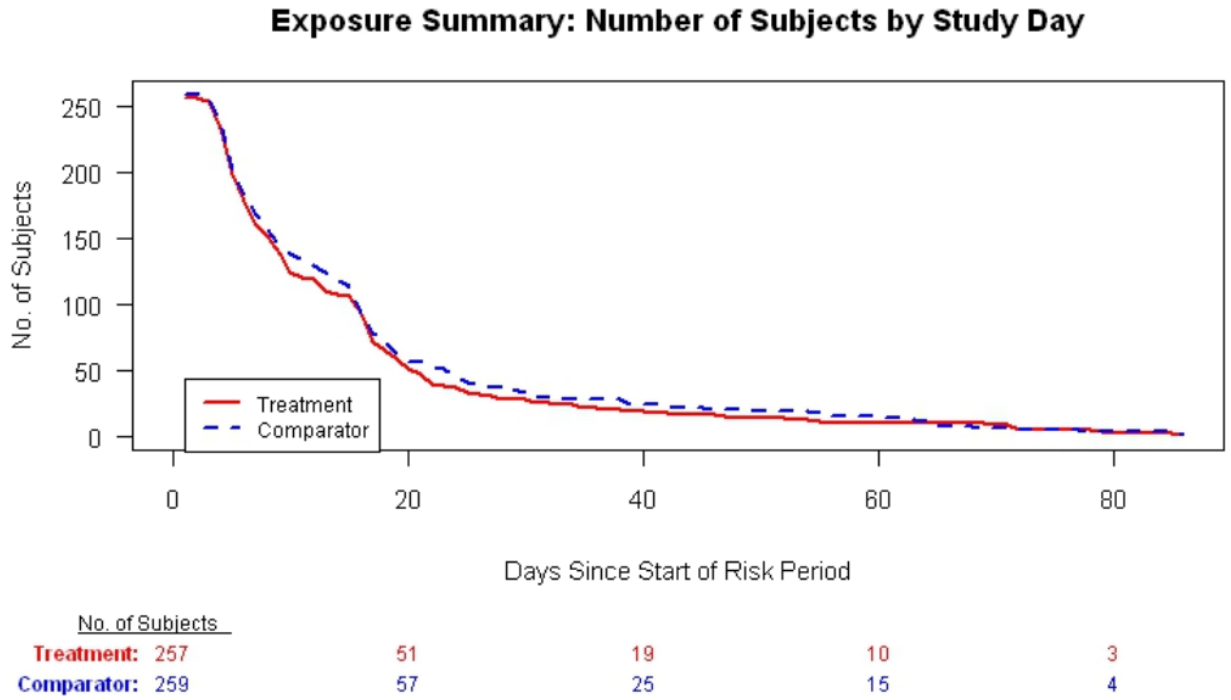
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 547 patients received at least one dose of isavuconazonium in the phase 2 and phase 3 studies, 144 patients in the phase 2 studies and 403 patients in the phase 3 studies. Mean exposure overall was 59.9 days.

A total of 309 of 547 patients (56.5%) received isavuconazonium for at least 21 days, 276 of 547 patients (50.5%) received isavuconazonium for at least 28 days, 144 of 547 patients (26.3%) received isavuconazonium for at least 84 days, and 52 of 547 patients (9.5%) received isavuconazonium for at least 180 days, 37 of the 52 received between 180 and 185 days and 15 received longer term isavuconazonium treatment (range 205-882 days) under the extension amendment of Study 9766-CL-0103.

Figure 8 depicts the relative exposure to study drug within the comparative phase 3 trial 9766-CL-0104, and Table 45 categorizes exposure by trial group.

Figure 8: Exposure Summary in Study 9766-CL-0104 to Isavuconazonium (Treatment) and Voriconazole (Comparator)



Source: Empirica Study using combined SDTM datasets from Study 9766-CL-0104

Table 45: Summary of Study Drug Exposure in the Integrated Phase 2 and 3 Study Safety Population

Characteristic	Phase 2 (n = 144)	Phase 3 (n = 403)	Total (n = 547)
Total Duration (days)			
Mean (SD)	14.8 (4.58)	76.1 (91.16)	59.9 (82.78)
Median	14.0	57.0	28.0
Min - Max	1 - 28	1 - 882	1 - 882
Total Duration Category (days)			
≤ 2	4 (2.8%)	9 (2.2%)	13 (2.4%)
> 2 to ≤ 7	3 (2.1%)	44 (10.9%)	47 (8.6%)
> 7 to ≤ 14	113 (78.5%)	35 (8.7%)	148 (27.1%)
> 14 to ≤ 21	15 (10.4%)	29 (7.2%)	44 (8.0%)
> 21 to ≤ 28	9 (6.3%)	18 (4.5%)	27 (4.9%)
> 28 to ≤ 42	0	33 (8.2%)	33 (6.0%)
> 42 to ≤ 56	0	33 (8.2%)	33 (6.0%)
> 56 to ≤ 84	0	97 (24.1%)	97 (17.7%)
> 84 to ≤ 126	0	38 (9.4%)	38 (6.9%)

> 126 to ≤ 180	0	33 (8.2%)	33 (6.0%)
> 180	0	34 (8.4%)	34 (6.2%)
Subject-years of Exposure (Total)	5.837	83.910	89.747

Source: Modified from Applicant Summary of Clinical Safety, Table 3.1

MO Comment: The exposures in the phase 3 studies adequately represent dosing and durations of treatment for the proposed indications, and allow a reasonable assessment of the safety in the intended population. It is noted, however, that drug exposure to African Americans is under-represented in the phase 3 study population relative to the population of the United States.The over-representation of older males is expected, as hematologic malignancy occurs more frequenctly in this population[13].

7.2.2 Explorations for Dose Response

The highest dose of isavuconazonium administered to healthy subjects was 600 mg per day in a thorough QT study (9766-CL-0017). The highest dose of isavuconazonium administered to patients in a phase 2 clinical study was a 24-hour loading dose of 1600mg isavuconazonium followed by 800 mg on day 2 and 400 mg per day thereafter (9766-CL-0102. Drug exposure by dose group is summarized in Table 46.

Table 46: Isavuconazonium Drug Exposure by Dose in the Overall Development Program

	Phase 2 Studies					**Phase 3 Studies**
N	**(n = 40)**	**(n = 41)**	**(n = 11)**	**(n = 12)**	**(n = 40)**	**(n = 403)**
Dose	**50 mg daily**	**100 mg daily**	**200 mg daily**	**400 mg daily**	**400 mg weekly**	**200 mg daily**

Summary of Study Drug Exposure in the Phase 1 Population (Safety Analysis Set)	
Category **Treatment Group**	**Number of Subjects Who Received At Least 1 Dose of Study Drug**
Single Dose	**293**
Isavuconazonium 40 mg	6/293 (2.0%)
Isavuconazonium 80 mg	6/293 (2.0%)
Isavuconazonium 100 mg	38/293 (13.0%)
Isavuconazonium 160 mg	6/293 (2.0%)
Isavuconazonium 200 mg	120/293 (41.0%)
Isavuconazonium 400 mg	103/293 (35.2%)
Total Single Dose Isavuconazonium	**279/293 (95.2%)**
Placebo	14/293 (4.8%)
Multiple Dose	**884**
Isavuconazonium 40 mg	6/884 (0.7%)
Isavuconazonium 50 mg	6/884 (0.7%)
Isavuconazonium 80 mg	6/884 (0.7%)

[13] Rodriguez-Abreu D, Bordoni A, Zucca E." Epidemiology of hematological malignancies." *Ann Oncol* (2007) 18 (suppl 1): i3-i8

Isavuconazonium 100 mg	175/884 (19.8%)
Isavuconazonium 150 mg	41/884 (4.6%)
Isavuconazonium 200 mg	490/884 (55.4%)
Isavuconazonium 600 mg	39/884 (4.4%)
Total Multiple Dose Isavuconazonium	**722/884 (81.7%)**
Placebo	128/884 (14.5%)
Number of Subjects Who Received At Least 1 Dose of	**1001**

Source: Adapted from Applicant Summary of Clinical Safety, Tables 3-4

In the phase 1 studies completed after the data cut-off date for inclusion in the integrated Phase 1 Population, 24 subjects received multiple doses of isavuconazonium 200 mg in Study 9766-CL-0053 and 24 subjects received multiple doses of isavuconazonium 200 mg in Study 9766-CL-0054.

In study 9766-CL-0018, 11 subjects with end-stage renal disease received 2 doses of isavuconazonium 200 mg and 21 subjects with various degrees of renal impairment received a single dose of isavuconazonium 200 mg.

In studies 9766-CL-0008 and 9766-CL-0014, 64 subjects with hepatic impairment received a single dose of isavuconazonium 100 mg.

7.2.3 Special Animal and/or In Vitro Testing

Nonclinical testing was adequate. The reader is referred to the Non-Clinical / Toxicology review by Dr. Owen McMaster for more detail.

7.2.4 Routine Clinical Testing

Standard safety evaluations were conducted in all studies and included physical examinations, vital signs, and clinical laboratory evaluations, as well as monitoring for AEs and concomitant medication usage. Comprehensive electrocardiogram (ECG) evaluations were conducted in two TQT studies. The laboratory safety tests included hematology, biochemistry and urinalysis. In the two phase 3 studies, physical exams were conducted at screening, EOT, and upon follow up. Vital signs were assessed at screening and on days 1, 2, 3, 7, 14, 28, 42, 84 (and additionally for study 9766-CL-0103 every 4 weeks) through EOT and follow-up visit. Twelve-lead ECG recordings were obtained at screening and on days 1, 14, 42 and 84 (and additionally for study 9766-CL-0103 every 4 weeks thereafter until EOT). Laboratory samples for the safety profile were collected at screening, days 7, 14, 28, 42, (and additionally for study 9766-CL-0103 on day 84, and every 4 weeks thereafter) through EOT, and at follow-up. In case of abnormalities observed at the follow-up visit, safety evaluations were performed at a second follow-up visit. Safety evaluations were performed while the patient was receiving study drug, with the exception of the screening and follow-up visits. The reader is referred to section 5.3 for individual study details.

MO Comment: Overall, routine clinical assessments in the isavuconazonium development program were adequate to assess the safety of the study drug.

7.2.5 Metabolic, Clearance, and Interaction Workup

Isavuconazonium pharmacokinetics were evaluated in healthy subjects, as well as in subjects with renal and hepatic impairment within the phase 1 clinical development program. *In vitro* studies demonstrated that isavuconazonium is hydrolyzed in blood to isavuconazonium by esterases, predominately by butyrylcholinesterase. *In vivo* studies indicate that CYP3A4, CYP3A5, and subsequently uridine diphosphate-glucuronosyltransferases (UGT) are involved in the metabolism of isavuconazonium. CYP3A inhibitors or inducers alter the plasma concentrations of isavuconazonium. *In vitro*, isavuconazonium is an inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2C19 and CYP2D6. Isavuconazonium is also an inhibitor of P-gp-, BCRP- and OCT2-mediated drug transports. Isavuconazonium is an inducer of CYP1A2, CYP3A4/5, CYP2B6, CYP2C8 and CYP2C9 *in vitro*. The effect of isavuconazonium on the pharmacokinetics of co-administered drugs was assessed in phase 1 studies after single and multiple doses of isavuconazonium were administered to healthy subjects.

The reader is referred to the Clinical Pharmacology Review by Dr. Dakshina Chilukuri.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Isavuconazonium is a member of the azole class of antifungal agents, which includes drugs such as voriconazole, posaconazole, fluconazole and itraconazole. Drug-drug interactions, elevated liver transaminases, QT prolongation/torsades de pointes are important azole class effects. Additional class effects include severe cutaneous adverse reactions, anaphylaxis, infusion site reactions, and visual disturbances or hallucinations.

Comprehensive electrocardiogram (ECG) evaluations were conducted in two TQT studies, 9766-CL-004 and 9766-CL-0017. Study, 9766-CL-0017, was performed because the first study,9766-CL-004, did not reflect a therapeutic, or supratherapeutic dose at steady state.

Routine clinical evaluations and laboratory testing conducted in the isavuconazonium development program allowed adequate assessment of the AEs associated with azoles. The results of these analyses are presented in sections 7.4.1 Common Adverse Events and 7.4.2 Laboratory Findings.

7.3 Major Safety Results

7.3.1 Deaths

The proportion of all known patient deaths was similar between treatment groups (ISA: 31.5%, 81/257; VRC: 33.6%, 87/259). All known deaths include all patient deaths regardless of the number of days after the last dose of study drug. All known deaths also include patient deaths during the course of the study due to an AE that started prior to the first dose of study drug. Deaths that occurred following drug exposure, up to 28 days from the day of the last drug exposure, are considered treatment emergent adverse effects (TEAE). A summary of the categories of all known deaths that occurred in this study is found below, in Table 47.

Table 47: Categorization of Deaths Occurring within the Phase 3 Controlled Population

Category	ISA (n = 257)	VRC (n = 259)
Deaths within 28 days after EOT, TEAE reported	61	69
Deaths within 28 days after the EOT, AE onset prior to treatment	1	1
Deaths > 28 days after the EOT, TEAE reported	1	3
Deaths > 28 days after the EOT, AE onset prior to treatment	13	11
Deaths > 28 days after the EOT, no AE reported	5	3
Total of all known deaths following drug exposure	81	87

AE: adverse event; EOT: end of treatment; ISA: isavuconazonium; TEAE: treatment-emergent AE; VRC: voriconazole.

Source: FDA Reviewer generated using JMP 11 and ADAE dataset from Study 9766-CL-0104

Treatment Emergent Adverse Events Leading to Death

The overall pattern of TEAEs leading to death was similar between treatment groups (ISA: 24.1%, 62/257; VRC: 27.8%, 72/259), and are summarized in Table 48.

Table 48: Summary of Treatment Emergent Adverse Events Leading to Death in the Phase 3 Controlled Population

MedDRA v12.1 System Organ Class Preferred Term	Isavuconazonium	Voriconazole (n = 259)
Overall	**62 (24.1%)**	**72 (27.8%)**
Blood and lymphatic system disorders	**2 (0.8%)**	**1 (0.4%)**
Haemorrhagic disorder	1 (0.4%)	0
Pancytopenia	0	1 (0.4%)
Thrombocytopenia	1 (0.4%)	0
Cardiac disorders	**4 (1.6%)**	**5 (1.9%)**
Acute myocardial infarction	0	1 (0.4%)
Cardiac arrest	1 (0.4%)	3 (1.2%)
Cardio-respiratory arrest	1 (0.4%)	1 (0.4%)
Congestive cardiomyopathy	1 (0.4%)	0
Pericarditis	1 (0.4%)	0

Gastrointestinal disorders	**0**	**1 (0.4%)**
Rectal haemorrhage	0	1 (0.4%)
General disorders and administration site conditions	**2 (0.8%)**	**8 (3.1%)**
Death	1 (0.4%)	1 (0.4%)
Multi-organ failure	1 (0.4%)	6 (2.3%)
Sudden cardiac death	0	1 (0.4%)
Hepatobiliary disorders	**1 (0.4%)**	**0**
Hepatitis acute	1 (0.4%)	0
Immune system disorders	**1 (0.4%)**	**0**
Acute graft versus host disease	1 (0.4%)	0
Infections and infestations	**28 (10.9%)**	**18 (6.9%)**
Acinetobacter bacteraemia	1 (0.4%)	0
Aspergillosis	3 (1.2%)	2 (0.8%)
Bronchopulmonary aspergillosis	1 (0.4%)	0
Endocarditis	1 (0.4%)	0
Fungal infection	3 (1.2%)	2 (0.8%)
Fusarium infection	1 (0.4%)	0
Infection	1 (0.4%)	0
Klebsiella sepsis	0	1 (0.4%)
Mucormycosis	1 (0.4%)	0
Pneumonia	1 (0.4%)	2 (0.8%)
Pseudomonal bacteraemia	0	1 (0.4%)
Pseudomonal sepsis	0	1 (0.4%)
Sepsis	7 (2.7%)	5 (1.9%)
Septic shock	8 (3.1%)	4 (1.5%)
Stenotrophomonas sepsis	0	1 (0.4%)
Metabolism and nutrition disorders	**0**	**2 (0.8%)**
Hypoglycaemia	0	1 (0.4%)
Metabolic acidosis	0	1 (0.4%)
Neoplasms benign, malignant and unspecified	**10 (3.9%)**	**21 (8.1%)**
Acute lymphocytic leukaemia recurrent	0	1 (0.4%)
Acute myeloid leukaemia	3 (1.2%)	7 (2.7%)
Acute myeloid leukaemia recurrent	0	4 (1.5%)
B-cell lymphoma	0	1 (0.4%)
Blast cell crisis	1 (0.4%)	1 (0.4%)
Burkitt's leukaemia	0	1 (0.4%)
Chronic lymphocytic leukaemia	0	2 (0.8%)
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

Source: Reviewer generated using JMP 11 and ADAE dataset from trial 9766-CL-0104

To further define the subjects with fatal outcomes, Table 49 provides information on all adverse events resulting in a fatal outcome within the controlled study population.

Table 49: All Treatment Emergent Adverse Events Resulting in Death in the Phase 3 Controlled Population

Subject ID	Age	Sex	Arm	Days on Study Drug	Study Day of Death	Verbatim Term	Relatedness†	Treatment Emergent
Blood and lymphatic system disorders					(b) (6)			
WSACS004-0118-20	69	F	Isavuconazonium	62		PROFOUND THROMBOCYTOPENIA	Unrelated	Y
WSACS004-0704-02	25	M	Isavuconazonium	21		HEMORRHAGIC SYNDROME	Unrelated	Y
Cardiac disorders								
WSACS004-0105-03	59	M	Isavuconazonium	10		CARDIAC ARREST	Unrelated	Y
WSACS004-0707-01	25	M	Isavuconazonium	91		ACUTE PERICARDITIS	Unrelated	Y
WSACS004-4910-14	72	F	Isavuconazonium	39		CARDIAC DECOMPENSATION	Unrelated	N
WSACS004-5407-02	35	M	Isavuconazonium	54		CARDIO RESPIRATORY ARREST	Unrelated	Y
WSACS004-8206-02	22	F	Isavuconazonium	33		DILATED CARDIOMYOPHATHY	Remotely related	Y
General disorders and administration site conditions								
WSACS004-3204-52	21	F	Isavuconazonium	35		MULTIORGAN FAILURE	Unrelated	Y
WSACS004-9104-03	25	F	Isavuconazonium	25		DEATH CAUSE UNKNOWN	Unrelated	Y
Hepatobiliary disorders								
WSACS004-9709-12	58	M	Isavuconazonium	4		ACUTE HEPATITIS	Remotely related	Y
Immune system disorders								
WSACS004-3204-34	18	F	Isavuconazonium	84		REFRACTORY ACUTE GVHD	Unrelated	Y
Infections and infestations								
WSACS004-0118-04	79	F	Isavuconazonium	14		SEPSIS	Unrelated	Y
WSACS004-2002-02	54	F	Isavuconazonium	3		SEPTIC SHOCK	Unrelated	Y
WSACS004-3203-05	64	M	Isavuconazonium	17		SEPTIC SHOCK	Unrelated	Y

					(b) (6)			
WSACS004-3204-03	42	F	Isavuconazonium	20		PROGRESSION PULMONARY INFECTION	Unrelated	N
WSACS004-3204-44	62	F	Isavuconazonium	8		PROGRESSION INVASIVE ASPERGILLOSIS	Unrelated	Y
WSACS004-3204-55	57	M	Isavuconazonium	10		PROGRESSION INVASIVE ASPERGILLOSIS	Unrelated	Y
WSACS004-3206-15	81	M	Isavuconazonium	9		PROGRESSION ASPERGILLOSIS	Unrelated	Y
WSACS004-3206-26	69	M	Isavuconazonium	6		PROGRESSIVE PULMONARY ASPERGILLOSIS	Unrelated	Y
WSACS004-3301-09	63	F	Isavuconazonium	15		SEPTIC SHOCK	Unrelated	Y
WSACS004-3301-21	74	M	Isavuconazonium	6		DISSEMINATED MUCORMYCOSIS	Unrelated	Y
WSACS004-3304-01	68	M	Isavuconazonium	3		ENDOCARDITIS (AORTIC)	Unrelated	Y
WSACS004-4909-02	65	M	Isavuconazonium	7		WORSENING OF PNEUMONIA	Unrelated	Y
WSACS004-4909-07	41	F	Isavuconazonium	18		SEPSIS	Unrelated	Y
WSACS004-4910-11	67	M	Isavuconazonium	7		PROGRESSIVE FUNGAL PNEUMONIA	Unrelated	N
WSACS004-4910-15	66	M	Isavuconazonium	21		SEPSIS	Unrelated	N
WSACS004-4910-21	70	F	Isavuconazonium	5		SEPSIS	Unrelated	N
WSACS004-4913-03	54	M	Isavuconazonium	7		KLEBSIELLA OXYTOCA SEPSIS	Unrelated	N
WSACS004-5410-02	53	M	Isavuconazonium	9		SEPTIC SHOCK	Unrelated	Y
WSACS004-5503-05	18	M	Isavuconazonium	7		FUNGICAL DISSEMINATED DISEASE (PROGRESSION OF FUNGAL DISEASE)	Unrelated	Y
WSACS004-5503-06	63	F	Isavuconazonium	20		SEPSIS (NOS)	Unrelated	Y
WSACS004-6606-04	55	M	Isavuconazonium	2		DEATH DUE TO SEVERE SEPSIS	Possibly related	Y
WSACS004-6607-09	49	F	Isavuconazonium	51		ACINETOBACTER BAUMANII MDR BACTEREMIA	Unrelated	Y
WSACS004-8205-11	68	F	Isavuconazonium	8		SEPSIS	Unrelated	Y

					(b) (6)			
WSACS004-8206-01	50	F	Isavuconazonium	16		DISEASE PROGRESSION OF INVASIVE FUNGAL DISEASE	Possibly related	Y
WSACS004-8208-02	43	F	Isavuconazonium	6		SEPTIC SHOCK	Unrelated	Y
WSACS004-9103-01	59	M	Isavuconazonium	11		REFRACTIVE SEPTIC SHOCK	Unrelated	Y
WSACS004-9114-04	67	F	Isavuconazonium	13		SEPTICEMIC SHOCK	Unrelated	Y
WSACS004-9114-07	34	M	Isavuconazonium	20		SEPSIS	Unrelated	Y
WSACS004-9703-08	44	F	Isavuconazonium	2		SEPTIC SHOCK	Unrelated	N
WSACS004-9704-03	76	F	Isavuconazonium	85		PSEUDOMONAS SEPTIC SHOCK	Unrelated	Y
WSACS004-9704-19	68	F	Isavuconazonium	5		DISSEMINATED FUSARIUM INFECTION	Unrelated	Y
WSACS004-9709-05	46	F	Isavuconazonium	9		EXACERBATION OF INFECTION	Unrelated	Y
WSACS004-9709-12	58	M	Isavuconazonium	4		SEPSIS	Unrelated	Y
WSACS004-9709-15	71	F	Isavuconazonium	24		INVASIVE FUNGAL DISEASE PROGRESSION	Probably related	Y
Neoplasms benign, malignant and unspecified (incl cysts and p								
WSACS004-0115-06	68	M	Isavuconazonium	7	(b) (6)	CHRONIC LYMPHOCYTIC LEUKEMIA, RELAPSED, PROGRESSION	Unrelated	Y
WSACS004-0118-09	41	M	Isavuconazonium	73		REFRACTORY MULTIPLE MYELOMA	Unrelated	Y
WSACS004-0118-15	62	F	Isavuconazonium	68		MYELOID LEUKEMIA PROGRESSION	Unrelated	Y
WSACS004-0118-20	69	F	Isavuconazonium	62		PROGRESSION OF MULTIPLE MYELOMA	Unrelated	Y
WSACS004-3204-17	65	F	Isavuconazonium	19		PROGRESSION NON HODGKIN LYMPHOMA (WALDENSTROM)	Unrelated	N
WSACS004-3204-54	71	M	Isavuconazonium	8		REFRACTORY LEUKEMIA	Unrelated	N
WSACS004-3301-18	82	F	Isavuconazonium	42		PROGRESSION OF MYELODYSPLASTIC SYNDROME	Unrelated	Y
WSACS004-4909-06	61	F	Isavuconazonium	17		BLAST CRISIS	Unrelated	Y

					(b) (6)			
WSACS004-4913-10	68	F	Isavuconazonium	35		PROGRESSIVE DISEASE OF ACUTE MYELOID LEUKEMIA	Unrelated	Y
WSACS004-5510-01	52	M	Isavuconazonium	5		ACUTE MYELOID LEUKEMIA	Unrelated	N
WSACS004-6602-05	45	F	Isavuconazonium	57		WORSENING ACUTE MYELOLIOD LEUKEMIA (AML)	Unrelated	Y
WSACS004-6602-09	66	F	Isavuconazonium	35		WORSENING NHL	Unrelated	N
WSACS004-8205-06	51	F	Isavuconazonium	12		AGGRAVATED REFRACTORY ACUTE MYELOGENOUS LEUKEMIA	Unrelated	Y
WSACS004-9703-09	51	M	Isavuconazonium	73		MALIGNANT NEOPLASM PROGRESSION	Unrelated	Y
Nervous system disorders								
WSACS004-0118-20	69	F	Isavuconazonium	62		INTRACRANIAL BLEED	Unrelated	Y
WSACS004-3601-01	36	F	Isavuconazonium	45		INTRACRANIAL BLEEDING	Unrelated	Y
WSACS004-5404-02	56	F	Isavuconazonium	46		CNS TOXICITY DUE TO TACROLIMUS	Unrelated	Y
WSACS004-5517-01	47	F	Isavuconazonium	43		HEMORRAGIC STROKE	Unrelated	N
Renal and urinary disorders								
WSACS004-0118-04	79	F	Isavuconazonium	14		RENAL FAILURE	Unrelated	Y
Respiratory, thoracic and mediastinal disorders								
WSACS004-0118-04	79	F	Isavuconazonium	14		RESPIRATORY FAILURE	Unrelated	Y
WSACS004-0118-23	30	M	Isavuconazonium	10		ACUTE RESPIRATORY FAILURE	Unrelated	Y
WSACS004-0708-01	29	F	Isavuconazonium	3		ACUTE RESPIRATORY INSUFFICIENCY	Unrelated	N
WSACS004-2001-01	32	F	Isavuconazonium	4		ACUTE RESPIRATORY FAILURE	Remotely related	Y
WSACS004-2004-04	22	M	Isavuconazonium	33		SEVERE RESPIRATORY DISTRESS	Remotely related	Y
WSACS004-3204-21	52	M	Isavuconazonium	84		ACUTE PULMONARY HEMORRHAGE	Unrelated	Y
WSACS004-5202-02	57	F	Isavuconazonium	4		SEVERE RESPIRATORY FAILURE	Unrelated	Y

					(b) (6)			
WSACS004-5503-05	18	M	Isavuconazonium	7		ACUTE REPIRATORY INSUFFICIENCY	Unrelated	Y
WSACS004-5602-01	43	M	Isavuconazonium	10		HEMOPTYSIS	Unrelated	Y
WSACS004-6001-02	63	M	Isavuconazonium	4		PULMONARY HAEMORRHAGE	Unrelated	Y
WSACS004-6607-01	56	M	Isavuconazonium	41		RESPIRATORY INSUFFICIENCY	Unrelated	Y
WSACS004-8205-05	38	M	Isavuconazonium	37		RESPIRATORY FAILURE	Unrelated	Y
WSACS004-8613-02	20	F	Isavuconazonium	15		SEVERE HEMOPTYSIS	Unrelated	Y
WSACS004-9119-01	20	M	Isavuconazonium	13		RESPIRATORY FAILURE	Unrelated	Y
WSACS004-9703-06	60	M	Isavuconazonium	8		RESPIRATORY INSUFICIENCY	Unrelated	N
WSACS004-9709-06	65	F	Isavuconazonium	9		RESPIRATORY INSUFFICIENCY	Unrelated	Y
Vascular disorders								
WSACS004-4913-07	72	M	Isavuconazonium	36		DIFFUSE BLEEDING	Unrelated	Y
WSACS004-8207-01	42	M	Isavuconazonium	14		HYPOVOLEMIC SHOCK	Unrelated	Y
Blood and lymphatic system disorders								
WSACS004-5517-02	53	F	Voriconazole	75		PANCYTOPENIA	Unrelated	Y
WSACS004-6602-03	66	M	Voriconazole	27		PROGRESSION OF APLASTIC ANEMIA	Unrelated	N
Cardiac disorders								
WSACS004-3201-12	54	M	Voriconazole	7		SUDDEN CARDIAC ARREST	Unrelated	Y
WSACS004-3308-01	55	F	Voriconazole	3		DEATH DUE TO CARDIOPULMONARY ARREST	Possibly related	Y
WSACS004-5601-01	61	F	Voriconazole	28		ASYSTOLE	Possibly related	Y
WSACS004-6602-02	70	F	Voriconazole	14		ACUTE MI	Unrelated	Y
WSACS004-6603-09	55	M	Voriconazole	2		CARDIAC ARREST	Possibly related	Y

Gastrointestinal disorders							
WSACS004-3206-16	87	M	Voriconazole	12	RECTAL BLEEDING	Unrelated	Y
General disorders and administration site conditions							
WSACS004-0108-02	44	F	Voriconazole	4	DEATH/UNKNOWN CAUSE		N
WSACS004-0115-09	61	F	Voriconazole	68	SUDDEN CARDIAC DEATH	Unrelated	Y
WSACS004-0118-18	58	M	Voriconazole	18	MULTI-ORGAN FAILURE NOS, RESPIRATORY FAILURE, RENAL FAILURE	Possibly related	Y
WSACS004-0706-01	61	F	Voriconazole	68	MULTIPLE ORGAN FAILURE	Unrelated	Y
WSACS004-3204-01	45	M	Voriconazole	20	MULTI ORGAN FAILURE	Unrelated	Y
WSACS004-3206-23	54	M	Voriconazole	13	MULTIPLE ORGAN FAILURE	Unrelated	Y
WSACS004-4909-01	48	M	Voriconazole	23	SEPTIC MULTIPLE ORGAN FAILURE	Unrelated	N
WSACS004-4909-05	47	F	Voriconazole	18	SEPTIC MULTIPLE ORGAN FAILURE	Unrelated	Y
WSACS004-4914-01	64	M	Voriconazole	11	MULTI-ORGAN-FAILURE	Unrelated	Y
WSACS004-5202-03	65	M	Voriconazole	5	MULTIPLE ORGAN FAILURE	Unrelated	N
WSACS004-8604-03	59	M	Voriconazole	7	UNKNOWN CAUSE OF DEATH	Unrelated	Y
Infections and infestations							
WSACS004-0118-21	74	M	Voriconazole	10	KLEBSIELLA PNEUMONIAE, SEPTIC SHOCK	Unrelated	N
WSACS004-0702-01	47	M	Voriconazole	10	SEPSIS DUE TO STENOTROPHOMONAS MALTOPHILIA	Unrelated	Y
WSACS004-0706-01	61	F	Voriconazole	68	SEVERE SEPSIS, SEPTIC SHOCK	Unrelated	Y
WSACS004-3204-11	58	M	Voriconazole	3	PROGRESSIVE INVASIVE ASPERGILLOSIS	Unrelated	Y
WSACS004-3204-14	57	M	Voriconazole	7	DISSEMINATED ANGIO-INVASIVE ASPERGILLOSIS (INVOLVING LUNG AND LIVER AT AUTOPSY)	Unrelated	Y
WSACS004-3204-18	67	F	Voriconazole	22	MULTIRESISTANT PSEUDOMONAS AERUGINOSA INFECTION	Unrelated	N

(b) (6)

					(b) (6)			
WSACS004-3204-22	64	M	Voriconazole	39		PSEUDOMONAS AERUGINOSA SEPTICAEMIA	Unrelated	Y
WSACS004-3204-32	34	M	Voriconazole	7		SEPTIC SHOCK DUE TO GRAM NEGATIVE BACTERIA	Unrelated	Y
WSACS004-3204-43	36	M	Voriconazole	29		PSEUDOMONAS AERUGINOSA BACTEREMIA [WORSENING]	Unrelated	Y
WSACS004-3301-12	59	M	Voriconazole	11		SEVERE SEPSIS DUE TO KLEBSIELLA PNEUMONIA BACTEREMIA	Unrelated	Y
WSACS004-4910-07	67	F	Voriconazole	5		WORSENING OF FUNGAL INFECTION	Unrelated	Y
WSACS004-4910-20	63	M	Voriconazole	15		SEPSIS	Unrelated	Y
WSACS004-5202-03	65	M	Voriconazole	5		UROSEPSIS	Unrelated	N
WSACS004-5202-03	65	M	Voriconazole	5		SEPTIC SHOCK	Unrelated	N
WSACS004-5503-02	59	M	Voriconazole	53		SEPTIC SHOCK	Unrelated	Y
WSACS004-5507-01	53	M	Voriconazole	42		FUNGAL INFECTION DISSEMINATED BY RHIZOPUS SP.	Unrelated	Y
WSACS004-6603-03	38	F	Voriconazole	47		HOSPITAL ACQUIRED PNEUMONIA	Unrelated	Y
WSACS004-6606-03	39	M	Voriconazole	54		SEPTIC SHOCK FROM MIXED BACTERIA PNEUMONIA WITH STAPHYLOCOCCUS AUREUS AND ACINETOBACTER SP.	Unrelated	Y
WSACS004-8613-01	43	M	Voriconazole	8		SEPSIS	Unrelated	Y
WSACS004-8613-01	43	M	Voriconazole	8		SEVERE PNEUMONIA WITH UNKNOWN CAUSATIVE ORGANISM	Unrelated	Y
WSACS004-9001-01	30	M	Voriconazole	5		SEPSIS (DISEASE PROGRESSION)	Unrelated	Y
WSACS004-9114-01	22	M	Voriconazole	14		SEPTICEMIA	Unrelated	Y
WSACS004-9114-06	54	M	Voriconazole	14		SEPTICEMIA (PSEUDOMONAS AERUGINOSA)	Unrelated	N
WSACS004-9114-08	44	M	Voriconazole	3		FUNGAL SEPTICEMIA	Unrelated	N
WSACS004-9701-05	51	F	Voriconazole	85		SEPSIS	Unrelated	Y
WSACS004-9704-02	54	M	Voriconazole	62		PROBABLE FUSARIUM INFECTION RELAPSE	Unrelated	N

					(b) (6)			
WSACS004-9709-07	51	M	Voriconazole	7		SEPTIC SHOCK	Unrelated	N
Metabolism and nutrition disorders								
WSACS004-3204-60	75	M	Voriconazole	48		HYPOGLYCAEMIA	Unrelated	Y
WSACS004-5507-01	53	M	Voriconazole	42		METABOLIC ACIDOSIS	Unrelated	Y
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
WSACS004-0113-04	67	F	Voriconazole	15	(b) (6)	WORSENING RELAPSE ACUTE MYELOCYTIC LEUKEMIA	Unrelated	Y
WSACS004-0115-05	69	M	Voriconazole	9		ACUTE MYELOID LEUKEMIA, REFRACTORY	Unrelated	Y
WSACS004-0115-07	47	F	Voriconazole	56		ACUTE MYELOID LEUKEMIA, RELAPSED	Unrelated	Y
WSACS004-0119-01	67	F	Voriconazole	7		PROGRESSION OF REFRACTORY AML	Unrelated	Y
WSACS004-0702-04	46	F	Voriconazole	84		TUMOR PROGRESSION OF T-CELLS MALIGNANT LYMPHOMA	Unrelated	Y
WSACS004-3201-01	26	M	Voriconazole	42		PROGRESSION OF ACUTE MYELOID LEUKEMIA	Unrelated	Y
WSACS004-3204-30	37	F	Voriconazole	84		PERSISTENT MYELOID LEUKEMIA	Unrelated	Y
WSACS004-3206-04	66	M	Voriconazole	32		PROGRESSION OF CHRONIC LYMPHOCYTIC LEUKEMIA	Unrelated	Y
WSACS004-3206-10	77	M	Voriconazole	14		PROGRESSION OF ACUTE MYELOID LEUCEMIA	Unrelated	Y
WSACS004-3206-14	66	F	Voriconazole	4		WORSENING OF TUMOR PROGRESSION	Unrelated	Y
WSACS004-3206-20	75	M	Voriconazole	12		PROGRESSION ACUTE MYELOID LEUCEMIA	Unrelated	Y
WSACS004-3206-31	69	M	Voriconazole	58		PROGRESSION ACUTE MYELOGENOUS LEUKEMIA	Unrelated	Y
WSACS004-3301-16	71	F	Voriconazole	81		PROGRESSION OF LARGE B CELL LYMPHOMA	Unrelated	Y
WSACS004-4909-04	64	F	Voriconazole	11		BLAST CRISIS	Unrelated	Y
WSACS004-4910-23	49	M	Voriconazole	4		BURKITT LIKE B-ALL	Unrelated	Y
WSACS004-	74	F	Voriconazole	17		PROGRESSIVE DISEASE OF AML	Unrelated	Y

4913-04								
WSACS004-4913-06	80	M	Voriconazole	35	(b) (6)	PROGRESSIVE DISEASE OF AML	Unrelated	Y
WSACS004-5502-02	21	F	Voriconazole	32		ACUTE LYMPHOCYTIC RELAPSE	Unrelated	Y
WSACS004-5503-07	62	M	Voriconazole	13		CHRONIC LYMPHOCYTIC LEUKEMIA PROGRESSION	Unrelated	Y
WSACS004-6601-01	20	M	Voriconazole	35		WORSENING ACUTE MYELOGENOUS LEUKEMIA	Unrelated	N
WSACS004-6603-05	18	M	Voriconazole	76		PROGRESSION OF LYMPHOBLASTIC LYMPHOMA	Unrelated	Y
WSACS004-9704-02	54	M	Voriconazole	62		RELAPSE OF ACUTE MYELOID LEUKEMIA	Unrelated	Y
WSACS004-9709-08	57	F	Voriconazole	24		RELAPSE OF MULTIPLE MYELOMA	Unrelated	N
WSACS004-9709-17	30	F	Voriconazole	1		ACUTE MYELOID LEUKEMIA	Unrelated	N
Nervous system disorders								
WSACS004-0118-08	65	M	Voriconazole	9		HEMORRHAGE INTRACRANIAL	Unrelated	Y
WSACS004-0118-17	31	M	Voriconazole	5		INTRACRANIAL HEMMORRHAGE	Unrelated	Y
WSACS004-3204-48	65	F	Voriconazole	63		MENIGO ENCEPHALITIS	Unrelated	Y
WSACS004-3301-11	61	F	Voriconazole	85		CEREBRAL HEMORRHAGE	Unrelated	Y
WSACS004-4913-09	70	M	Voriconazole	6		SUSPECTED INTRACRANIAL HAEMORRHAGE (CONFIRMED)	Unrelated	Y
WSACS004-5401-01	58	F	Voriconazole	17		SPONTANEOUS ACUTE SUBARACNOID HEMORRAGE	Possibly related	Y
WSACS004-9704-06	61	F	Voriconazole	22		STUPOR	Unrelated	Y
Respiratory, thoracic and mediastinal disorders								
WSACS004-0118-13	59	M	Voriconazole	50		ACUTE RESPIRATORY FAILURE	Unrelated	Y
WSACS004-0119-01	67	F	Voriconazole	7		PULMONARY EMBOLISM	Unrelated	Y
WSACS004-3204-25	77	M	Voriconazole	7		RESPIRATORY FAILURE	Unrelated	Y

					(b) (6)			
WSACS004-3204-36	30	F	Voriconazole	44		SEVERE PULMONARY HYPERTENSION	Unrelated	Y
WSACS004-3204-40	60	M	Voriconazole	16		RESPIRATORY INSUFFICIENCY	Unrelated	Y
WSACS004-3903-01	39	F	Voriconazole	13		HEMOPTYSIS	Unrelated	Y
WSACS004-6607-07	36	F	Voriconazole	21		LUNG HEMORRHAGE	Unrelated	Y
WSACS004-8604-02	41	M	Voriconazole	1		RESPIRATORY FAILURE	Unrelated	Y
WSACS004-8616-03	36	M	Voriconazole	5		RESPIRATORY FAILURE	Remotely related	Y
WSACS004-9101-02	38	M	Voriconazole	5		IMPENDING RESPIRATORY FAILURE REQUIRING ICU ADMISSION AND INTRAPULMONARY HAEMORHAGE LEADING TO DEATH	Unrelated	Y
WSACS004-9104-05	60	M	Voriconazole	10		ACUTE RESPIRATORY DISTRESS SYNDROME	Unrelated	Y
WSACS004-9709-02	45	F	Voriconazole	25		SEVERE RESPIRATORY INSUFFICIENCY	Unrelated	Y
Vascular disorders								
WSACS004-0119-01	67	F	Voriconazole	7		DEEP VEIN THROMBOSIS	Unrelated	Y

Source: Reviewer generated using JMP 11and ADAE dataset from Study 9766-CL-0104
*Excludes Deaths > 28 days after the EOT in which no AE was reported
† Investigator reported

The TEAEs leading to death that occurred in ≥ 2% of patients in the isavuconazonium or voriconazole groups, respectively, were septic shock (3.1% vs 1.5%), sepsis (2.7% vs 1.9%), respiratory failure (2.3% vs 2.3%), acute myeloid leukemia (1.2% vs 2.7%) and multi-organ failure (0.4% vs 2.3%). A case of fatal acute hepatitis and second patient with acute liver failure within the isavuconazonium treatment groups are discussed in Section 7.3.4, Significant Adverse Events.

One subject within the isavuconazonium group, and two subjects within the voriconazole groups were classified as death due to unknown causes. The subject who received isavuconazonium, WSACS004-9104-03, was a 25 year old female / with non-Hodgkin's Lymphoma, who underwent chemotherapy at (b) (6) days before study enrollment. She was neutropenic, with mucositis, and probable pulmonary invasive fungal disease diagnosed by CT and a positive serum galactomannan. On Day (b) (6) the patient was taken off the study and discharged from the hospital with progression of non-Hodgkin's lymphoma. The myeloblast count on Day 25 was 62 x 10^3/uL. The patient died at home on Day (b) (6), from an unknown cause, but presumably this was due to complications from progression of malignancy.

MO Comment: Given that the ITT population contains immunosuppressed subjects with malignancy, significant mortality due to progression of infections and malignancy is not unexpected. As such, mortality was the primary endpoint for the analysis of isavuconazonium efficacy (Section 6). The patient population treated with isavuconazonium had a similar incidence and distribution of adverse events resulting in death to the voriconazole comparator group.

In the Phase 2 and 3 Population, 107 deaths occurred through 28 days after the last dose of study drug, as summarized in Tables 50 and 51.

Table 50: Summary of Mortality in the Phase 2 and 3 Population

Parameter	Phase 2 (n = 144)	Phase 3 (n = 403)	Total (n = 547)
Number of deaths occurring through 28 days after last dose	3	104	107
Number of deaths occurring beyond 28 days after last dose	0	24	24
Total deaths†	3	128	131

† 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.

Source: FDA Reviewer generated using JMP 11 and Integrated safety dataset

Table 51: Treatment Emergent Adverse Events Leading to Death in the Phase 2 and 3 Populations

MedDRA v12.1 System Organ Class Preferred Term	Phase 2 (n = 144)	Phase 3 (n = 403)	Total (n = 547)
Overall	**3 (2.1%)**	**106 (26.3%)**	**109 (19.9%)**
Blood and lymphatic system disorders	**0**	**2 (0.5%)**	**2 (0.4%)**
Haemorrhagic disorder	0	1 (0.2%)	1 (0.2%)
Thrombocytopenia	0	1 (0.2%)	1 (0.2%)
Cardiac disorders	**0**	**7 (1.7%)**	**7 (1.3%)**
Cardiac arrest	0	1 (0.2%)	1 (0.2%)
Cardiac failure acute	0	1 (0.2%)	1 (0.2%)
Cardio-respiratory arrest	0	3 (0.7%)	3 (0.5%)
Congestive cardiomyopathy	0	1 (0.2%)	1 (0.2%)
Pericarditis	0	1 (0.2%)	1 (0.2%)
General disorders and administration site conditions	**0**	**7 (1.7%)**	**7 (1.3%)**
Death	0	4 (1.0%)	4 (0.7%)
General physical health deterioration	0	1 (0.2%)	1 (0.2%)
Multi-organ failure	0	2 (0.5%)	2 (0.4%)
Hepatobiliary disorders	**0**	**1 (0.2%)**	**1 (0.2%)**
Hepatitis acute	0	1 (0.2%)	1 (0.2%)
Immune system disorders	**0**	**2 (0.5%)**	**2 (0.4%)**
Acute graft versus host disease	0	1 (0.2%)	1 (0.2%)
Graft versus host disease	0	1 (0.2%)	1 (0.2%)
Infections and infestations	**3 (2.1%)**	**49 (12.2%)**	**52 (9.5%)**
Acinetobacter bacteraemia	0	1 (0.2%)	1 (0.2%)
Aspergillosis	0	4 (1.0%)	4 (0.7%)
Bacterial sepsis	0	1 (0.2%)	1 (0.2%)
Bronchopulmonary aspergillosis	0	1 (0.2%)	1 (0.2%)
Empyema	0	1 (0.2%)	1 (0.2%)
Endocarditis	0	1 (0.2%)	1 (0.2%)
Fungal infection	0	3 (0.7%)	3 (0.5%)
Fungal sepsis	0	1 (0.2%)	1 (0.2%)
Fusarium infection	0	1 (0.2%)	1 (0.2%)
Infection	0	1 (0.2%)	1 (0.2%)
Lung infection	0	1 (0.2%)	1 (0.2%)
Lung infection pseudomonal	0	1 (0.2%)	1 (0.2%)
Meningitis tuberculosis	1 (0.7%)	0	1 (0.2%)
Mucormycosis	0	2 (0.5%)	2 (0.4%)
Pneumonia	0	3 (0.7%)	3 (0.5%)
Pneumonia blastomyces	0	1 (0.2%)	1 (0.2%)
Pneumonia fungal	0	2 (0.5%)	2 (0.4%)
Pneumonia primary atypical	0	1 (0.2%)	1 (0.2%)
Pseudomonal sepsis	0	1 (0.2%)	1 (0.2%)
Pulmonary tuberculosis	1 (0.7%)	0	1 (0.2%)
Sepsis	0	8 (2.0%)	8 (1.5%)
Septic shock	0	12 (3.0%)	12 (2.2%)
Sinusitis fungal	0	1 (0.2%)	1 (0.2%)
Staphylococcal sepsis	0	1 (0.2%)	1 (0.2%)
Tuberculous pleurisy	1 (0.7%)	0	1 (0.2%)
Neoplasms benign, malignant and unspecified	**0**	**17 (4.2%)**	**17 (3.1%)**
Acute lymphocytic leukaemia recurrent	0	1 (0.2%)	1 (0.2%)
Acute myeloid leukaemia	0	4 (1.0%)	4 (0.7%)
Acute myeloid leukaemia recurrent	0	1 (0.2%)	1 (0.2%)
Blast cell crisis	0	1 (0.2%)	1 (0.2%)
Chronic lymphocytic leukaemia	0	1 (0.2%)	1 (0.2%)

Chronic lymphocytic leukaemia recurrent	0	1 (0.2%)	1 (0.2%)
Leukaemia recurrent	0	1 (0.2%)	1 (0.2%)
Malignant neoplasm progression	0	3 (0.7%)	3 (0.5%)
Multiple myeloma	0	2 (0.5%)	2 (0.4%)
Myelodysplastic syndrome	0	1 (0.2%)	1 (0.2%)
Myeloid leukaemia	0	1 (0.2%)	1 (0.2%)
Nervous system disorders	**0**	**5 (1.2%)**	**5 (0.9%)**
Cerebral infarction	0	2 (0.5%)	2 (0.4%)
Haemorrhage intracranial	0	2 (0.5%)	2 (0.4%)
Neurotoxicity	0	1 (0.2%)	1 (0.2%)
Renal and urinary disorders	**0**	**2 (0.5%)**	**2 (0.4%)**
Renal failure	0	1 (0.2%)	1 (0.2%)
Renal failure acute	0	1 (0.2%)	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	**0**	**18 (4.5%)**	**18 (3.3%)**
Acute respiratory failure	0	4 (1.0%)	4 (0.7%)
Dyspnoea	0	1 (0.2%)	1 (0.2%)
Haemoptysis	0	3 (0.7%)	3 (0.5%)
Pulmonary haemorrhage	0	2 (0.5%)	2 (0.4%)
Respiratory distress	0	1 (0.2%)	1 (0.2%)
Respiratory failure	0	7 (1.7%)	7 (1.3%)
Vascular disorders	**0**	**3 (0.7%)**	**3 (0.5%)**
Arteritis	0	1 (0.2%)	1 (0.2%)
Haemorrhage	0	1 (0.2%)	1 (0.2%)
Hypovolaemic shock	0	1 (0.2%)	1 (0.2%)

Source: FDA Reviewer generated using JMP 11 and Integrated safety dataset, in agreement with Applicant's Summary of Clinical Safety, Table 29.

MO Comment: The tables are in agreement with Applicant's analysis. The small number of deaths in the phase 2 studies (3/144) reflects the lower morbidity burden in the 9766-CL-0101 study in esophageal candidiasis patients (n=121), as well as and the duration of observation. Within the overall population, trends observed in the controlled study are consistent in the global isavuconazonium- treated population, with complications from infection (9.5%), malignancy (3.1%), and pulmonary disease (3.3%) most frequently accounting for fatal outcomes.

There were no deaths within the Phase 1 study population.

A subject death occurring beyond 28 days from the last exposure to the study drug was not considered treatment emergent. Deaths occurring beyond 28 days from the last exposure to the study drug in the phase 3 controlled population, are presented in Table 52. Within this group mortality was balanced between treatment arms, with 12 deaths occurring in the isavuconazonium –treated group, and 13 deaths in the voriconazole-treated group.

Table 52: Adverse Events with Fatal Outcome Occurring beyond 28 Days from Last Dose of Study Drug, Study 9766-CL-0104.

		TRT01A		
		ISAVUCONAZOLE	VORICONAZOLE	All
AEBODSYS	AEDECOD	N	N	N
Blood and lymphatic system disorders	Aplastic anaemia	0	1	1
	All	0	1	1
Cardiac disorders	Cardiac failure	1	0	1
	All	1	0	1
General disorders and administration site conditions	Death	0	1	1
	Multi-organ failure	0	2	2
	All	0	3	3
Infections and infestations	Fusarium infection	0	1	1
	Klebsiella sepsis	1	0	1
	Lung infection	1	0	1
	Pneumonia fungal	1	0	1
	Pseudomonal sepsis	0	1	1
	Pseudomonas infection	0	1	1
	Sepsis	2	0	2
	Septic shock	1	3	4
	Urosepsis	0	1	1
	All	6	7	13
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute myeloid leukaemia	0	1	1
	Leukaemia	1	0	1
	Multiple myeloma	0	1	1
	Non-Hodgkin's lymphoma	2	0	2
	All	3	2	5
Nervous system disorders	Haemorrhagic stroke	1	0	1
	All	1	0	1
Respiratory, thoracic and mediastinal disorders	Respiratory failure	1	0	1
	All	1	0	1
All	All	12	13	25

Source: Reviewer generated using JMP 11 and ADAE dataset from Study 9766-CL-0104

7.3.2 Nonfatal Serious Adverse Events

Within the Phase 3 controlled trial population, more than half of the subjects experienced a treatment emergent serious adverse event (SAE) in either treatment group. The overall incidence was lower in the isavuconazonium-treated subjects, 134/257 (52.1%), than in the voriconazole-treated subjects 149/259 (57.5%). After excluding the subjects with a fatal outcome, 99/257 (38.5%) of isavuconazonium-treated subjects and 121/259 (46.7%) of voriconazole- treated subjects experienced a serious treatment emergent adverse event. The incidence of nonfatal, treatment emergent, SAE by system organ class is categorized in Table 53. The categories for which isavuconazonium had a higher incidence than voriconazole of treatment emergent SAE are expanded to the lowest level term. A TEAE with a missing seriousness value was considered a serious TEAE.

Table 53: Nonfatal Serious Treatment Emergent Adverse Events by System Organ Class in the Phase 3 Controlled Population

	Isavuconazonium (n = 257)		Voriconazole (n = 259)	
MedDRA v12.1 System Organ Class Patient Term	**Number of Subjects**	**Proportion (%)**	**Number of Subjects**	**Proportion (%)**
Overall	**99**	**38.5**	**121**	**46.7**
Blood and lymphatic system disorders	27	10.5	17	6.6
Agranulocytosis	2	0.8	0	0.0
Anaemia	1	0.4	2	0.8
Febrile neutropenia	14	5.4	5	1.9
Haemorrhagic anaemia	0	0.0	1	0.4
Leukocytosis	1	0.4	0	0.0
Microangiopathic haemolytic anaemia	0	0.0	1	0.4
Neutropenia	4	1.6	3	1.2
Pancytopenia	4	1.6	3	1.2
Splenic infarction	1	0.4	0	0.0
Thrombocytopenia	2	0.8	4	1.5
Thrombocytopenic purpura	0	0.0	1	0.4
Respiratory, thoracic and mediastinal disorders	27	10.5	33	12.7
Infections and infestations	26	10.1	46	17.8
Nervous system disorders	14	5.5	10	3.9
Aphasia	0	0.0	1	0.4
Brain stem stroke	1	0.4	0	0.0
Central nervous system lesion	1	0.4	1	0.4
Cerebral ischaemia	1	0.4	0	0.0
Convulsion	3	1.2	1	0.4
Dizziness	0	0.0	1	0.4
Encephalopathy	1	0.4	1	0.4
Epilepsy	2	0.8	1	0.4
Febrile convulsion	1	0.4	0	0.0
Grand mal convulsion	0	0.0	1	0.4
Headache	1	0.4	0	0.0
Hemiplegia	0	0.0	1	0.4
Ischaemic stroke	1	0.4	1	0.4
Paraplegia	1	0.4	1	0.4
Polyneuropathy	2	0.8	0	0.0
Tremor	0	0.0	1	0.4
VIIth nerve paralysis	0	0.0	1	0.4
General disorders and administration site conditions	10	3.9	12	4.6
Gastrointestinal disorders	9	3.5	11	4.3
Neoplasms benign, malignant and unspecified (including cysts and polyps)	9	3.5	9	3.5
Renal and urinary disorders	9	3.5	10	3.9
Cardiac disorders	7	2.7	7	2.7
Immune system disorders	3	1.2	6	2.3
Injury, poisoning and procedural complications	3	1.2	3	1.2
Investigations	3	1.2	6	2.3
Musculoskeletal and connective tissue disorders	3	1.2	0	0.0

Skin and subcutaneous tissue disorders	3	1.2	2	0.8
Decubitus Ulcer	1	0.4	0	0.0
Dermatitis	1	0.4	0	0.0
Panniculitis	1	0.4	0	0.0
Rash	0	0.0	2	0.8
Eye disorders	2	0.8	1	0.4
Hepatobiliary disorders	2	0.8	6	2.3
Metabolism and nutrition disorders	2	0.8	6	2.3
Vascular disorders	2	0.8	5	1.9
Psychiatric disorders	1	0.4	6	2.3

Source: Reviewer generated using JMP 11 and ADAE dataset from trial 9766-CL-0104
*Individual subjects may have several closely related nonfatal SAE (i.e. WSAC004-3301-11 voriconazole arm: aphasia, hemiplegia and 7th nerve palsy)

MO Comment: The high incidence of SAEs within the blood and lymphatic system disorders SOC is expected, as 23 of 27 isavuconazonium-treated subjects and 14 of the 17 voriconazole-treated subjects had an uncontrolled hematologic malignancy at baseline. An examination of the nervous system disorders SOC in Table 53 at the lowest level term reveals more serious, non-fatal convulsive AEs (convulsion, epilepsy, febrile convulsion, and grand mal convulsion) within the isavuconazonium treatment arm when combining these preferred terms, (7 events in 6 subjects) than within the voriconazole arm (3 events in 3 subjects). In each case, there was confounding by underlying conditions and/or exposure to other medications with seizure potential. All of the patients recovered from the seizures. Convulsions have been described at the case report level for other systemic antifungal azoles, such as fluconazole[14], which also contains a precaution on the label advising against operating a vehicle due to dizziness or seizure.

When all SAE are tabulated by frequency at the preferred term level (Table 54), the number of patients who experienced serious TEAEs remained generally similar between treatment groups with the exception of febrile neutropenia (5.4% vs 1.9%), septic shock (5.4% vs 3.9%) and dyspnea (1.9% vs 0.4%), which were more often experienced by isavuconazonium- treated patients. Hallucination and visual hallucination, were experienced by voriconazole-treated, but not by isavuconazonium-treated patients.

Table 54: Serious Treatment Emergent Adverse Events (≥ 1%) in the Phase 3 Controlled Population

MedDRA v12.1 Preferred Term	Isavuconazonium (n = 257)	Voriconazole (n = 259)

[14] Matsumoto K, Ueno K, Yoshimura H, Morii M, Takada M, Sawai T, Mitsutake K, & Shibakawa M. "Fluconazole-induced convulsions at serum trough concentrations of approximately 80 microg/mL". *Ther Drug Monit.* 2000 Oct;22(5):635-6.

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%)
Dyspnea	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 leukemia	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%)
Hemorrhage 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 hemorrhage	0	3 (1.2%)
Bacterial sepsis	0	4 (1.5%)
Staphylococcal bacteremia	0	3 (1.2%)
Acute myeloid leukemia recurrent	0	5 (1.9%)
Epistaxis	0	4 (1.5%)
Lung infiltration	0	3 (1.2%)
Pulmonary embolism	0	3 (1.2%)

Source: Reviewer generated using JMP 11 and ADAE dataset from trial 9766-CL-0104

Standardized medical queries (SMQ) were next used to group SAEs that occurred at incidence greater than 2% (Table 55). This broad analysis included SAEs that occurred at any point during the study and also included fatal outcomes. There were no significant differences between the treatment arms.

Table 55: Most Common Severe Adverse Events (>2%) by SMQ in the Phase 3 Controlled Population

	ISAVUCONAZONIUM (N = 257)			VORICONAZOLE (N = 259)			
SMQ (Narrow Search)	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)	Risk Difference (%)
Haematopoietic cytopenias	43	26	10.12	43	19	7.34	2.78
Acute central respiratory depression	21	20	7.78	25	23	8.88	-1.1
Leukopenia	26	19	7.39	20	10	3.86	3.53
Agranulocytosis	23	18	7	13	11	4.25	2.76

Shock	20	18	7	28	24	9.27	-2.26
Malignancies	17	17	6.61	33	30	11.58	-4.97
Hepatic disorders	16	14	5.45	36	21	8.11	-2.66
Drug related hepatic disorders - comprehensive search	16	14	5.45	36	21	8.11	-2.66
Toxic-septic shock conditions	14	14	5.45	14	13	5.02	0.43
Liver related investigations, signs and symptoms	15	13	5.06	31	19	7.34	-2.28
Haemorrhages	12	12	4.67	25	20	7.72	-3.05
Gastrointestinal nonspecific inflammation and dysfunctional conditions	12	10	3.89	14	11	4.25	-0.36
Gastrointestinal nonspecific symptoms and therapeutic procedures	12	10	3.89	14	11	4.25	-0.36
Acute renal failure	10	9	3.5	13	13	5.02	-1.52
Thrombocytopenia	12	7	2.72	19	11	4.25	-1.52
Central nervous system haemorrhages and cerebrovascular conditions	7	7	2.72	7	7	2.7	0.02
Convulsions	6	6	2.33	2	2	0.77	1.56

Source: Reviewer generated using MAED, JMP 11 and ADAE dataset from trial 9766-CL-0104

Serious TEAEs occurred in 42.0% of patients in the Phase 2 and 3 Population. The highest incidence of serious TEAEs were infections (20.3%) and respiratory events (11.3%) (Table 56).

Table 56: Serious Treatment Emergent Adverse Events by System Organ Class in the Integrated Phase 2 and 3 Population

MedDRA v12.1 System Organ Class	**Phase 2 (n = 144)**	**Phase 3 (n = 403)**	**Total (n = 547)**
Overall	**7 (4.9%)**	**223 (55.3%)**	**230 (42.0%)**
Infections and Infestations	5 (3.5%)	106 (26.2%)	111 (20.3%)
Respiratory, Thoracic and Mediastinal Disorders	1 (0.7%)	61 (15.1%)	62 (11.3%)
Blood and Lymphatic System Disorders	0	33 (8.2%)	33 (6.0%)
Gastrointestinal Disorders	0	27 (6.7%)	27 (4.9%)
Neoplasms Benign, Malignant and Unspecified	0	26 (6.5%)	26 (4.8%)
Nervous System Disorders	0	26 (6.5%)	26 (4.8%)
Cardiac Disorders	1 (0.7%)	19 (4.7%)	20 (3.7%)

General Disorders and Administration Site Conditions	0	20 (5.0%)	20 (3.7%)
Renal and Urinary Disorders	0	19 (4.7%)	19 (3.5%)
Immune System Disorders	0	9 (2.2%)	9 (1.6%)
Metabolism and Nutrition Disorders	0	9 (2.2%)	9 (1.6%)
Vascular Disorders	0	9 (2.2%)	9 (1.6%)
Hepatobiliary Disorders	0	8 (2.0%)	8 (1.5%)
Musculoskeletal and Connective Tissue Disorders	0	7 (1.7%)	7 (1.3%)
Eye Disorders	0	4 (1.0%)	4 (0.7%)
Injury, Poisoning and Procedural Complications	0	3 (0.7%)	3 (0.5%)
Investigations	0	3 (0.7%)	3 (0.5%)
Psychiatric Disorders	0	3 (0.7%)	3 (0.5%)
Skin and Subcutaneous Tissue Disorders	0	3 (0.7%)	3 (0.5%)
Reproductive System and Breast Disorders	0	1 (0.2%)	1 (0.2%)

Source: Adapted from Applicant Summary of Clinical Safety, Table 33, in agreement with Reviewer nnalysis using JMP 11 and Integrated Data Set.

MO comment: The general pattern of treatment emergent SAEs was similar among the clinical trials involving isavuconazonium.

Phase 1 Serious Adverse Events

Four subjects experienced serious adverse events in the phase 1 studies (0.4%, 4/1001), 1 subject received a single dose of isavuconazonium and 3 subjects received multiple doses:

1. [Study 9766-CL-0005 isavuconazonium and ketoconazole or rifampicin interaction study, subject no. 55)]. A 33-year-old healthy male subject experienced elevation of ALT from study day 36 through day 183. The subject received isavuconazonium alone on days 1 through 14, rifampicin alone on days 36 through 43, isavuconazonium/rifampicin combined on days 44 through 57, and rifampicin alone on days 58 through 71. On Day 36 just before the first dose of rifampicin, an SAE of ALT increased (ALT 84 U/L [normal range 0-40]) was reported. Elevated AST (44 U/L [normal range 0-40 U/L]) was also reported on Day 36. ALT increased to 108 U/L on day 39 during dosing with rifampicin alone, and to 179 U/L on day 58, after dosing with combined isavuconazonium/rifampicin. Alkaline phosphatase (ALP) and bilirubin levels were within normal limits throughout the study. The subject completed treatment, but thereafter a further increase in ALT to a maximum of 844 U/L on day 99 (28 days after last dose) was noted. ALT levels gradually returned to normal on day 183. The subject received no concurrent medications, and laboratory tests for causes of infectious hepatitis were negative, and the subject denied alcohol and drug use. The SAE was resolved on day 183 and was considered possibly related to study drug.

   MO Comment: The elevation in liver enyzmes appears to be temporally related to rifampicin exposure, but I cannot exclude contribution from isavuconazonium since the LFT elevations began following ISV exposure, continued during co-administration, and resolved with de-challenge.

2. [Study 9766-CL-0014 (hepatic impairment pharmacokinetic study, subject no. 34)] A 64-year-old healthy female subject received one dose of oral isavuconazonium 100 mg on study day 1. The subject initially experienced a TEAE of facial neuritis 2 weeks after the single dose of

isavuconazonium. The subject received chloropyramine, drotaverine, metamizole, nimesulide, pentoxyfylline, and platyphyline for the treatment of this event and for the treatment of a TEAE of back pain.

On Day 18, the subject experienced muscular weakness, pain in joints and pain in the muscles and an SAE of Guillain-Barre syndrome was diagnosed. Adverse events of elevated ALT (112 U/L [nl range 9-52]) and AST (149 U/L [nl range 14-36]) were reported on Day 21, 20 days after the last dose of isavuconazonium. Also observed were elevations of alkaline phosphatase (258 U/L [nl range 38-126]) and GGT (137 U/L [nl range 12-43]). Further increases of AST (203 U/L), alkaline phosphatase (331 U/L), GGT (463 U/L) were noted on Day 26 in association with elevation of total bilirubin (54.72 µmol/L [nl range 3.42-22.23]). The subject's condition worsened with increasing muscle weakness and muscle pain and she was hospitalized on Day(b) (6) An SAE of bacterial meningoencephalitis was reported. The subject's condition improved and she was discharged on Day (b) (6) The SAEs of Guillain-Barre Syndrome and meningoencephalitis were considered severe by the investigator and not related to study drug; the sponsor assessed the SAEs as unlikely to be related to isavuconazonium. The elevated liver chemistries were resolved by Day 56 and were considered by the investigator to be unrelated to isavuconazonium..

MO Comment: I agree that the SAEs of Guillain-Barre Syndrome and meningoencephalitis and probably not related to isavuconazonium exposure.

3. [Study 9766-CL-0031 (oral contraceptive interaction study, subject no. 22391003)] A 64-year-old healthy female experienced SAEs of gastritis and gastroesophageal reflux disease during follow-up, (b) (6) after her last dose of isavuconazonium 200 mg. The subject was hospitalized and the events resolved on Days 54 and 32, respectively. The investigator considered the SAE of gastritis to be mild in intensity and the gastroesophageal reflux disease to be severe in intensity; both events were considered by the investigator to be probably related to isavuconazonium and oral contraceptives.

   MO Comment: I agree that the SAEs of gastritis and gastroesophageal reflux may be related Isavuconazonium exposure.

4. [Study 9766-CL-0042 (dextromethorphan interaction study, subject no. 22741022)] A 38-year-old female received dextromethorphan on study day 1 (single dose) and isavuconazonium 200 mg tid on Days 6 and 7 and isavuconazonium 200 mg qd on Day 8. The subject experienced perioral numbness and numbness in the right arm and right leg on Da (b) (6) Both events were considered SAEs because they were events of medical importance. An additional adverse event of lightheadedness was reported and resolved on Day 7. The subject was withdrawn from the study on day 8 and all numbness resolved by Day 9. The investigator considered the serious adverse events of perioral numbness and numbness right arm and right leg to be mild in intensity, probably related to isavuconazonium and not related to dextromethorphan.

   MO Comment: I agree that the SAEs numbness may be related Isavuconazonium exposure, since it is temporally related and resolved with de-challenge.

7.3.3 Dropouts and/or Discontinuations

There were fewer isavuconazonium patients (14.4%) than voriconazole patients (22.8%) with at least one adverse event leading to permanent discontinuation of study drug
(Table 57). Patients in the isavuconazonium group compared to the voriconazole group had fewer events in the hepatobiliary disorders (0.4% vs 2.3%), skin and subcutaneous tissue disorders (0.8% vs 1.9%) and psychiatric disorders (0.8% vs 2.3%) SOCs leading to discontinuation of study drug. The proportion of patients was similar between treatment groups for the remaining SOCs.

Table 57: Treatment Emergent Adverse Events Leading to Permanent Discontinuation in the Phase 3 Controlled Population

MedDRA v12.1 **System Organ Class** Patient Term	**Isavuconazonium (n = 257)**		**Voriconazole (n = 259)**	
	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)
Overall	**37**	**14.4**	**59**	**22.8**
Blood and lymphatic System Disorders	**1**	**0.4**	**3**	**1.2**
Microangiopathic haemolytic anaemia	0	0	1	0.4
Pancytopenia	1	0.4	1	0.4
Splenic lesion	0	0	1	0.4
Cardiac disorders	**4**	**1.6**	**3**	**1.2**
Cardiac arrest	1	0.4	1	0.4
Cardio-respiratory arrest	1	0.4	1	0.4
Congestive cardiomyopathy	1	0.4	0	0
Supraventricular tachycardia	1	0.4	0	0
Ventricular tachycardia	0	0	1	0.4
Eye Disorders	**1**	**0.4**	**1**	**0.4**
Eyelid oedema	0	0	1	0.4
Optic neuropathy	1	0.4	0	0
Gastrointestinal Disorders	**2**	**0.8**	**3**	**1.2**
Dysphagia	1	0.4	0	0
Nausea	0	0	2	0.8
Small intestinal obstruction	1	0.4	0	0
Vomiting	1	0.4	2	0.8
General Disorders	**1**	**0.4**	**1**	**0.4**
Chills	1	0.4	1	0.4
Hepatobiliary disorders	**1**	**0.4**	**6**	**2.3**
Hepatic failure	0	0	2	0.8
Hepatic function abnormal	0	0	1	0.4
Hepatic lesion	0	0	1	0.4
Hepatitis	0	0	1	0.4
Hepatitis acute	1	0.4	0	0
Hyperbilirubinaemia	0	0	2	0.8
Hypertransaminasaemia	0	0	1	0.4

Immune System Disorders	**0**	**0**	**1**	**0.4**
Acute graft versus host disease in liver	0	0	1	0.4
Infections and infestations	**11**	**4.3**	**15**	**5.8**
Aspergillosis	1	0.4	1	0.4
Bacterial sepsis	0	0	3	1.2
Bronchopneumonia	1	0.4	0	0
Bronchopulmonary aspergillosis	1	0.4	0	0
Endocarditis	1	0.4	0	0
Fungal infection	2	0.8	1	0.4
Infection	1	0.4	0	0
Lung infection	0	0	2	0.8
Meningitis	0	0	1	0.4
Mucormycosis	0	0	1	0.4
Pneumonia	1	0.4	1	0.4
Pseudomonal sepsis	0	0	1	0.4
Sepsis	1	0.4	3	1.2
Septic shock	2	0.8	0	0
Staphylococcal infection	0	0	1	0.4
Systemic candida	0	0	1	0.4
Injury, Poisoning and Procedural	**1**	**0.4**	**0**	**0**
Overdose	1	0.4	0	0
Investigations	**4**	**1.6**	**6**	**2.3**
Alanine aminotransferase increased	0	0	1	0.4
Aspartate aminotransferase increased	0	0	1	0.4
Blood alkaline phosphatase increased	0	0	1	0.4
Blood bilirubin increased	2	0.8	0	0
Blood sodium decreased	1	0.4	0	0
Electrocardiogram QT prolonged	0	0	1	0.4
Hepatic enzyme increased	0	0	1	0.4
Liver function test abnormal	0	0	2	0.8
Transaminases increased	1	0.4	0	0
Metabolism and Nutrition Disorders	**0**	**0**	**1**	**0.4**
Metabolic acidosis	0	0	1	0.4
Musculoskeletal and Connective Tissue	**1**	**0.4**	**0**	**0**
Myositis	1	0.4	0	0
Neoplasms Benign, Malignant and	**0**	**0**	**7**	**2.7**
Acute myeloid leukaemia	0	0	4	1.5
Acute myeloid leukaemia recurrent	0	0	1	0.4
Chronic lymphocytic leukaemia	0	0	1	0.4
Lung neoplasm malignant	0	0	1	0.4
Nervous system Disorders	**5**	**1.9**	**4**	**1.5**
Convulsion	2	0.8	0	0
Encephalopathy	1	0.4	0	0
Epilepsy	2	0.8	0	0
Grand mal convulsion	0	0	1	0.4
Stupor	0	0	1	0.4
Subarachnoid haemorrhage	0	0	1	0.4
Tremor	0	0	1	0.4
Psychiatric Disorders	**2**	**0.8**	**6**	**2.3**
Confusional state	2	0.8	2	0.8

Depressed mood	0	0	1	0.4
Dysphoria	0	0	1	0.4
Hallucination	0	0	1	0.4
Hallucination, visual	0	0	3	1.2
Renal and Urinary Disorders	**3**	**1.2**	**3**	**1.2**
Renal failure	2	0.8	1	0.4
Renal failure acute	1	0.4	2	0.8
Respiratory, Thoracic and Mediastinal	**6**	**2.3**	**5**	**1.9**
Acute respiratory failure	1	0.4	0	0
Dyspnoea	2	0.8	0	0
Respiratory distress	1	0.4	1	0.4
Respiratory failure	2	0.8	4	1.5
Skin and Subcutaneous Tissue Disorders	**2**	**0.8**	**5**	**1.9**
Dermatitis	1	0.4	0	0
Dermatitis allergic	1	0.4	0	0
Drug eruption	0	0	1	0.4
Rash	0	0	4	1.5
Vascular disorders	**1**	**0.4**	**0**	**0**
Hypotension	1	0.4	0	0

Source: Reviewer generated using JMP 11 and ADAE dataset from trial 9766-CL-0104

The most common TEAEs leading to study drug discontinuation that were reported in ≥ 1.0% of either the isavuconazonium or voriconazole treatment groups, respectively, were respiratory failure (0.8%, 2 patients vs 1.5%, 4 patients), sepsis (0.4%, 1 patient vs 1.2%, 3 patients), and acute myeloid leukemia (0 patients vs 1.5%, 4 patients), rash (0 patients vs 1.5%, 4 patients), bacterial sepsis (0 patients vs 1.2%, 3 patients) and visual hallucination (0 patients vs 1.2%, 3 patients)

MO Comment: Visual hallucinations are a known adverse reaction associated with voriconazole use. There were no instances of visual hallucination leading to discontinuation in the isavuconazonium treatment group.

Adverse reactions leading to discontinuation within the combined phase 2 and 3 pool is less informative due to differences in the length of exposure and the absence of a control group in study 9766-CL-0103. Seventeen subjects in the multiple dose groups in the Phase 1 Population (1 of 6 subjects in the 40 mg multiple dose group, 9 of 490 subjects in the multiple dose 200 mg group, and 7 of 39 subjects in the multiple dose 600 mg group) prematurely discontinued study medication due to an adverse event. Sixteen of the 17 subjects who discontinued study drug in the multiple dose groups had TEAEs that were considered related to study drug. Table 58 lists the TEAE which led to drug discontinuation in at least two subjects in the phase 1 population. In the highest dose group, AEs of anxiety (3/39), flushing (3/39), headache (3/39), dizziness (2/39) and attention disturbances (2/39) accounted for the most frequent reasons for discontinuation.

Table 58: Treatment Emergent Adverse Events Leading to Discontinuation of Study Drug in ≥2 Subjects in the Phase 1 Population

	Multiple									
MedDRA (v12.1) System	**40 mg (n = 6)**	**50 mg (n = 6)**	**80 mg (n = 6)**	**100 mg (n = 175)**	**150 mg (n =41)**	**200 mg (n = 490)**	**600 mg (n = 39)**	**Total ISA (n = 722)**	**Placebo (n = 128)**	**Moxi (n = 122)**
Overall	**1 (16.7%)**	**0**	**0**	**0**	**0**	**9 (1.8%)**	**7 (17.9%)**	**17 (2.4%)**	**0**	**0**
Gastrointestinal Disorders										
Diarrhea	1 (16.7%)	0	0	0	0	1 (0.2%)	1 (2.6%)	3 (0.4%)	0	0
Nausea	0	0	0	0	0	0	2 (5.1%)	2 (0.3%)	0	0
Vomiting	0	0	0	0		2 (0.4%)	1 (2.6%)	3 (0.4%)	0	0
Investigations										
ALT increased	0	0	0	0	0	0	0	0	0	0
AST increased	0	0	0	0	0	0	0	0	0	0
Blood creatinine increased	0	0	0	0	0	3 (0.6%)	0	3 (0.4%)	0	0
Blood pressure increased	0	0	0	0	0	0	0	0	0	0
Nervous System Disorders										
Disturbance in attention	0	0	0	0	0	0	2 (5.1%)	2 (0.3%)	0	0
Dizziness	0	0	0	0	0	0	2 (5.1%)	2 (0.3%)	0	0
Headache	1 (16.7%)	0	0	0	0	1 (0.2%)	3 (7.7%)	5 (0.7%)	0	0
Psychiatric Disorders										
Anxiety	0	0	0	0	0	0	3 (7.7%)	3 (0.4%)	0	0
Vascular Disorders										
Hot flush	0	0	0	0	0	0	3 (7.7%)	3 (0.4%)	0	0

Source: Adapted from Summary of Clinical Safety, Table 38, in agreement with Reviewer analysis of the integrated safety set with JMP 11.

7.3.4 Significant Adverse Events

Hepatotoxicity and Elevated Liver Test Results:

Hepatotoxic TEAEs by severity and outcome in the phase 3, controlled study population, are listed in Table 59. No hepatotoxic TEAEs were reported among isavuconazonium-treated subjects in the phase 1 population.

Table 59: Hepatobiliary TEAEs by Severity and Outcome in the Phase 3 Controlled Study Population

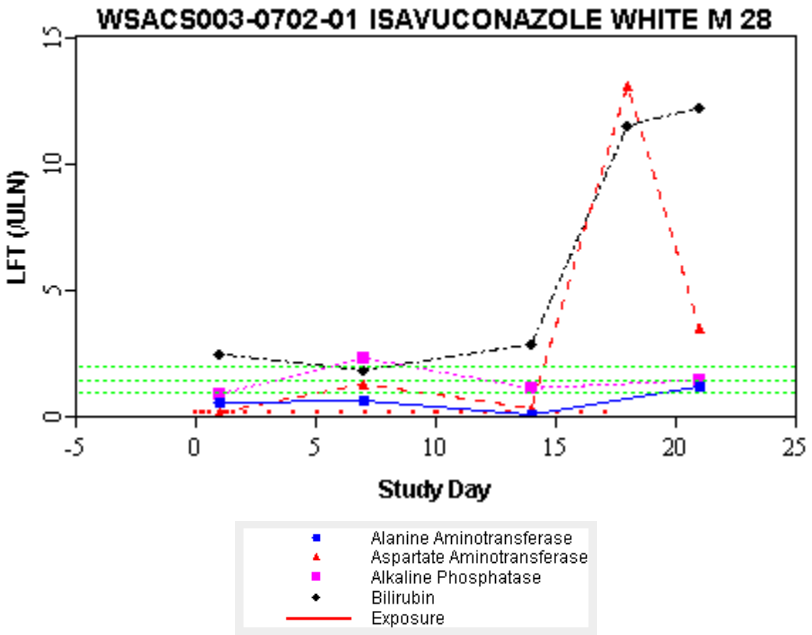
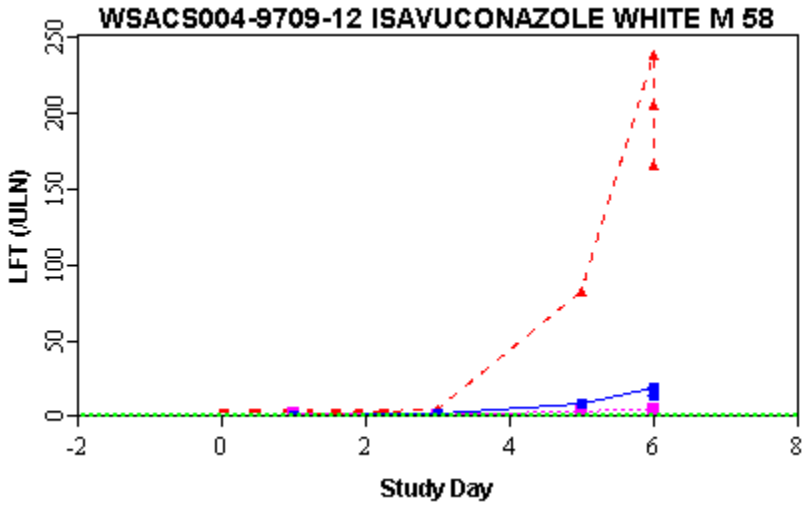
MedDRA v12.1 Hepatobiliary System Organ Class	Phase 3 Controlled Study	
	Isavuconazonium (n = 257)	Voriconazole (n = 259)
Any TEAE	**23 (8.9%)**	**42 (16.2%)**
Mild*	6 (2.3%)	14 (5.4%)
Moderate*	12 (4.7%)	16 (6.2%)
Severe*	5 (1.9%)	12 (4.6%)
Serious TEAEs	**3 (1.2%)**	**6 (2.3%)**
TEAEs Leading to Discontinuation	**1 (0.4%)**	**6 (2.3%)**
TEAEs Leading to Death	**1 (0.4%)**	**0**

*Investigator Assessment
Source: Reviewer generated using JMP 11 and ADAE dataset from study 9766-CL-0104

In the combined Phase 2 and 3 Population, 8 serious TEAEs in the hepatobiliary disorders SOC were reported with the following preferred terms, PTs: 2 patients with cholecystitis, and 1 patient each with cholangitis, cholelithiasis, liver disorder, acute hepatic failure, hepatitis, and acute hepatitis. Within the phase 3 controlled population, the 3 serious adverse events were hepatitis, acute hepatitis, and cholecystitis. A patient (Subject 9709-12) treated with isavuconazonium experienced acute hepatitis with a fatal outcome without a clear alternative etiology. A second patient (Subject 0702-01) had a suspected drug related hepatotoxic adverse reaction of acute hepatic failure, also resulting in a fatal outcome but a number of alternative etiologies were possible. Both patients are detailed in Table 60.

Table 60: Description of Selected Phase 3 Isavuconazonium-Treated Subjects with Serious Hepatotoxic TEAEs

Study	Subject No.	Preferred Term	Comments
9766-CL-0103	0702-01	Acute hepatic failure	28 year old White male with history of chronic hepatitis C, AML s/p BMT day 223 c/b GVHD. Isavuconazonium discontinued day 18 due to acute hepatic failure, and patient died from multi-organ failure (b) (6) days later with ongoing hepatic failure. Possible etiologies include activation o chronic hepatitis C, sepsis, AML progression, GVHD, and drug toxicity (isavuconazonium, haloperidol, meropenem, quetiapine, and/or oliclinomel). Patient had ALT or AST > 3xULN and ALP < 2xULN and T-Bili > 2xULN within 3 days apart, thus satisfying Hy's Law.

			 Source: Empirica Study 3.1, SDTM Dataset, Study 9766-CL-0103
9766-CL-0104	9709-12	Acute Hepatitis	58 year old White male with a history of large B-cell lymphoma, chronic lymphocytic leukemia, and unstaged SCC of the lung, being treated for *Aspergillus fumigatus* pneumonia. Drug discontinued Day 4 due to acute hepatitis (reported Day 5). Days 5-6 ALT and AST rose above 5x ULN. Subject died on Day (b)(6) due to septic shock per investigator. Blood cultures were not positive, and hepatitis serology was not available. Autopsy was not performed. Concomitant medications include acetaminophen. The subject did not have bilirubin values reported, and as such, was not included in the list of subjects that satisfied Hy's Law. 

Source: Empirica Study 3.1, SDTM Dataset, Study 9766-CL-0104

In the controlled phase 3 trial, there were a total of 24 hepatobiliary adverse events in the isavuconazonium treatment group for the entire study period. Of these events, 12 (50%) resolved, 2 (8%) were improving, 9 (38%) were not resolved, and 1 (4%) event proved fatal (acute hepatitis). This is in comparison to voriconazole, in which there were 44 events: 21 (48%) resolved, 21 (48%) were not resolved, and 2 (4%) were recovering. Isavuconazonium therapy was discontinued in the one patient (Subject 9709-12) with fatal hepatitis, so reversibility, as well as re-challenge data are not available.

Hy's Law

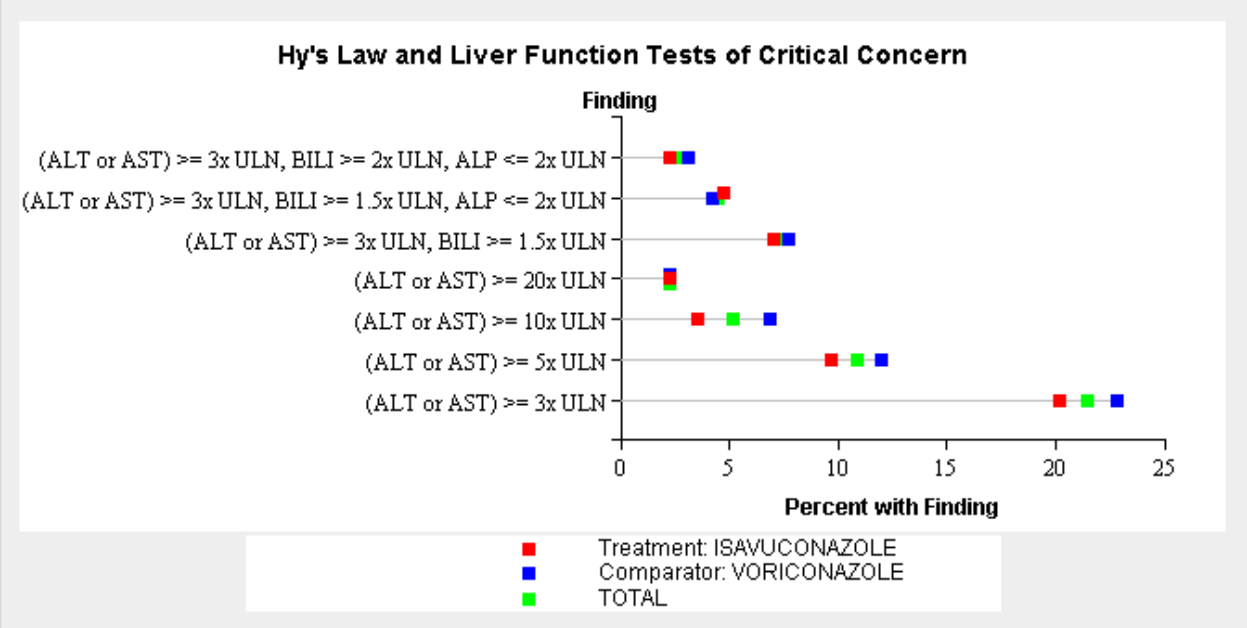
In general, fewer isavuconazonium- than voriconazole-treated patients experienced increases in transaminases or increases in transaminases concurrently with increases in total bilirubin. Table 61 and Figure 9 list coincident maximum laboratory values as multiples of baseline values, at any point during the trial.

Table 61: Maximum laboratory values for liver tests relative to baseline at any point during the trial (9766-CL-104) in the phase 3 controlled population

	Treatment (N=257)		Comparator (N=259)		Total (N=516)	
Finding	#	%	#	%	#	%
(ALT or AST) >= 3x ULN, BILI >= 2x ULN, ALP <= 2x ULN	6	2.3%	8	3.1%	14	2.7%
(ALT or AST) >= 3x ULN, BILI >= 1.5x ULN, ALP <= 2x ULN	12	4.7%	11	4.2%	23	4.5%
(ALT or AST) >= 3x ULN, BILI >= 1.5x ULN	18	7%	20	7.7%	38	7.4%
(ALT or AST) >= 20x ULN	6	2.3%	6	2.3%	12	2.3%
(ALT or AST) >= 10x ULN	9	3.5%	18	6.9%	27	5.2%
(ALT or AST) >= 5x ULN	25	9.7%	31	12%	56	10.9%
(ALT or AST) >= 3x ULN	52	20.2%	59	22.8%	111	21.5%

Source: Empirica Study 3.1, SDTM Dataset, Study 9766-CL-0104

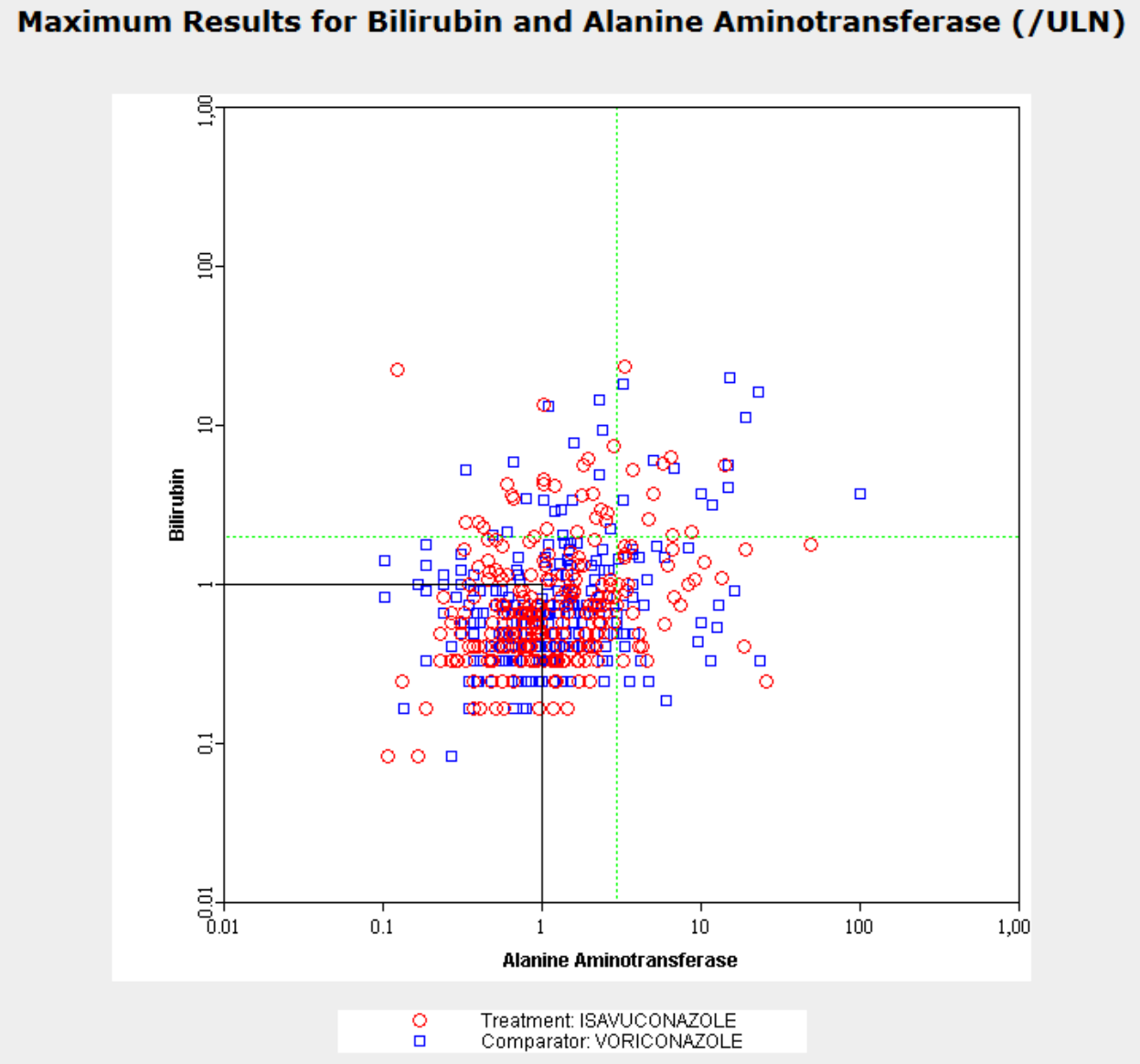
Figure 9: Maximum laboratory values for liver tests relative to baseline at any point during the trial (9766-CL-104) in the phase 3 controlled population



Source: Empirica Study 3.1, SDTM Dataset, Study 9766-CL-0104

Patients who had elevated ALT ≥ 3X ULN or total bilirubin ≥ 2X ULN at any time during the trial are represented in the right upper quadrant of the graphic, Figure 10.

Figure 10: A graphic representation of the maximum lab values for each subject relative to baseline in the phase 3 controlled study population



Source: Empirica Study 3.1, SDTM Dataset, Study 9766-CL-0104

Due to the large number of coincident hepatotoxic medications and underlying disease progression, the analysis timeframe was adjusted from first exposure to 10 days, approximately 2 half lives of isavuconazonium following the last dose of study drug. Three isavuconazonium-treated patients and seven voriconazole-

treated patients satisfied Hy's Law (combined ALT or AST > 3 x ULN and ALP < 2 x ULN and total bilirubin > 2 x ULN) (Table 62).

Table 62: Assessment of Hepatotoxicity from First Study Exposure to 10 Days after Last Dose of Drug in the Phase 3 Controlled Population

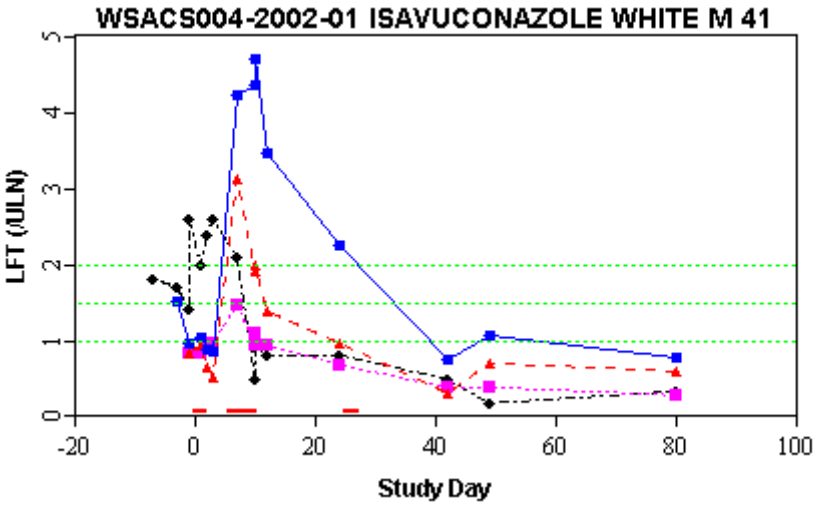
Parameter	Criteria	Isavuconazonium	Voriconazole (n =259)
ALT	> 3 x ULN	31/249 (12.4%)	35/255 (13.7%)
	> 5 x ULN	17/249 (6.8%)	18/255 (7.1%)
	> 10 x ULN	5/249 (2.0%)	12/255 (4.7%)
	> 20 x ULN	1/249 (0.4%)	3/255 (1.2%)
AST	> 3 x ULN	24/249 (9.6%)	39/255 (15.3%)
	> 5 x ULN	13/249 (5.2%)	19/255 (7.5%)
	> 10 x ULN	4/249 (1.6%)	8/255 (3.1%)
	> 20 x ULN	3/249 (1.2%)	4/255 (1.6%)
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%)
	> 20 x ULN	4/250 (1.6%)	5/255 (2.0%)
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 > 1.5 x ULN	12/251 (4.8%)	14/255 (5.5%)
	(ALT or AST) > 3 x ULN and Total Bilirubin > 2 x ULN	8/251 (3.2%)	10/255 (3.9%)
(ALT or AST) and ALP and Total Bilirubin†	(ALT or AST) > 3 x ULN and ALP < 2 x ULN and Total Bilirubin > 2 x ULN	3/251 (1.2%)	7/255 (2.7%)

Baseline, pre-exposure lab values in comparison to maximum values from initial drug exposure to 10 days after last dose of study drug.
Source: Modified from 9766-CL-0104 Clinical Study Report End-of-Text Tables 12.6.2.4.1 and 12.6.2.4.2

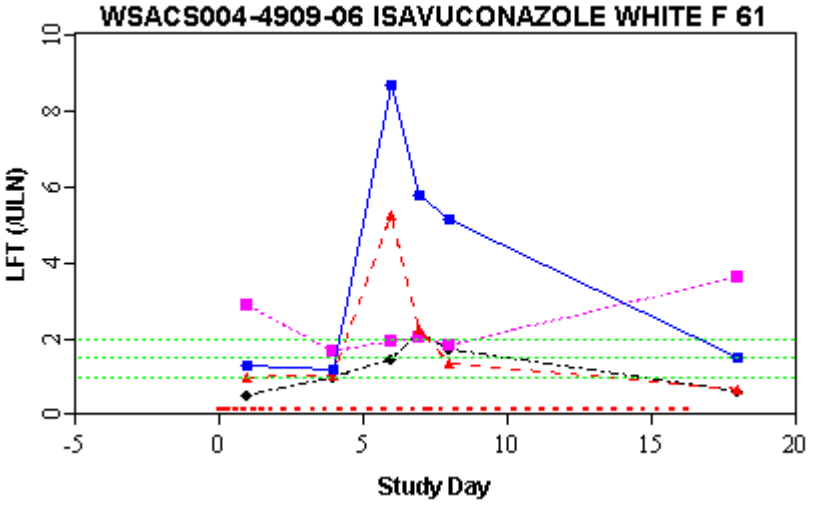
The laboratory profiles of the subjects (3 isavuconazonium, and 7 voriconazole) that satisfy Hy's Law are graphically illustrated below (Graphs generated from Empirica Study 3.1 using SDTM Data Sets):

Note: Exposure only relates to IV dosing

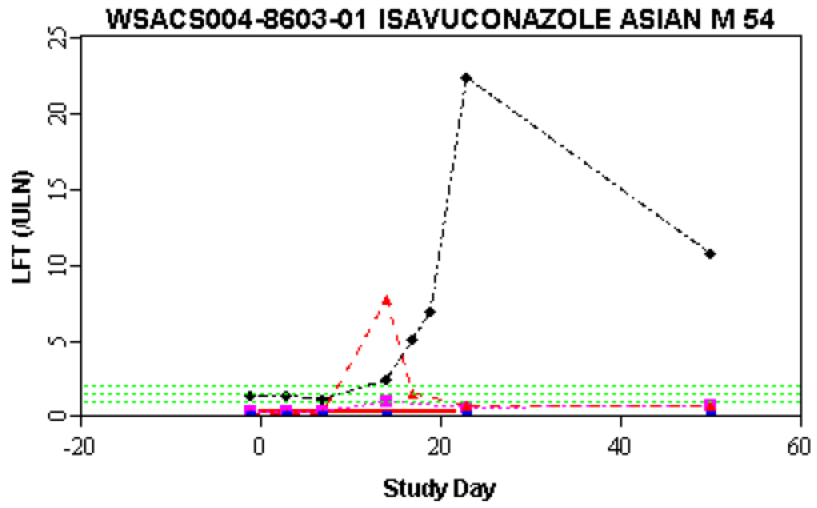
Isavuconazonium-Treated Subjects:



49 Days of treatment; successful outcome. Patient had mildly elevated transaminases at baseline. The patient also received acetaminophen prior to elevated transaminases.

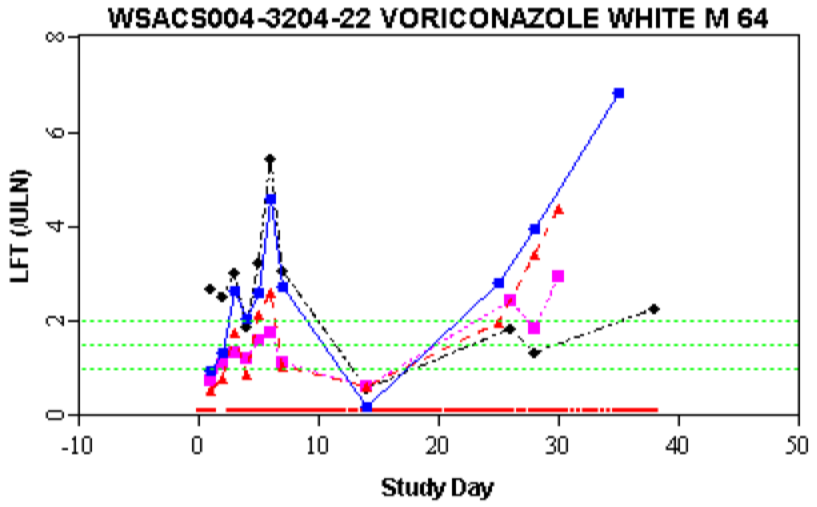


17 Days of treatment; patient died of Blast cell crisis on Day (b) (6) Elevations in transaminases improved under continuous treatment with stu drug. The patient received multiple potentially hepatotoxic medications.

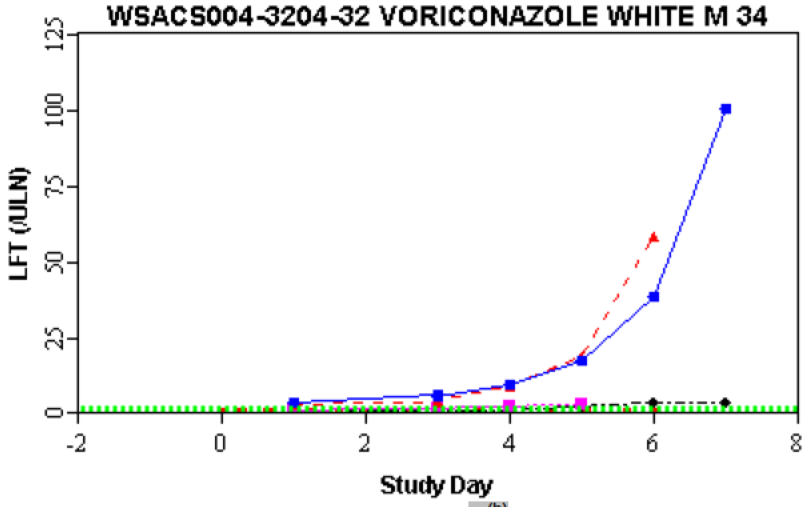


23 Days of treatment, discontinued due to insufficient response to isavuconazonium. Concurrent CMV infection and GVHD, and transaminases improved under continuous treatment with study drug.

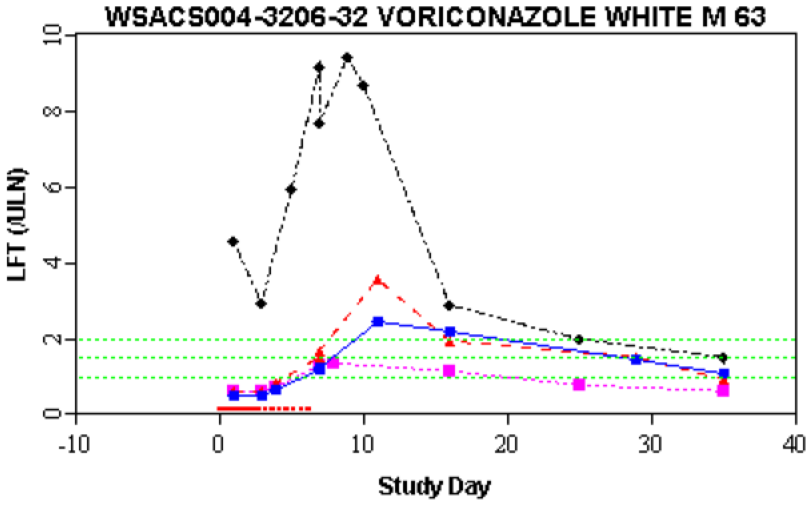
Voriconazole-treated Subjects



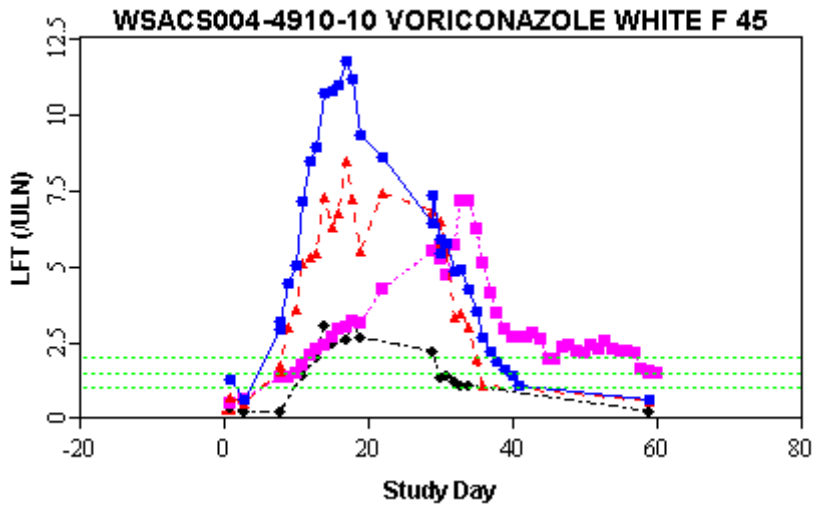
39 Days of treatment, patient died on study Day (b) (6) due to *Pseudomonas* sepsis. Transaminases increased after initiation of study drug and stayed elevated during the course of treatment.



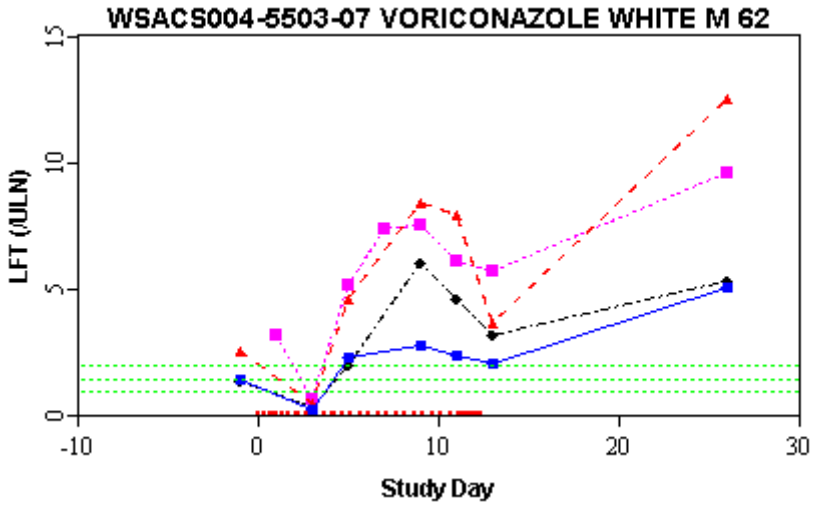
7 Days of treatment; died on Day (b) (6) due to septic shock. Liver enzymes elevated at baseline but rapidly increased aft first dose of voriconazole. The patient developed hepatic failure with concurrent septic shock.



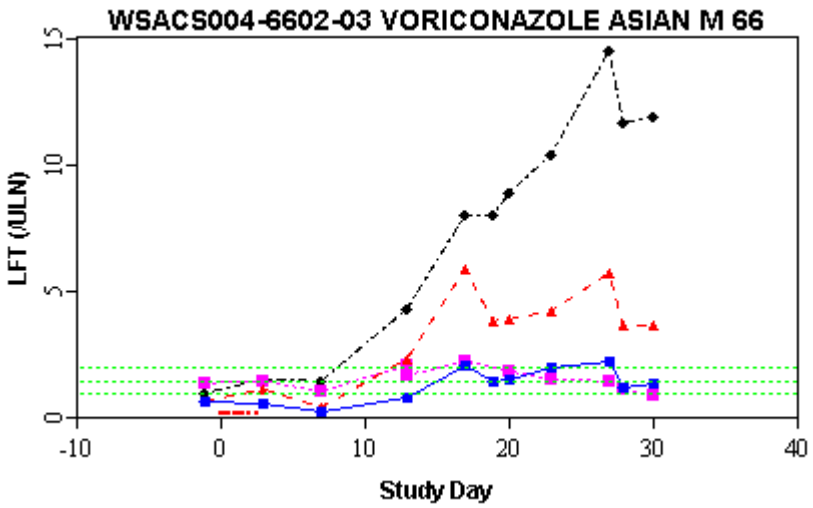
8 Days of treatment; drug withdrawn due to hyperbilirubinemia. Relatively mild elevation in transaminases. Concurrent bilirubin elevation to > 2 x ULN in a patient with a medical history of Gilbert syndrome.



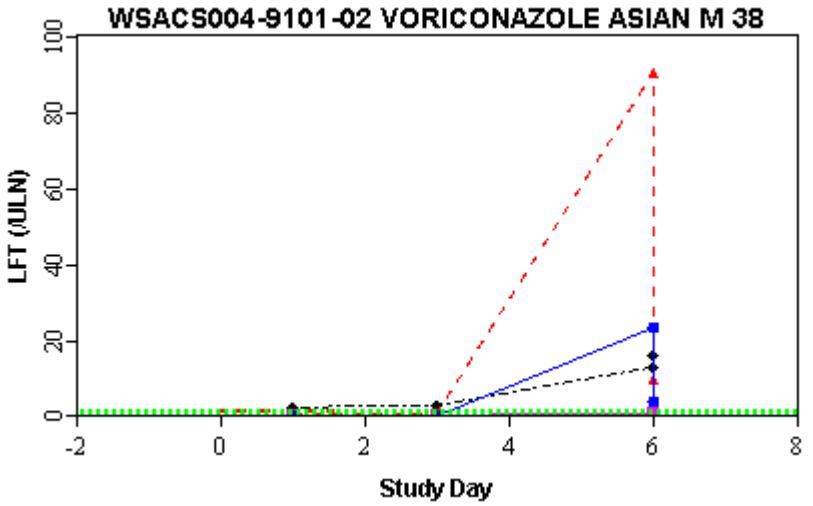
29 Days of treatment; drug withdrawn due to insufficient therapeutic response. ALT was mildly elevated at baseline. The patient had concurrent hepatitis B, CMV and EBV infections.



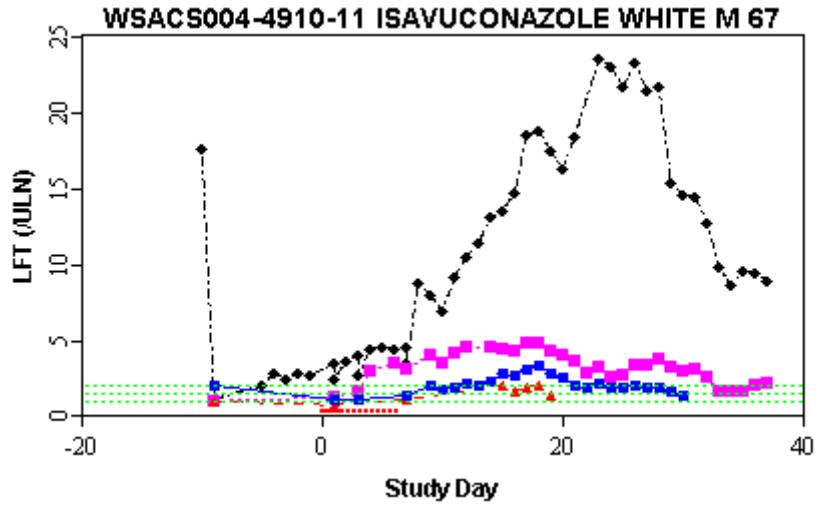
13 Days of treatment; discontinued due to lack of probable fungal infection. Patient death on Day (b) (6) due to progression of CLL. Elevated transaminases at baseline may be due to previous voriconazole treatment, Days -4 to -1.



27 Days of tr_atment; drug withdrawn onDay 27 due to hyperbilirubinemia. The patient died on Day (b) (6) due to progression of aplastic anemia. Transaminases and bilirubin increase tem_orally with drug exposure.

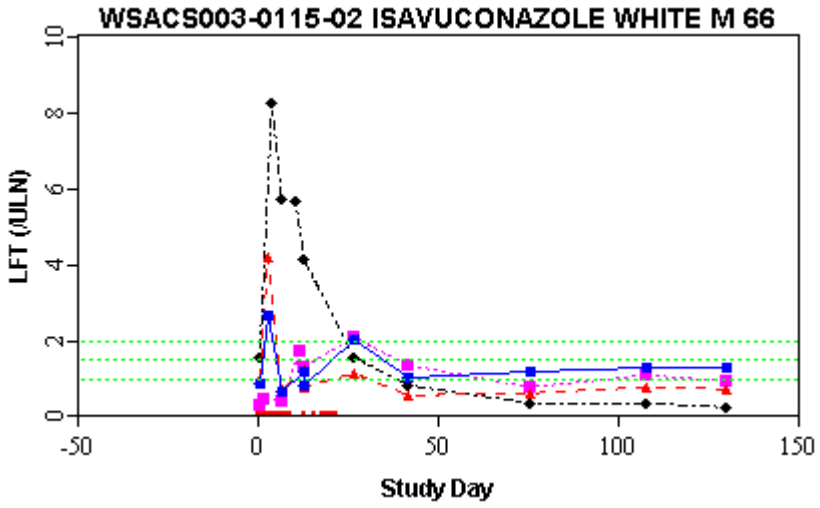


5 Days of treatment; drug withdra_n on Day 5 due to respiratory failure secondary to septic shock. Patient died on Day (b) (6) Patient was receiving multiple hepatotoxic concomitant medications.



7 Days of treatment; drug withdrawn due to elevated transaminases. History of GVHD and CMV reactivation on Day 4. Patient died on Day (b) (6) due to progression of fungal pneumonia.

In the Phase 2 and 3 population, 5/535 (0.9%) isavuconazonium-treated patients met the criteria of Hy's Law. The additional two cases come from the phase 3 open-label trial. The first, subject 0702-01, was described in the hepatotoxicity section above for SAE of acute hepatic failure leading to death. The second patient is described below:



74 Days of treatment; completed therapy. Blood culture was positive for gram negative rods on Day 1. Cholangitis from Days 2 to 76. Cholecystotomy on Day (b) (6). Liver test abnormalities resolved while on continued treatment with isavuconazonium.

MO Comment: The cases of elevated liver laboratory tests and hepatobiliary adverse events are consistent with azole-class drug induced liver injury. This is an expected

finding for the class, and occurred at a lower incidence rate in isavuconazonium-treated subjects than in voriconazole-treated subjects. In the controlled phase 3 trial, there were a total of 24 hepatobiliary adverse events in the isavuconazonium treatment group. Of these events, 12 (50%) resolved, 2 (8%) were improving, 9 (38%) were not resolved, and 1 (4%) event was fatal (acute hepatitis). This is in comparison to voriconazole, in which there were 44 events. 21 (48%) resolved, 21(48%) were not resolved, and 2 (4%) were recovering.Only 1 patient receiving isavuconazonium discontinued therapy due to a hepatobiliary AE, so reversibility is not evaluable. Approximately one half of the events resolved without altering therapy.

Hypersensitivity Reactions: Anaphylaxis and Severe Cutaneous Reactions (SCAR)

Potential anaphylaxis and severe cutaneous reactions (SCAR) were reported in the same proportion of isavuconazonium- (1.9%) and voriconazole-treated (1.9%) patients, and are summarized in Table 63 below. There were no events of anaphylaxis or severe cutaneous adverse reactions in the Phase 1 or Phase 2 integrated safety populations.

Table 63: Treatment Emergent Anaphylaxis/SCAR in the Phase 3 Controlled Population

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

Source: Reviewer generated using datasets from study 9766-CL-0104

The patient (Subject 3203-04) who experienced anaphylactic shock in the isavuconazonium treatment arm had the reaction during an infusion of human immunoglobulin. Therapy was instituted with methylprednisolone, and treatment with isavuconazonium was not interrupted.

The AE of circulatory collapse (Subject 4910-14) occurred and resolved on Day 39 in a patient with history of tachyarrythmias, and cardiac failure, while on oral therapy. No specifics regarding the circulatory collapse were provided. Vital sign measurements reported on Day 40 included blood pressure of 140/70 mm Hg, pulse rate of 88 bpm and an oral equivalent temperature of 36.6°C. The investigator reported the results from an ECG performed on Day 40 as abnormal but not clinically significant with a “minimal P value prolongation”. The patient refused further study drug treatment beyond Day 39. On Day (b) (6) the patient experienced cardiac decompensation, which was reported as an SAE of cardiac failure; the patient died that same day.

The AE of exfoliative dermatitis occurred in a patient (Subject 3304-05) with a history of toxiderma on Day 109, 15 days after the last dose of study medication.

There were 2 cases of erythema multiforme. The first, (Subject 4910-15) had episodes of erythema on Days 9, 31 and 32. The event of interest occurred on Day 31, 10 days after the last dose of study medication.

The second (Subject 3206-01) had erythema reported subsequent to an AE of vasculitis affecting torso, back, arms and legs from study Day 31 to 115. The patient completed 84 days of treatment with isavuconazonium.

There were, however, instances of AEs recorded as infusion reactions that could be considered hypersensitivity reactions:

1) Subject 004-4910-21 experienced a SAE listed as dyspnea that occurred during infusion. The patient improved with both diuresis and steroids. The study drug, isavuconazonium, was stopped and not reinstated. It is reasonable to consider anaphylaxis as a possible etiology of the SAE.

2) Subject 004-9703-08 discontinued IV isavuconazonium on study Day 2 due to an AE of “allergic dermatitis”, treated with steroids. The investigator considered the reaction probably related to isavuconazonium infusion.

3) Patient 004-5604-01 discontinued isavuconazonium due to severe chills/rigors on infusion Day 11. The adverse reactions recurred on re-challenge the next day. Vital signs were unremarkable. Isavuconazonium was permanently discontinued.

MO Comment: The cases of anaphylaxis identified within the phase 3 controlled isavuconazonium-treated population are confounded by underlying medical conditions, and concurrent medications. In the healthy phase 1 population there were no reported instances of anaphylactic or cutaneous reactions. The 3 cases outlined above, while not definitive, do suggest the potential for hypersensitivity reactions with isavuconazonium by temporal association and resolution following de-challenge.

Infusion-Related Reactions

Infusion-related reactions are defined as serious adverse reactions occurring within 2 days following IV dosing. The overall frequency of potential infusion-related serious TEAEs occurring within 2 days after IV dosing among isavuconazonium-treated patients in the phase 3 controlled trial was 10.1% compared to 6.9% in the voriconazole treatment group. All patients in this trial were included in this analysis as all received at least one IV dose of study medication.

In the following tables, infusion-related serious TEAE are considered in the controlled phase 3 study (Table 64), those resulting in discontinuation (Table 65), and all infusion-related TEAE resulting in discontinuation in the phase 2 and 3 combined safety population (Table 66)

Table 64: Potential infusion-related serious TEAEs: Phase 3 Controlled Study

MedDRA v12.1 Preferred Term	Isavuconazonium (n = 257)	Voriconazole (n = 259)
Overall	26 (10.1%)	18 (6.9%)
Acute myocardial infarction	0	1 (0.4%)
Acute respiratory failure	4 (1.6%)	3 (1.2%)
Anaphylactic shock	1 (0.4%)	0
Chills	1 (0.4%)	1 (0.4%)
Convulsion	2 (0.8%)	1 (0.4%)
Dyspnoea	3 (1.2%)	0
Epilepsy	1 (0.4%)	0
Hypersensitivity	1 (0.4%)	0
Hypotension	1 (0.4%)	0
Hypoxia	1 (0.4%)	1 (0.4%)
Pyrexia		1 (0.4%)
Respiratory distress	3 (1.2%)	2 (0.8%)
Respiratory failure	10 (3.9%)	9 (3.5%)

Source: Modified from Applicant "Isavuconazole Risk Management Plan", Table 32

Table 65: Potential infusion-related TEAEs that led to study drug discontinuation: Phase 3 Controlled Study

MedDRA v12.1 Preferred Term	Isavuconazonium (n = 257)	Voriconazole (n = 259)
Overall	8 (3.1%)	6 (2.3%)
Acute respiratory failure	1 (0.4%)	0
Chills	1 (0.4%)	1 (0.4%)
Convulsion	2 (0.8%)	0
Dyspnoea	2 (0.8%)	0
Epilepsy	1 (0.4%)	0
Hypotension	1 (0.4%)	0
Respiratory distress	0	1 (0.4%)
Respiratory failure	2 (0.8%)	4 (1.5%)

Source: Modified from Applicant "Isavuconazole Risk Management Plan", Table 32

Table 66: Potential infusion-related TEAEs that led to study drug discontinuation: Phase 2 and 3 Population

MedDRA v12.1 Preferred Term	Phase 2 & 3 Isavuconazonium (n = 380)	Phase 3 Isavuconazonium (n = 259)
Overall	11 (2.9%)	8 (2.2%)
Acute respiratory failure	1 (0.3%)	1 (0.3%)
Chills	1 (0.3%)	1 (0.3%)
Convulsion	2 (0.5%)	2 (0.6%)

Dyspnoea	2 (0.5%)	2 (0.6%)
Epilepsy	1 (0.3%)	1 (0.3%)
Hypersensitivity	2 (0.5%)	0
Hypotension	1 (0.3%)	1 (0.3%)
Infusion Reaction	1 (0.3%)	0
Respiratory failure	2 (0.5%)	2 (0.6%)

Source: Modified from Applicant "Isavuconazole Risk Management Plan", Table 32

The 11 patients with potential infusion-related TEAEs that led to study drug discontinuation in the Phase 2 and 3 Population are summarized below in Table 67. There were no infusion-related serious TEAEs or TEAEs that led to study drug discontinuation reported among isavuconazonium-treated subjects who received at least one IV dose in the phase 1 population.

Table 67: Narratives of infusion-related reaction TEAEs that led to study drug discontinuation: Phase 2 and 3 Population

Study Subject No. Age/Sex	Patient Term	Comments
9766-CL-0102 11-11005 33/Female	Hypersensitivity	**Received IV ISA on Day 1. On Day 1, IV ISA infusion discontinued approximately 2 hrs after start due to rapid BP decrease (predose BP 125/80 mmHg; BP 80/40 mmHg 2 hours 10 min after infusion started). Event resolved 1.5 hrs after discontinuing ISA infusion. Timing of event suggests an association with study medication (event onset, resolution on discontinuation)**
9766-CL-0102 11-11007 32/Female	**Infusion related reaction**	**Received IV ISA on Days 1-2. On Day 1, completed 1st ISA infusion without untoward events, stable vital signs. On Day 1, decreased BP observed during 2nd ISA infusion (predose BP 110/70 mm Hg, postdose BP 90/60 mm Hg). On Day 1 during 3rd infusion, TEAE of infusion reaction (unknown type) reported 2.5 hrs after starting infusion (predose BP 90/60 mmHg, BP 85/60 mmHg 4 hrs later). On Day 2, ISA infusion discontinued due to infusion reaction and headache (no change in BP). Patient was treated with dimethindene and ranitidine. Events resolved 14 hrs later. Timing of events of hypotension and infusion related reaction suggests an association with study medication (positive dechallenge with treatment); event of headache also reported.**
9766-CL-0102 31-31005 48/Female	**Hypersensitivity**	**Received IV ISA Day 1. On Day 1, events of dizziness (30 min after infusion started, resolved 20 min later), allergic reaction (prick in hands and numb feeling, "rambling to the cheek" 50 min after infusion started, resolved 1.5 hrs later), and nausea (~2.5 hrs after infusion started) were reported. Patient completed full dose with no change in vital signs and did not receive any treatment for events. Timing of events suggests infusion-related reaction associated with study medication (event onset, positive dechallenge).**
9766-CL-0104 0105-03 59/Male	**Hypotension; Respiratory failure**	**Received IV ISA on Days 1-10. On Day (b) (6) SAEs of acute renal failure, respiratory failure, septic shock, and severe hypotension reported. Sponsor assessed events to be not related to study medication; alternative etiology of neutropenic sepsis with underlying condition of AML.**
9766-CL-0104 2001-01 32/Female	**Acute respiratory failure**	**Received IV ISA Days 1-4, switched to oral ISA on Day 4. On Day (b) (6) patient died of acute respiratory failure. Sponsor assessed event to be not related to study medication; alternative etiology of underlying pulmonary *Pseudomonas* infection and tuberculosis along with metabolic acidosis consistent with sepsis**
9766-CL-0104 3201-07 45/Male	**Epilepsy**	**Received IV ISA on Days 1-5, oral ISA Day 5, IV ISA Days 5-12, oral ISA Days 12-14, IV ISA Days 14-33, oral ISA Day 34. On Day (b) (6) event of epilepsy reported. Sponsor assessed event to be not related to study medication; alternative etiology of underlying right thalamic glioblastoma that presented with seizures.**
9766-CL-0104 4910-21	**Dyspnea**	**Received IV ISA on Days 1-5. On Day 5, ISA discontinued due to SAE of dyspnea during IV ISA infusion. Timing of event suggests possible infusion-related reaction**

70/Female		**associated with study medication; alternative etiology of underlying obstructive lung disease suggested by dyspnea at baseline; confounding condition of right sided effusion and progressive atelectasis findings on chest x-ray.**
9766-CL-0104 5604-01 24/Male	**Chills**	**Received IV ISA Days 1-12. On Day 11, received 23rd IV ISA infusion, during infusion developed moderate chills, chattering teeth, tachycardia, and hypertension. Infusion stopped; Investigator suspected that infusion was too cold. Chills resolved after a few minutes. On Day 12, 24th infusion started at 09:45, at 10:30 developed SAE chills with tremors. Stopped infusion, recovered in 30 minutes. Timing of chills suggests probable infusion-related reaction associated with study medication (event onset, positive rechallenge and positive dechallenge x 2 episodes)**
9766-CL-0104 6607-09 49/Female	**Respiratory failure**	**Received IV ISA Days 1-3, oral ISA days 4-47; switched to IV ISA on Da (b) (6) in association with SAE septic shock, SAE respiratory failure on Day (b) (6) and patient died on Day (b) (6) Sponsor assessed event to be not related to study medication; alternative etiology of *Klebsiella* sepsis and drug resistant *Acinetobacter* bacteremia with respiratory failure**
9766-CL-0104 8206-01 50/Female	**Convulsion**	**Received IV ISA Day 1-16. On Day (b) (6) patient had convulsion x 3 with invasive fungal disease that led to death on Day (b) (6) Sponsor assessed event to be not related to study medication; alternative etiolog f invasive fungal disease to CNS (focal lesion on MRI).**
9766-CL-0104 9114-07 34/Male	**Convulsion; Dyspnea**	**Received IV ISA Day 1-20. On y (b) (6) the patient experienced tachycardia, pyrexia and vomiting. On Day (b) (6) ISA discontinued in response to events of dyspnea and SAE of convulsion atient was taken to the ICU, intubated, was hemodynamically unstable, had oxygen desaturation with respiratory acidosis. SAEs of convulsion were reported as resolved on Day (b) (6) On Day (b) (6) the patient developed SAE of sepsis. The patient died on Day (b) (6) ue to SAE of sepsis.**

Source: Modified from Applicant "Isavuconazole Risk Management Plan", Table 32

MO Comment: Several cases are consistent with infusion related reactions, which are known to occur with a variety of intravenously administered agents, including antifungal agents such as amphotericin B and voriconazole[15].

7.3.5 Submission Specific Primary Safety Concerns

Particulate Formation in the IV Formulation

In the intravenous formulation, following reconstitution, isavuconazonium sulfate may spontaneously hydrolyze in aqueous solution to relatively insoluble isavuconazonium. As a result, the study drug was administered through an inline filter to remove particulate. An information request was sent to the Applicant on September, 5, 2014 to identify patients who received study drug in the absence of an in-line filter. Twenty-one patients in Study 9766-CL-0104 (Invasive Aspergillosis) and 6 patients in Study 9766-CL-0103 (Rare Fungal Infections) were known to have been administered intravenous isavuconazonium in the absence of an inline filter. There were no embolic, or thromboembolic AEs observed within this patient subpopulation. The analysis is applied to the phase 3 study population, occurring at any point in time, in Table 68.

[15] Walsh TJ et al. "Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever." N Engl J Med. 2002 Jan 24;346(4):225-34.

Table 68: TEAEs Potentially Related to the Infusion of Particulate Drug Material at Any Point During the Phase 3Trials

	9766-CL-0103		Phase 3 Controlled Trial, 9766-CL-0104			
	ISAVUCONAZONIUM (N = 146)		ISAVUCONAZONIUM (N = 257)		VORICONAZOLE (N = 259)	
AE	**Number of subjects**	**Proportion (%)**	**Number of subjects**	**Proportion (%)**	**Number of subjects**	**Proportion (%)**
Pulmonary Embolism (PT)	1	0.7%	0	0	3	1.2%
Embolic and Thrombotic Events (nSMQ)	12	8.2%	9	3.5%	17	6.7%
Pulmonary Hypertension (nSMQ)	0	0	0	0	2	0.8%
Endocarditis (PT)	0	0	1	0.39%	0	0
Infusion Site Reactions (HLT)	3	2.1%	7	2.7%	2	0.8%

PT: Patient level term; nSMQ: Narrow standardized medical query; HLT: High level term
Source: Reviewer generated using MAED and JMP 11 from ADAE datasets from studies 9766-CL-0103 and 9766-CL-0104

Overall, there were more embolic and thrombotic events associated with voriconazole use as compared to isavuconazonium. Treatment emergent infusion site reactions associated with isavuconazonium and voriconazole administration are listed below. None of the reactions were considered serious, and all resolved. Significant infusion related adverse reactions associated with isavuconazonium administration are considered in section 7.3.4.

Subject	Treatment	Patient Term
WSACS004-0118-23	ISAVUCONAZONIUM	Infusion site pain
WSACS004-3204-09	ISAVUCONAZONIUM	Infusion site irritation
WSACS004-3204-20	ISAVUCONAZONIUM	Infusion related reaction
WSACS004-3204-34	ISAVUCONAZONIUM	Infusion related reaction
WSACS004-3204-35	ISAVUCONAZONIUM	Infusion related reaction
WSACS004-3903-04	ISAVUCONAZONIUM	Infusion site pain
WSACS004-6602-09	ISAVUCONAZONIUM	Infusion site oedema
WSACS004-0105-02	VORICONAZOLE	Infusion site extravasation
WSACS004-3204-06	VORICONAZOLE	Infusion related reaction

MO Comment: I agree with the applicant's assessment that there were no significant embolic, or thromboembolic safety signals identified in conjunction with isavuconazonium administration during the clinical trials.

QT Shortening

Two TQT studies were conducted [9766-CL-0004; 9766-CL-0017, discussed in section 7.3.5], neither of which showed QT prolongation, and both showed QT shortening. For the isavuconazonium 200- and 600-mg treatment groups, the mean change from placebo baseline-adjusted in QTcF decreased by 9 to 13 msec and by 19 to 25 msec, respectively, within 1 hour and 24 hours post dose. No QTcF < 330 msec was observed. No QTcF prolongation was observed in the isavuconazonium treatment groups.

The frequency of QT shortening TEAEs among isavuconazonium-treated patients in the Phase 3 Controlled Study was 0.4% (1 patient) compared to none in the voriconazole treatment group. This was the single incident, Subject 004-5202-01, in the combined safety database of phase 1, 2 and 3 trials.

Study subject 004-5202-01, a 39 year-old female with a history significant for hyponatremia, hypochloremia, hypomagnesemia, and hypokalemia received ISA for 10 days. Baseline QTcF 394 msec. On Day 2, ECG showed sinus tachycardia (HR 135 bpm), QT 275 msec, QTcF 360 msec. On Day 8, patient experienced non-serious TEAEs of abnormal T wave and 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 ISA. No treatment was administered. TEAE of QT shortened was reported as resolved on Day 9; TEAE of abnormal T wave was ongoing. The patient withdrew consent and was discontinued from the study on Day 10.

In Table 69 below, absolute values and changes from baseline for QTcF based on post-baseline extreme values in the Phase 3 Controlled Study are summarized. Five isavuconazonium-treated patients (2.0%) experienced post-baseline QTcF < 330 msec. In all of these patients, QTcF < 330 msec was a single, transient finding. None were associated with ventricular arrhythmias or adverse clinical sequelae. No action was taken with regard to isavuconazonium treatment as a result of these ECG observations.

Table 69: QTcF Interval: Number and percentage of patients meeting threshold criteria and decreases from baseline (post baseline): Phase 3 Controlled Study

QTcF Category	Isavuconazonium (N = 257)	Voriconazole (N = 259)
N‡	250	252
< 360 msec	51 (20.4%)	41 (16.3%)
< 330 msec	5 (2.0%)	5 (2.0%)
< 300 msec	1 (0.4%)	0
N‡	227	224
Decrease > 30 msec	73 (32.2%)	68 (30.4%)

Decrease > 60 msec	17 (7.5%)	10 (4.5%)

Post baseline: Includes all post-baseline measurements up to 10 days following last dose of study medication.

‡ Number of patients with both baseline and at least one post-baseline value within 10 days after last dose of study drug.

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.

Source: 9766-CL-0104 Clinical Study Report, End-of-Text Tables 12.6.4.3 and 12.6.4.4.

MO Comment: A consult response from the QT-IRT group (September 29, 2014) indicated that there was no significant prolongation of the QT interval. Due to the lack of consensus on QT shortening, no specific recommendations on the decreased QT interval were offered (Personal communication from Jiang Liu, Scientific Leader QT-IR group, October 22, 2014). Short QT syndrome (SQTS) is a rare genetic condition, defined as a QT interval < 320 msec[16]. SQTS diagnostic criteria including QTc (QT interval corrected for heart rate), clinical history, family history, and genotype were developed based on a systematic review of SQTS cases reported in the literature. These criteria specify QTc < 330 msec, in the absence of other risk factors, as being associated with an intermediate probability of SQTS[17]. While familial QT shortening is a well-described clinical syndrome that can result in severe life-threatening ventricular arrhythmias, there is no consensus in the scientific literature regarding thresholds of concern for drug induced QT shortening[18]. Drug induced QT shortening due to isavuconazonium therefore presents a risk in patients with familial short QT syndrome, but it is difficult to estimate risk for the general patient population.

Cardiac Arrhythmias Related to QT Segment Duration Alteration

As indicated in the thorough QT study (9766-CL-0017) isavuconazonium reduces the duration of the QT segment in a dose dependent fashion. Voriconazole is known to prolong the QT segment, increasing the risk of ventricular arrhythmias, specifically torsades de pointes. There was a numerically lower proportion of isavuconazonium-treated patients (5.8%) compared to voriconazole-treated patients (7.3%) who experienced TEAEs in the torsade de pointes SMQ (Table 70). The more common events that occurred in ≥ 1% of patients in either the isavuconazonium or voriconazole treatment groups, respectively, were syncope (2.7% vs 0.8%), loss of consciousness (1.2% vs 0), ECG prolonged QT (0.8% vs 3.1%) and cardiac arrest (0.4% vs 2.3%). Loss of consciousness and syncope were reported in a higher proportion of

[16] Webster G, Berul CI, An update on channelopathies from mechanisms to management. Circulation. 2013;127(1):126-40.

[17] Gollob MH, Redpath CJ, Roberts JD. The short QT syndrome: proposed diagnostic criteria. J Am Coll Cardiol. 2011;57(7):802-12.

[18] Shah RR. Drug-induced QT interval shortening: potential harbinger of proarrhythmia and regulatory perspectives. Br J Pharmacol. Jan 2010; 159(1): 58–69.

isavuconazonium-treated patients compared to voriconazole-treated patients, while QT prolongation and cardiac arrest were reported in a lower proportion of isavuconazonium- than voriconazole-treated patients.

Table 70: Treatment Emergent Torsade de Pointes Adverse Events of Interest in the Phase 3 Controlled Population

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

Source: Reviewer generated using MAED and JMP 11 from ADAE dataset from study 9766-CL-0104, in agreement with Study Report Table 12.6.1.13.5.

In Table 71 below, cases of syncope and loss of consciousness are listed individually.

Table 71: Patients in the Phase 3 Controlled Population with Syncope or Loss of

Patient No. / Treatment Duration (d)	Age (y), Race, Sex	TEAE / Intensity	Onset and End Day / Resolution	Comment
070606 / 76	60, White, male	Syncope / moderate	22 / 22 resolved	Patient on last dose of chemotherapy
200205 / 81	24, White, male	Syncope / mild	39 / 39 resolved	Patient with anemia and recently initiated chemotherapy and ondansetron
320305 / 17	64, White, male	LOC / severe	18 / 30 Recovered with sequelae	2 episodes of syncope/LOC (1 and 13 days after last dose), ECG showed atrial tachycardia, patient had concurrent lymphomatous meningitis
320449 / 84	41, White, female	Syncope / severe	29 / 39 resolved	Patient on concurrent morphine
320450 / 84	65, White, male	Syncope / mild	108 / 108 resolved	Event occurred 24 days after last dose, no ECG changes during course of the study
320615 / 9	81, White, male	LOC / moderate	9 / ongoing	Patient with previous medication of midazolam and morphine
330401 / 3	68, White, male	LOC / severe	17 / ongoing	Event occurred 14 days after last dose

541001 / 61	63, White, male	Syncope / mild	27 / 27 resolved	Patient was receiving rituximab and diphenhydramine
910104 / 84	41, Asian, male	Syncope / mild	43 / 43 resolved	Concurrent febrile neutropenia and event occurred subsequent to vomiting
970409 / 85	62, White, male	Syncope / mild	87 / 87 resolved	Event occurred 2 days after last dose
320418 / 22	67, White, female	Syncope / moderate	47 / 47 resolved	Event occurred 25 days after last dose
320627 / 84	58, White, male	Syncope / severe	91 / 91 resolved	Event occurred 7 days after last dose, but during course of study, patient experienced 2 episodes of ventricular tachycardia

Source: Modified from Study Report 9766-CL0104 Appendix 13.2.7.9.5

MO Comment: The higher incidence of syncope and loss of consciousness in the Isavuconazonium treatment arm may not necessarily be cardiac in origin, as a multitude of processes may result in syncope. A number of cases occurred several days after study drug was discontinued. Nevertheless, syncope and loss of consciousness are adverse effects that should be considered for product labeling.

Acute Pancreatitis

There were no acute pancreatitis events of interest in the phase 3 controlled population (9766-CL-0104). One patient in the Phase 2 and 3 Population reported a medical history of pancreatitis, which was active at screening. There were no events of acute pancreatitis in the phase 1 studies.

Psychiatric Events

Visual hallucinations have been associated with voriconazole use. Overall, psychiatric events of interest were reported in a similar proportion of isavuconazonium (28.4%) than voriconazole treated patients (30.5%). The most frequently reported TEAEs occurring in ≥ 5% in the isavuconazonium or voriconazole treatment groups, respectively, were insomnia (8.9% vs 9.3%), anxiety (7.8% vs 6.6%), and confusional state (6.2% vs 7.7%). Hallucinations were reported by 2.3% vs 4.2% of isavuconazonium- vs voriconazole- treated patients, respectively. Visual hallucinations were reported by 1.2% versus 4.2% of isavuconazonium- vs voriconazole-treated patients, respectively. In the voriconazole treatment group, 3 patients discontinued study treatment due to visual hallucination compared to no patients in the isavuconazonium treatment group. Patient level TEAEs of interest within the psychiatric disorders SOC are presented below in Table 72.

Table 72: Treatment Emergent Psychiatric Adverse Events of Interest in the Phase 3 Controlled Population

MedDRA v12.1 Preferred Term	Isavuconazonium	Voriconazole (n = 259)
Overall	**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%)
Agitation	2 (0.8%)	7 (2.7%)
Mood altered	2 (0.8%)	3 (1.2%)
Aggression	2 (0.8%)	1 (0.4%)
Disorientation	1 (0.4%)	1 (0.4%)
Dysarthria	1 (0.4%)	1 (0.4%)
Nervousness	1 (0.4%)	1 (0.4%)
Lethargy	1 (0.4%)	0
Panic attack	1 (0.4%)	0
Altered state of consciousness	0	2 (0.8%)
Abnormal dreams	0	1 (0.4%)
Cognitive disorder	0	1 (0.4%)
Dysphoria	0	1 (0.4%)
Paranoia	0	1 (0.4%)
Stress	0	1 (0.4%)

Source: Adapted from Study Report 9766-CL-0104 Table 12.6.1.13.2

With the exception of insomnia (2 of 144 subjects, 1.4%), no psychiatric events of interest occurred in the phase 2 studies. In the phase 1 multiple dose groups, 65 of 722 subjects (9.0%) experienced a psychiatric event of interest, lower than the rate observed in the placebo group (13/128, 10.2%). Three patients in the isavuconazonium 400 mg single dose group (3/103, 2.9%,) had adverse events of somnolence. No subjects in the other single dose groups (40 mg, 80 mg, 100 mg, 160 mg, 200 mg, placebo) experienced a psychiatric event of interest.

Ocular Toxicity

There was a numerically lower proportion of isavuconazonium patients (8.2%) compared to voriconazole patients (16.6%) who experienced potential ocular toxicity events of interest (Table 73). The difference between treatment groups was influenced by visual impairment and visual acuity reduced-type events. The most common adverse events in the isavuconazonium and voriconazole groups, respectively, were visual impairment (1.6% vs 7.3%), vision blurred (1.6% vs 2.3%), visual acuity reduced (0.4% vs 2.3%), eye pain (0.4% vs 1.5%) and cataract (0.4% vs 1.2%).

Table 73: Treatment Emergent Ocular Adverse Events of Interest in the Phase 3 Controlled Population

MedDRA v 12.1 Preferred Term	Isavuconazonium	Voriconazole (n = 259)
Overall	**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%)
Presbyopia	0	1 (0.4%)
Pupils unequal	0	1 (0.4%)

Source: Adapted from Study Report 9766-CL-0104 Table 12.6.1.13.4

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the Phase 3 Controlled Population, one or more TEAEs were reported by 96.1% of isavuconazonium-treated patients and 98.5% of voriconazole-treated patients. Significant differences were observed for the following SOCs: hepatobiliary disorders (8.9% v 16.2%), eye disorders (15.2% vs 26.6%), skin disorders (33.5% vs 42.5%), psychiatric disorders (27.2% vs 33.2%), cardiac disorders (16.7% vs 22.0%). Table 74 presents TEAE by SOC.

Table 74: Treatment Emergent Adverse Events by System Organ Class in the Phase 3 Controlled Population

System Organ Class	Isavuconazonium (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%)

Source: JMP 11 using ADAE Dataset from Study 9766-CL-0104

Within the SOCs, the lower incidence of TEAEs in patients receivingisavuconazonium as compared to voriconazole was influenced by the following TEAEs:

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

In the Phase 3 Controlled Population, the more common adverse events (occurring with an incidence ≥ 5%) in either the isavuconazonium or voriconazole treatment groups are shown in Table 75.

Table 75: Treatment Emergent Adverse Events in ≥ 5% of Patients in the Phase 3 Controlled Population

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

Source: Reviewer generated using JMP 11 and ADAE dataset from Trial 9766-CL-0104

In the Phase 2 and 3 Population, the more common adverse events (occurring with an incidence ≥ 5%) are shown in Table 76. Nausea (21.4%), vomiting (19.6%), diarrhea (18.6%), pyrexia (17.2%), and headache (13.3%) were the more frequently reported events. The relative proportions of TEAEs by SOC in the phase 2 studies had an order of frequency generally similar to that observed in the phase 3 studies.

Table 76: Treatment Emergent Adverse Events in ≥ 5% of Patients in Any Treatment Group in the Phase 2 and 3 Population

MedDRA v12.1 Preferred Term	Phase 2 Isavuconazonium (n = 144)	Phase 3 Isavuconazonium (n = 403)	Total Isavuconazonium (n = 547)
Overall	**91 (63.2%)**	**386 (95.8%)**	**477 (87.2%)**
Nausea	12 (8.3%)	105 (26.1%)	117 (21.4%)
Vomiting	7 (4.9%)	100 (24.8%)	107 (19.6%)
Diarrhoea	14 (9.7%)	88 (21.8%)	102 (18.6%)
Pyrexia	13 (9.0%)	81 (20.1%)	94 (17.2%)
Headache	6 (4.2%)	67 (16.6%)	73 (13.3%)
Cough	11 (7.6%)	48 (11.9%)	59 (10.8%)
Constipation	5 (3.5%)	52 (12.9%)	57 (10.4%)
Hypokalaemia	0	57 (14.1%)	57 (10.4%)
Dyspnoea	1 (0.7%)	48 (11.9%)	49 (9.0%)
Febrile neutropenia	8 (5.6%)	39 (9.7%)	47 (8.6%)
Oedema peripheral	1 (0.7%)	43 (10.7%)	44 (8.0%)
Back pain	3 (2.1%)	40 (9.9%)	43 (7.9%)
Abdominal pain	3 (2.1%)	38 (9.4%)	41 (7.5%)
Hypertension	5 (3.5%)	33 (8.2%)	38 (6.9%)
Insomnia	2 (1.4%)	36 (8.9%)	38 (6.9%)
Chills	2 (1.4%)	35 (8.7%)	37 (6.8%)
Fatigue	4 (2.8%)	33 (8.2%)	37 (6.8%)
Hypotension	4 (2.8%)	32 (7.9%)	36 (6.6%)
Decreased appetite	1 (0.7%)	32 (7.9%)	33 (6.0%)
Epistaxis	3 (2.1%)	28 (6.9%)	31 (5.7%)
Mucosal inflammation	2 (1.4%)	28 (6.9%)	30 (5.5%)
Pruritus	2 (1.4%)	28 (6.9%)	30 (5.5%)
Rash	8 (5.6%)	21 (5.2%)	29 (5.3%)
Asthenia	2 (1.4%)	24 (6.0%)	26 (4.8%)
Confusional state	0	26 (6.5%)	26 (4.8%)
Gamma-glutamyltransferase	0	26 (6.5%)	26 (4.8%)
Pneumonia	1 (0.7%)	24 (6.0%)	25 (4.6%)
Abdominal pain upper	2 (1.4%)	21 (5.2%)	23 (4.2%)
Anxiety	0	23 (5.7%)	23 (4.2%)
Hypomagnesaemia	0	23 (5.7%)	23 (4.2%)
Respiratory failure	0	23 (5.7%)	23 (4.2%)
Haemoptysis	0	21 (5.2%)	21 (3.8%)
Hyperkalaemia	0	21 (5.2%)	21 (3.8%)
Septic shock	0	21 (5.2%)	21 (3.8%)

Source: Adapted from Summary of Clinical Safety Table 17, in Agreement with Reviewer Analysis of Integrated Safety Dataset.

MO Comment: The pattern of frequency by SOC was generally similar between the phase 2 and phase 3 populations though the frequencies were lower in the phase 2 population than in the phase 3 population, which is consistent with the relatively healthier patient population and lower degree of exposure.

Within the phase 1 multiple dose groups, the highest incidence of TEAEs occurred in the 600 mg group (34/39, 87.2%). TEAEs in the 600 mg group that occurred at a higher rate than that seen in the other multiple dose groups included hot flush (20/39, 51.3%), nausea (10/39, 25.6%), anxiety (5/39, 12.8%), paresthesia (6/39, 15.4%), dry mouth (5/39, 12.8%), dysgeusia (4/39, 10.3%), hypoesthesia oral (4/39, 10.3%), disturbance in attention (4/39, 10.3%), palpitations (4/39, 10.3%), vomiting (3/39, 7.7%), and paresthesia oral (2/39, 5.1%) (Table 77).

Table 77: Treatment Emergent Adverse Events in ≥ 5% of Patients in the Phase 1 Multiple Dose Population

MedDRA (v12.1) System Organ Class	40 mg (n = 6)	50 mg (n = 6)	80 mg (n = 6)	100 mg (n = 175)	150 mg (n =41)	200 mg (n = 490)	600 mg (n = 39)	Total ISA (n = 722)	Placebo (n = 128)
Overall	**5 (83.3%)**	**3 (50.0%)**	**6 (100.0%)**	**127 (72.6%)**	**26 (63.4%)**	**246 (50.2%)**	**34 (87.2%)**	**426 (59.0%)**	**69 (53.9%)**
Headache	2 (33.3%)	0	2 (33.3%)	59 (33.7%)	4 (9.8%)	62 (12.7%)	14 (35.9%)	141 (19.5%)	30 (23.4%)
Nausea	0	0	0	22 (12.6%)	3 (7.3%)	43 (8.8%)	10 (25.6%)	78 (10.8%)	6 (4.7%)
Diarrhoea	1 (16.7%)	0	0	26 (14.9%)	2 (4.9%)	32 (6.5%)	3 (7.7%)	63 (8.7%)	1 (0.8%)
Dizziness	0	1 (16.7%)	0	17 (9.7%)	2 (4.9%)	34 (6.9%)	7 (17.9%)	61 (8.4%)	13 (10.2%)
Somnolence	0	0	0	10 (5.7%)	3 (7.3%)	33 (6.7%)	3 (7.7%)	48 (6.6%)	8 (6.3%)
Fatigue	1 (16.7%)	0	1 (16.7%)	22 (12.6%)	1 (2.4%)	8 (1.6%)	2 (5.1%)	35 (4.8%)	5 (3.9%)
Hot flush	0	0	0	2 (1.1%)	1 (2.4%)	11 (2.2%)	20 (51.3%)	33 (4.6%)	5 (3.9%)
Feeling hot	0	0	0	5 (2.9%)	1 (2.4%)	26 (5.3%)	0	32 (4.4%)	0
Abdominal pain	0	1 (16.7%)	0	13 (7.4%)	2 (4.9%)	8 (1.6%)	2 (5.1%)	26 (3.6%)	8 (6.3%)
Nasopharyngitis	3 (50.0%)	1 (16.7%)	2 (33.3%)	9 (5.1%)	1 (2.4%)	6 (1.2%)	0	22 (3.0%)	5 (3.9%)
Oropharyngeal pain	0	0	0	16 (9.1%)	0	6 (1.2%)	0	22 (3.0%)	2 (1.6%)
Vomiting	0	0	0	6 (3.4%)	1 (2.4%)	10 (2.0%)	3 (7.7%)	20 (2.8%)	0
Paraesthesia	0	0	0	1 (0.6%)	0	12 (2.4%)	6 (15.4%)	19 (2.6%)	5 (3.9%)
Dry mouth	0	0	0	5 (2.9%)	0	6 (1.2%)	5 (12.8%)	16 (2.2%)	1 (0.8%)
Decreased appetite	0	0	0	3 (1.7%)	0	8 (1.6%)	2 (5.1%)	13 (1.8%)	1 (0.8%)
Catheter site pain	0	0	0	6 (3.4%)	5 (12.2%)	0	0	11 (1.5%)	5 (3.9%)
Dysgeusia	0	0	0	1 (0.6%)	0	5 (1.0%)	4 (10.3%)	10 (1.4%)	1 (0.8%)
Lip dry	0	0	0	1 (0.6%)	0	6 (1.2%)	2 (5.1%)	9 (1.2%)	0
Rhinitis	1 (16.7%)	1 (16.7%)	2 (33.3%)	3 (1.7%)	0	2 (0.4%)	0	9 (1.2%)	2 (1.6%)
Cough	1 (16.7%)	0	0	4 (2.3%)	0	3 (0.6%)	0	8 (1.1%)	0
Vessel puncture site pain	0	0	0	0	2 (4.9%)	4 (0.8%)	2 (5.1%)	8 (1.1%)	1 (0.8%)
Catheter site haematoma	0	0	0	2 (1.1%)	5 (12.2%)	0	0	7 (1.0%)	3 (2.3%)
Hypoaesthesia oral	0	0	0	0	0	3 (0.6%)	4 (10.3%)	7 (1.0%)	0
Paraesthesia oral	0	0	0	0	0	5 (1.0%)	2 (5.1%)	7 (1.0%)	0
Anxiety	0	0	0	0	0	1 (0.2%)	5 (12.8%)	6 (0.8%)	2 (1.6%)
Pain in extremity	1 (16.7%)	0	0	2 (1.1%)	0	2 (0.4%)	1 (2.6%)	6 (0.8%)	2 (1.6%)
Arthralgia	0	0	0	2 (1.1%)	0	1 (0.2%)	2 (5.1%)	5 (0.7%)	0
Back Pain	1 (16.7%)	0	0	3 (1.7%)	0	0	1 (2.6%)	5 (0.7%)	4 (3.1%)
Disturbance in attention	0	0	0	1 (0.6%)	0	0	4 (10.3%)	5 (0.7%)	1 (0.8%)
Euphoric mood	0	0	0	1 (0.6%)	0	2 (0.4%)	2 (5.1%)	5 (0.7%)	1 (0.8%)
Insomnia	0	0	0	1 (0.6%)	1 (2.4%)	1 (0.2%)	2 (5.1%)	5 (0.7%)	1 (0.8%)
Palpitations	0	0	0	0	0	1 (0.2%)	4 (10.3%)	5 (0.7%)	2 (1.6%)

Gingivitis	0	0	1 (16.7%)	3 (1.7%)	0	0	0	4 (0.6%)	0
Photophobia	0	0	0	0	0	1 (0.2%)	3 (7.7%)	4 (0.6%)	0
Polydipsia	0	0	0	1 (0.6%)	0	1 (0.2%)	2 (5.1%)	4 (0.6%)	1 (0.8%)
Vessel puncture site reaction	1 (16.7%)	1 (16.7%)	0	0	0	2 (0.4%)	0	4 (0.6%)	0
Poisoning	0	0	0	0	0	1 (0.2%)	2 (5.1%)	3 (0.4%)	0
Restlessness	0	0	0	1 (0.6%)	0	0	2 (5.1%)	3 (0.4%)	0
Puncture site pain	0	0	2 (33.3%)	0	0	0	0	2 (0.3%)	0
Tachycardia	0	0	0	0	0	0	2 (5.1%)	2 (0.3%)	0
Haematoma	1 (16.7%)	0	0	0	0	0	0	1 (0.1%)	0

Source: Adapted from Summary of Clinical Safety Table 23, in Agreement with Reviewer Analysis of Integrated Safety Dataset.

7.4.2 Laboratory Findings

Hematology

Analysis of hematology laboratory tests to evaluate drug- related toxicity is of limitted utility in a population with a high prevalence of hematologic malignancies, bone marrow transplantation, and treatment for these conditions. Within the phase 1 study population, however, two subjects with normal baseline platelet counts each had one isolated post-dosing platelet count < 100 x 10^9/L which returned to baseline values without intervention. One subject with low baseline platelet count had one isolated post-dosing platelet count < 100 x 10^9/L which returned to baseline without intervention.

Chemistry

The number and percentage of patients with a shift from one category (i.e., low, normal, high) at baseline to another category for the highest or lowest post-baseline value for an individual chemistry parameter was similar between isavuconazonium and voriconazole treated patients (Table 78)

Table 78: Shifts in Chemistry Parameters from Baseline to Postbaseline in the Phase 3 Controlled Population

Parameter	Shift from baseline to postbaseline	Isavuconazonium (n = 257)	Voriconazole (n = 259)
Sodium (µmol/L)†	Increase	32/232 (13.8%)	39/234 (16.7%)
	Decrease	32/210 (15.2%)	21/209 (10.0%)
Potassium (µmol/L)†	Increase	61/226 (27.0%)	65/232 (28.0%)
	Decrease	56/183 (30.6%)	53/176 (30.1%)
Chloride (µmol/L)†	Increase	29/228 (12.7%)	30/226 (13.3%)
	Decrease	24/221 (10.9%)	23/224 (10.3%)
Calcium (µmol/L)†	Increase	91/233 (39.1%)	94/236 (39.8%)
	Decrease	38/102 (37.3%)	48/95 (50.5%)
ALT (U/L)	Increase	64/174 (36.8%)	82/188 (43.6%)
	Decrease	12/239 (5.0%)	18/246 (7.3%)
AST (U/L)	Increase	79/202 (39.1%)	101/206 (49.0%)
	Decrease	16/219 (7.3%)	13/222 (5.9%)
Total Bilirubin	Increase	32/199 (16.1%)	37/208 (17.8%)
	Decrease	11/242 (4.5%)	12/243 (4.9%)
Direct Bilirubin (µmol/L)	Increase	32/172 (18.6%)	32/163 (19.6%)
	Decrease	13/230 (5.7%)	12/228 (5.3%)
GGT (U/L)	Increase	48/78 (61.5%)	66/93 (71.0%)
	Decrease	2/236 (0.8%)	0/243
Alkaline Phosphatase (U/L)	Increase	62/172 (36.0%)	79/167 (47.3%)
	Decrease	3/230 (1.3%)	2/231 (0.9%)
LDH (U/L)	Increase	70/161 (43.5%)	63/141 (44.7%)

	Decrease	7/219 (3.2%)	4/226 (1.8%)
Creatine kinase (U/L)	Increase	71/230 (30.9%)	76/232 (32.8%)
	Decrease	14/136 (10.3%)	11/146 (7.5%)
BUN (µmol/L)	Increase	64/216 (29.6%)	58/207 (28.0%)
	Decrease	3/234 (1.3%)	5/235 (2.1%)
Creatinine (µmol/L)	Increase	44/231 (19.0%)	43/228 (18.9%)
	Decrease	2/233 (0.9%)	3/238 (1.3%)
Amylase (U/L)	Increase	33/85 (38.8%)	31/90 (34.4%)
	Decrease	3/63 (4.8%)	5/65 (7.7%)
Triacylglycerol Lipase (U/L)	Increase	12/85 (14.1%)	13/94 (13.8%)
	Decrease	4/94 (4.3%)	1/101 (1.0%)
Albumin (g/L)	Increase	7/92 (7.6%)	4/99 (4.0%)
	Decrease	20/35 (57.1%)	15/28 (53.6%)
Urate (µmol/L)	Increase	106/233 (45.5%)	110/236 (46.6%)
	Decrease	6/97 (6.2%)	2/102 (2.0%)

Source: Adapted from Study 9766-CL-0104 Report Table 12.6.2.3.1

There was a lower number of isavuconazonium- than voriconazole-treated patients, respectively, with a decrease in calcium (37.3% and 50.5%), and with an increase in AST (39.1% and 49.0%), GGT (61.5% and 71.0%) and ALP (36.0% and 47.3%).

Hepatoxicity, including liver test laboratory values, are discussed in Section 7.3.4

MO Comment: Shifts in chemistry lab tests were generally similar between the treatment arms.

7.4.3 Vital Signs

There were no mean vital sign changes (blood pressure, pulse, temperature) of clinical importance observed during scheduled assessments in either treatment group in the Phase 3 Controlled Population.

7.4.4 Electrocardiograms (ECGs)

The number and proportion of patients with 12-lead ECG abnormalities, are presented in Table 79. No events of ventricular tachycardia or ventricular fibrillation were observed on centrally read ECGs.

Table 79: Treatment Emergent 12-Lead ECG Abnormalities by Central Reader in the Phase 3 Controlled Population

	End of Treatment		**Postbaseline**	
Findings	**Isavuconazonium**	**Voriconazole (n = 259)**	**Isavuconazonium**	**Voriconazole (n = 259)**
n	250 (97.3%)	252 (97.3%)	250 (97.3%)	252 (97.3%)
Any Abnormality	**71 (28.4%)**	**75 (29.8%)**	**110 (44.0%)**	**103 (40.9%)**
Hypertrophy patterns	**0**	**1 (0.4%)**	**0**	**1 (0.4%)**

Left ventricular hypertrophy, without secondary ST-T changes	0	1 (0.4%)	0	1 (0.4%)
ST segment changes	**1 (0.4%)**	**2 (0.8%)**	**5 (2.0%)**	**3 (1.2%)**
Abnormal ST pattern in precordial leads	0	1 (0.4%)	0	2 (0.8%)
Abnormal ST pattern widespread	0	0	1 (0.4%)	0
Non specific ST depression	1 (0.4%)	0	3 (1.2%)	0
Non specific ST elevation	0	1 (0.4%)	1 (0.4%)	1 (0.4%)

	End of Treatment		**Postbaseline**	
Findings	**Isavuconazonium**	**Voriconazole (n = 259)**	**Isavuconazonium**	**Voriconazole (n = 259)**
T/U wave abnormalities	**54 (21.6%)**	**56 (22.2%)**	**75 (30.0%)**	**75 (29.8%)**
Abnormal T pattern in precordial leads	1 (0.4%)	3 (1.2%)	3 (1.2%)	5 (2.0%)
Abnormal T pattern in standard leads	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)
Abnormal T pattern widespread	2 (0.8%)	4 (1.6%)	3 (1.2%)	7 (2.8%)
Absence of U wave	24 (9.6%)	27 (10.7%)	24 (9.6%)	27 (10.7%)
Flat T wave	8 (3.2%)	17 (6.7%)	18 (7.2%)	26 (10.3%)
Non specific T wave abnormalities	18 (7.2%)	12 (4.8%)	31 (12.4%)	25 (9.9%)
T wave inversion	6 (2.4%)	4 (1.6%)	8 (3.2%)	6 (2.4%)
AV conduction disorders	**2 (0.8%)**	**7 (2.8%)**	**8 (3.2%)**	**17 (6.7%)**
Borderline first degree A-V block	0	4 (1.6%)	3 (1.2%)	11 (4.4%)
First degree A-V block	1 (0.4%)	3 (1.2%)	1 (0.4%)	6 (2.4%)
Short PR interval	1 (0.4%)	0	4 (1.6%)	2 (0.8%)
Sinus pause	0	0	0	1 (0.4%)
W.P.W.	1 (0.4%)	0	1 (0.4%)	0
Ventricular conduction disorders	**12 (4.8%)**	**14 (5.6%)**	**18 (7.2%)**	**20 (7.9%)**
Complete left bundle branch block	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)
Complete right bundle branch block	1 (0.4%)	3 (1.2%)	3 (1.2%)	4 (1.6%)
Incomplete right bundle branch block	8 (3.2%)	9 (3.6%)	12 (4.8%)	14 (5.6%)
Left anterior fascicular block	1 (0.4%)	3 (1.2%)	1 (0.4%)	3 (1.2%)
Left posterior fascicular block	1 (0.4%)	0	1 (0.4%)	0
Supraventricular/junctional rhythm disorders	**12 (4.8%)**	**10 (4.0%)**	**25 (10.0%)**	**23 (9.1%)**
Atrial bigeminy	0	0	1 (0.4%)	1 (0.4%)
Atrial ectopic pace-maker	1 (0.4%)	0	1 (0.4%)	0
Atrial fibrillation	2 (0.8%)	3 (1.2%)	5 (2.0%)	3 (1.2%)
Atrial flutter	0	0	0	1 (0.4%)
Atrial tachycardia	0	1 (0.4%)	0	2 (0.8%)
Atrial trigeminy	0	1 (0.4%)	0	1 (0.4%)
Coronary sinus pace-maker	0	0	1 (0.4%)	1 (0.4%)
Couplet atrial premature beat	0	0	0	1 (0.4%)
Isolated atrial premature beat	9 (3.6%)	5 (2.0%)	17 (6.8%)	15 (6.0%)
Ventricular rhythm disorders	**4 (1.6%)**	**4 (1.6%)**	**13 (5.2%)**	**11 (4.4%)**
Couplet ventricular premature beat	0	1 (0.4%)	1 (0.4%)	1 (0.4%)
Isolated ventricular premature beat, monomorphic	4 (1.6%)	4 (1.6%)	12 (4.8%)	11 (4.4%)

Postbaseline includes all postbaseline measurements up to 10 days following end of treatment.
Source: Sponsor Study Report 9766-CL-0104 Table 12.6.4.7

MO Comment: Other than a lower incidence of atrioventricular conduction disorders in isavuconazonium-treated patients compared to voriconazole-treated patients, there were no significant differences observed.

7.4.5 Special Safety Studies/Clinical Trials

Thorough QT Study

A randomized, double-blind, placebo- and active-controlled, parallel-group study was conducted to further investigate the effect of repeat doses of isavuconazonium on cardiac repolarization in healthy adult subjects [9766-CL-0017]. Subjects were randomized to 1 of 4 treatment groups (approximately 40 subjects per group);

- Group 1: 200 mg isavuconazonium TID for 2 days then 200 mg isavuconazonium QD for 11 days;
- Group 2: 200 mg isavuconazonium TID for 2 days then 600 mg isavuconazonium QD for 11 days;
- Group 3: placebo for all 13 days;
- Group 4: placebo for 12 days then 400 mg moxifloxacin on Day 13.

For the isavuconazonium 200mg and 600mg treatment groups, the mean change from placebo baseline-adjusted in QTcF decreased by 9 to 13 msec and by 19 to 25 msec, respectively, within 1 hour and 24 hours post dose. No QTcF < 330 msec was observed. No QTcF prolongation was observed in the isavuconazonium treatment groups. In addition, there was a negative relationship between QTcF and isavuconazonium plasma concentrations. Assay sensitivity was confirmed for this study.

MO Comment: Thorough QT study (Study 9766-CL-0017) was reviewed by the Interdisciplinary Review Team for QT Studies (QT-IRT) in a consult dated September 29, 2014. The QT-IRT concluded that "No significant QTc prolongation effect of isavuconazonium (200 mg and 600 mg) was detected in this TQT study."

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Isavuconazole (200 mg and 600 mg) and the Largest Lower Bound for Moxifloxacin on Day 13 (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Isavuconazole 200 mg	2	-13.1	(-18.1, -8.1)
Isavuconazole 600 mg	2	-24.6	(-29.8, -19.3)
Moxifloxacin 400 mg	2	11.0	(6.1, 15.9)

Source: QT-IRT Consult,September 29, 2014, Table 1.

The IRT had the following comments:

1. At a dose 3 times the recommended therapeutic maintenance dose, isavuconazonium capsule did not prolong the QT interval to any clinically relevant extent. In fact, a dose-and-concentration-related shortening of the QTc interval was observed with isavuconazonium, probably correctly attributed by the sponsor to slight block of the calcium channel.

2. Because of the significant higher exposure of isavuconazonium and BAL8728 following intravenous administration compared to that isavuconazonium after oral administration, the results from this capsule TQT study cannot be adequately applied to intravenous administration, although QT prolongation with intravenous administration is unlikely based on the results from study 9766-CL-0004, and, even if there were some inhibition of IKr or hERG at higher exposure, the earlier onset calcium current block would render it benign.

3. There is also a small effect (about 10 ms at the highest tested exposure) reducing the PR interval. We do not believe this is clinically relevant.

Mild to Moderate Hepatic Impairment (Child-Pugh A or B)

In study 9766-CL-0008, 32 subjects with hepatic impairment due to liver cirrhosis were assessed following exposure to isavuconazonium. No SAEs, deaths or TEAEs leading to study discontinuation occurred in this study. Compared to healthy subjects, after intravenous administration of isavuconazonium, total isavuconazonium AUC_{inf} increased in mildly and moderately impaired subjects by 58.9% and 119.1%, respectively. After oral administration, AUC_{inf} increased by 117.5% and 40.7%, respectively. TEAEs reported with oral dosing were upper abdominal pain, hyperhidrosis, incomplete right bundle branch block, and hypertension. No TEAEs were reported by subjects who received the intravenous formulation.

In study 9766-CL-0014, 32 subjects with mild and moderate hepatic impairment due to chronic hepatitis B and/or C were also assessed following systemic exposure to isavuconazonium. No deaths occurred during the study and no subjects discontinued the study due to a TEAE. One healthy subject experienced SAEs of Guillain-Barre syndrome and meningoencephalitis. More subjects with liver impairment experienced TEAEs compared with healthy subjects and more subjects with moderate liver impairment experienced TEAEs compared with subjects with mild liver impairment. Blood pressure increased, body temperature increased and headache were the most frequently reported TEAEs.

Renal Impairment

The incidence of TEAEs for some SOCs was higher in patients with renal impairment compared to those with eGFR ≥ 60 mL/min (normal renal function), as depicted in Table 80.

Table 80: Treatment Emergent Adverse Events by SOC and Baseline Renal Status in the Phase 3 Controlled Population

	Renally Impaired (baseline eGFR < 60 mL/min/1.73m^2)		Non Renally Impaired (baseline eGFR ≥ 60 mL/min/1.73m^2)	
	Isavuconazonium (n = 20)	Voriconazole (n = 33)	Isavuconazonium (n = 230)	Voriconazole (n = 218)
Overall	**20 (100%)**	**32 (97.0%)**	**220 (95.7%)**	**215 (98.6%)**
Blood and Lymphatic System Disorders	4 (20.0%)	14 (42.4%)	71 (30.9%)	64 (29.4%)
Cardiac Disorders	4 (20.0%)	6 (18.2%)	38 (16.5%)	50 (22.9%)
Congenital, Familial and Genetic Disorders	0	1 (3.0%)	3 (1.3%)	1 (0.5%)
Ear and Labyrinth Disorders	1 (5.0%)	0	12 (5.2%)	13 (6.0%)
Endocrine Disorders	1 (5.0%)	0	4 (1.7%)	3 (1.4%)
Eye Disorders	4 (20.0%)	14 (42.4%)	32 (13.9%)	52 (23.9%)
Gastrointestinal Disorders	15 (75.0%)	23 (69.7%)	154 (67.0%)	154 (70.6%)
General Disorders and Administration Site	12 (60.0%)	17 (51.5%)	133 (57.8%)	124 (56.9%)
Hepatobiliary Disorders	3 (15.0%)	5 (15.2%)	20 (8.7%)	34 (15.6%)
Immune System Disorders	1 (5.0%)	2 (6.1%)	19 (8.3%)	22 (10.1%)
Infections and Infestations	13 (65.0%)	21 (63.6%)	136 (59.1%)	132 (60.6%)
Injury, Poisoning and Procedural	5 (25.0%)	4 (12.1%)	25 (10.9%)	33 (15.1%)
Investigations	6 (30.0%)	15 (45.5%)	77 (33.5%)	79 (36.2%)
Metabolism and Nutrition Disorders	7 (35.0%)	18 (54.5%)	99 (43.0%)	99 (45.4%)
Musculoskeletal and Connective Tissue	4 (20.0%)	5 (15.2%)	63 (27.4%)	71 (32.6%)
Neoplasms Benign, Malignant and	2 (10.0%)	4 (12.1%)	17 (7.4%)	26 (11.9%)
Nervous System Disorders	8 (40.0%)	12 (36.4%)	85 (37.0%)	77 (35.3%)
Psychiatric Disorders	6 (30.0%)	7 (21.2%)	63 (27.4%)	76 (34.9%)
Renal and Urinary Disorders	6 (30.0%)	11 (33.3%)	49 (21.3%)	46 (21.1%)
Reproductive System and Breast Disorders	0	0	8 (3.5%)	12 (5.5%)
Respiratory, Thoracic and Mediastinal	8 (40.0%)	22 (66.7%)	132 (57.4%)	121 (55.5%)
Skin and Subcutaneous Tissue Disorders	5 (25.0%)	11 (33.3%)	79 (34.3%)	95 (43.6%)
Social Circumstances	0	1 (3.0%)	0	0
Vascular Disorders	2 (10.0%)	11 (33.3%)	64 (27.8%)	64 (29.4%)

Source: Adapted from Applicant Summary of Clinical Safety, Table 73

MO Comment: Adverse events appear to generally less frequent within the isavuconazonium treatment arm relative to voriconazole. Patients with renal impairment are expected to have higher morbidity, regardless of cause.

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The subjects within the Phase 3 studies received a loading dose of 200 mg q8 for 2 days, followed by maintenance dosing of 200 mg per day. The Phase 1 study results provide limited exposure data, and are discussed in Sections 7.3 and 7.4.

7.5.2 Time Dependency for Adverse Events

No clear time dependency was observed for adverse events (Table 81). The overall incidence of TEAEs was similar regardless of treatment duration and no difference was observed between treatment groups.

Table 81: Overview of Serious TEAEs, TEAEs Leading to Discontinuations and Deaths by Treatment Duration in the Phase 3 Controlled Population

	≤ 42 Days		>42 to ≤ 84 Days		>84 Days	
	Isavuconazonium	**Voriconazole**	**Isavuconazonium**	**Voriconazole**	**Isavuconazonium**	**Voriconazole**
All TEAEs	**119 (96.7%)**	**122**	**105 (95.5%)**	**113**	**23 (95.8%)**	**20 (100%)**
Serious TEAEs	69 (56.1%)	80 (64.0%)	53 (48.2%)	61 (53.5%)	12 (50.0%)	8 (40.0%)
TEAEs Leading to Discontinuation of Study	32 (26.0%)	51 (40.8%)	5 (4.5%)	8 (7.0%)	0	0
TEAEs Leading to Death	49 (39.8%)	53 (42.4%)	11 (10.0%)	17 (14.9%)	2 (8.3%)	2 (10.0%)

Source: Adapted from Applicant Summary of Clinical Safety, Table 78

7.5.3 Drug-Demographic Interactions

Age

The profile of TEAEs, serious TEAEs, TEAEs leading to discontinuation, and TEAEs leading to death in the Phase 3 Controlled Population were more frequent in geriatric (>

65 years of age) patients when compared to non-geriatric patients (Table 82). The AE distribution when analyzed by SOC was similar to the profile of the overall population.

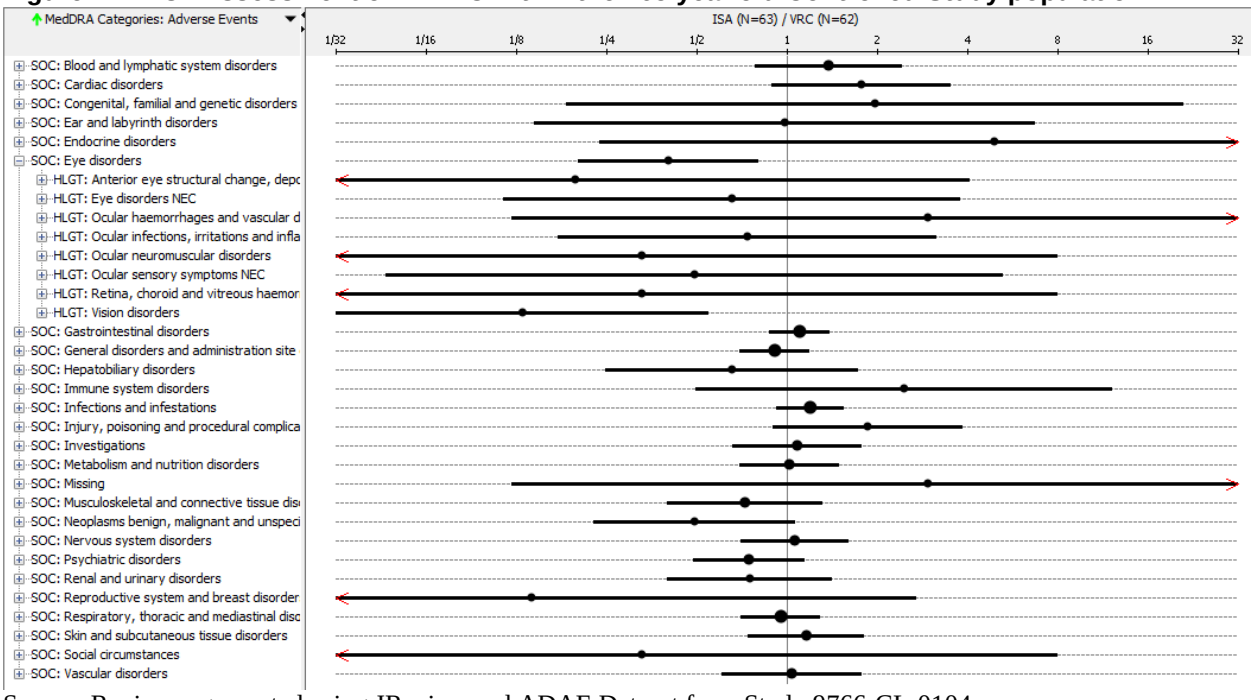
Table 82: Overview of Serious TEAEs, TEAEs Leading to Discontinuations and Deaths in the Phase 3 Controlled Population by Age Group

	≤ 65 years of age		> 65 years of age	
	Isavuconazonium	**Voriconazole (n = 201)**	**Isavuconazonium**	**Voriconazole (n = 58)**
All TEAEs	**192 (95.5%)**	**197 (98.0%)**	**55 (98.2%)**	**58 (100%)**
Serious TEAEs	99 (49.3%)	116 (57.7%)	35 (62.5%)	33 (56.9%)
TEAEs Leading to Discontinuation of Study Drug	29 (14.4%)	44 (21.9%)	8 (14.3%)	15 (25.9%)
TEAEs Leading to Death	47 (23.4%)	55 (27.4%)	15 (26.8%)	17 (29.3%)

Source: Adapted from Study Report 9766-CL-0104 Tables 12.6.1.14.1-2, 12.6.1.15.1-2, Applicant Summary of Clinical Safety, Table 65.

The risk assessment for subjects >65 years of old is expressed in Figure 11 below. The incidence of eye disorders, specifically vision disorders is less frequent in the geriatric population treated with isavuconazonium.

Figure 11: Risk Assessment of TEAEs within the >65 year old Controlled Study population



Source: Reviewer generated using JReview and ADAE Dataset from Study 9766-CL-0104

MO Comment: It is expected that elderly patients will experience more frequent and severe adverse events than younger patients. Patient deaths, discontinuations and overall adverse events are consistent between the two populations.

Gender

The summary of TEAEs, TEAEs leading to death, serious TEAEs, and TEAEs leading to discontinuation of study drug in the Phase 3 Controlled Population are presented in Table 83 for male and female patients.

Table 83: Overview of Serious TEAEs, TEAEs Leading to Discontinuations and Deaths by Gender in the Phase 3 Controlled Population

	Males		Females	
	Isavuconazonium	**Voriconazole (n = 163)**	**Isavuconazonium**	**Voriconazole (n = 96)**
All TEAEs	**139 (95.9%)**	**161 (98.8%)**	**108 (96.4%)**	**94 (97.9%)**
Serious TEAEs	75 (51.7%)	93 (57.1%)	59 (52.7%)	56 (58.3%)
TEAEs Leading to Discontinuation of Study Drug	19 (13.1%)	43 (26.4%)	18 (16.1%)	16 (16.7%)
TEAEs Leading to Death	30 (20.7%)	44 (27.0%)	32 (28.6%)	28 (29.2%)

Source: Adapted from Applicant Summary of Clinical Safety, Table 69

MO Comment: Gender differences to not appear to produce a significantly different AE profile.

Race

Within the isavuconazonium treatment arm of the phase 3 controlled trial, there were proportionately more deaths in Asian subjects (17, 38.6%) than Caucasian subjects (45, 21.3%), (Table 84). Similarly, there were proportionately more TEAEs leading to discontinuation. The overall proportion of serious TEAEs and TEAEs remained similar.

Table 84: Overview of TEAEs, Serious TEAEs, TEAEs Leading to Discontinuations and Deaths by Race, in the Controlled Population

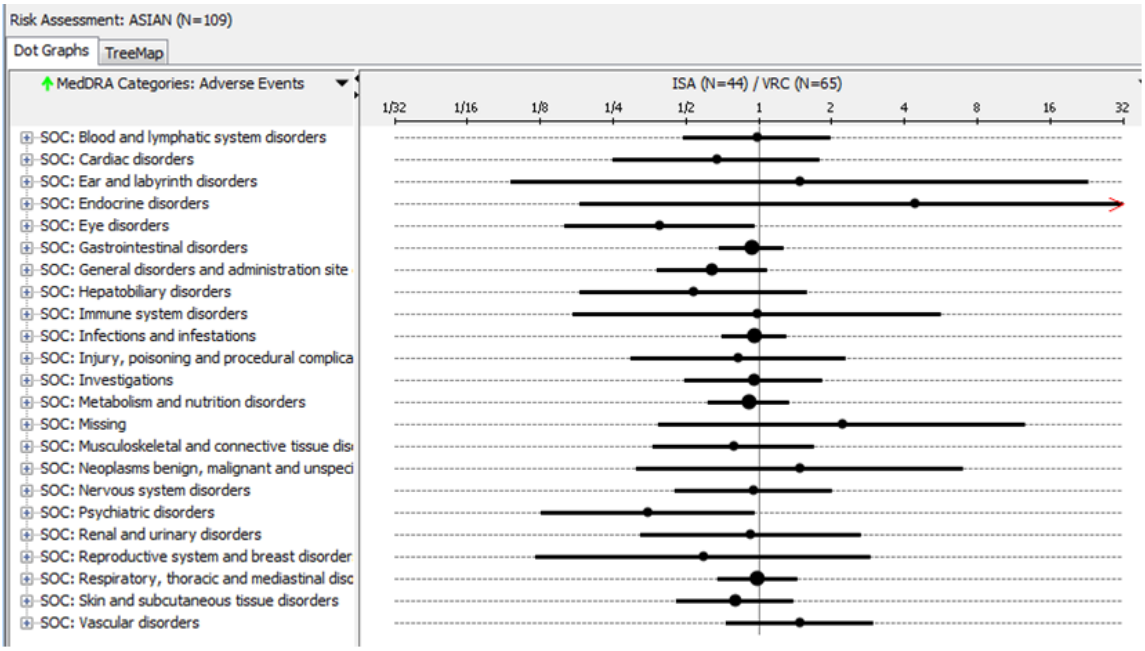
	Caucasian		Asian	
	Isavuconazonium (n = 211)	**Voriconazole (n = 191)**	**Isavuconazonium (n = 44)**	**Voriconazole (n = 65)**
All TEAEs	**204 (96.7%)**	**189 (98.6%)**	**41 (93.2%)**	**63 (96.9%)**
Serious TEAEs	110 (52.1%)	112 (58.6%)	22 (50.0%)	34 (52.3%)
TEAEs Leading to Discontinuation of Study Drug	27 (12.8%)	47 (24.6%)	10 (22.7%)	12 (18.5%)

TEAEs Leading to Death	45 (21.3%)	57 (29.8%)	17 (38.6%)	13 (20.0%)

Source:

To further explore the differences in mortality, Figure 12 and Table 85 lists mortality by SOC and patient term by race and treatment group.

Figure 12: Relative Risk of TEAE by SOC within the Asian Population, Comparing Isavuconazonium to Voriconazole Treatment



Source: Reviewer generated using JReview and ADAE Dataset from Study 9766-CL-0104

Table 85: Comparative Causes of Mortality between Asian and Caucasian Subjects in the Controlled Phase 3 Study Population

SOC	Isavuconazonium				Voriconazole			
	White (n = 211)		Asian (n = 44)		White (n = 191)		Asian (n = 65)	
Patient Term	N	%	N	%	N	%	N	%
Infections and infestations	20	9.5%	8	18.2 %	13	6.8%	6	9.2%
Sepsis	4	1.9%	3	6.8%	3	1.6%	2	3.1%
Septic shock	5	2.4%	3	6.8%	3	1.6%	1	1.5%
Aspergillosis	3	1.4%	0	0.0%	2	1.0%	0	0.0%
Fungal infection	2	0.9%	1	2.3%	2	1.0%	0	0.0%
Pneumonia	1	0.5%	0	0.0%	0	0.0%	2	3.1%
Acinetobacter bacteraemia	0	0.0%	1	2.3%	0	0.0%	0	0.0%

Bronchopulmonary aspergillosis	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Endocarditis	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Fusarium infection	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Infection	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Klebsiella sepsis	0	0.0%	0	0.0%	1	0.5%	0	0.0%
Mucormycosis	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Pseudomonal bacteraemia	0	0.0%	0	0.0%	0	0.0%	1	1.5%
Pseudomonal sepsis	0	0.0%	0	0.0%	1	0.5%	0	0.0%
Stenotrophomonas sepsis	0	0.0%	0	0.0%	1	0.5%	0	0.0%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8	3.8%	2	4.5%	20	10.5%	1	1.5%
Acute myeloid leukaemia	1	0.5%	2	4.5%	7	3.7%	0	0.0%
Acute myeloid leukaemia recurrent	0	0.0%	0	0.0%	4	2.1%	0	0.0%
Blast cell crisis	1	0.5%	0	0.0%	1	0.5%	0	0.0%
Chronic lymphocytic leukaemia	0	0.0%	0	0.0%	2	1.0%	0	0.0%
Malignant neoplasm progression	1	0.5%	0	0.0%	0	0.0%	1	1.5%
Multiple myeloma	2	0.9%	0	0.0%	0	0.0%	0	0.0%
Myeloid leukaemia	1	0.5%	0	0.0%	1	0.5%	0	0.0%
Acute lymphocytic leukaemia recurrent	0	0.0%	0	0.0%	1	0.5%	0	0.0%
B-cell lymphoma	0	0.0%	0	0.0%	1	0.5%	0	0.0%
Burkitt's leukaemia	0	0.0%	0	0.0%	1	0.5%	0	0.0%
Chronic lymphocytic leukaemia recurrent	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Lymphoma	0	0.0%	0	0.0%	1	0.5%	0	0.0%
Myelodysplastic syndrome	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Neoplasm progression	0	0.0%	0	0.0%	1	0.5%	0	0.0%
Respiratory, thoracic and mediastinal disorders	9	4.3%	5	11.4 %	8	4.2%	4	6.2%
Respiratory failure	3	1.4%	3	6.8%	3	1.6%	3	4.6%
Acute respiratory failure	3	1.4%	0	0.0%	1	0.5%	0	0.0%
Haemoptysis	1	0.5%	1	2.3%	1	0.5%	0	0.0%
Pulmonary haemorrhage	1	0.5%	1	2.3%	0	0.0%	1	1.5%
Acute respiratory distress syndrome	0	0.0%	0	0.0%	1	0.5%	0	0.0%
Pulmonary embolism	0	0.0%	0	0.0%	1	0.5%	0	0.0%
Pulmonary hypertension	0	0.0%	0	0.0%	1	0.5%	0	0.0%
Respiratory distress	1	0.5%	0	0.0%	0	0.0%	0	0.0%
General disorders and administration site conditions	2	0.9%	0	0.0%	7	3.7%	1	1.5%
Multi-organ failure	1	0.5%	0	0.0%	6	3.1%	0	0.0%
Death	1	0.5%	0	0.0%	0	0.0%	1	1.5%
Sudden cardiac death	0	0.0%	0	0.0%	1	0.5%	0	0.0%
Nervous system disorders	3	1.4%	0	0.0%	7	3.7%	0	0.0%

Haemorrhage intracranial	2	0.9%	0	0.0%	3	1.6%	0	0.0%
Cerebral haemorrhage	0	0.0%	0	0.0%	1	0.5%	0	0.0%
Encephalitis	0	0.0%	0	0.0%	1	0.5%	0	0.0%
Neurotoxicity	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Stupor	0	0.0%	0	0.0%	1	0.5%	0	0.0%
Subarachnoid haemorrhage	0	0.0%	0	0.0%	1	0.5%	0	0.0%
Cardiac disorders	3	1.4%	1	2.3%	1	0.5%	2	3.1%
Cardiac arrest	1	0.5%	0	0.0%	1	0.5%	1	1.5%
Cardio-respiratory arrest	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Acute myocardial infarction	0	0.0%	0	0.0%	0	0.0%	1	1.5%
Congestive cardiomyopathy	0	0.0%	1	2.3%	0	0.0%	0	0.0%
Pericarditis	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Blood and lymphatic system disorders	2	0.9%	0	0.0%	1	0.5%	0	0.0%
Haemorrhagic disorder	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Pancytopenia	0	0.0%	0	0.0%	1	0.5%	0	0.0%
Thrombocytopenia	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Vascular disorders	1	0.5%	1	2.3%	1	0.5%	0	0.0%
Deep vein thrombosis	0	0.0%	0	0.0%	1	0.5%	0	0.0%
Haemorrhage	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Hypovolaemic shock	0	0.0%	1	2.3%	0	0.0%	0	0.0%
Metabolism and nutrition disorders	0	0.0%	0	0.0%	2	1.0%	0	0.0%
Hypoglycaemia	0	0.0%	0	0.0%	1	0.5%	0	0.0%
Metabolic acidosis	0	0.0%	0	0.0%	1	0.5%	0	0.0%
Gastrointestinal disorders	0	0.0%	0	0.0%	1	0.5%	0	0.0%
Rectal haemorrhage	0	0.0%	0	0.0%	1	0.5%	0	0.0%
Hepatobiliary disorders	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Hepatitis acute	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Immune system disorders	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Acute graft versus host disease	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Renal and urinary disorders	1	0.5%	0	0.0%	0	0.0%	0	0.0%
Renal failure	1	0.5%	0	0.0%	0	0.0%	0	0.0%

Source: Reviewer generated using JMP 11 and ADAE Dataset from Study 9766-CL-0104

MO Comment: The deaths were mostly due to respiratory and sepsis syndromes within the Asian population, which was similar to Caucasians. A search of lower level aggregate terms (HLGT, HLT) did not yield a particular safety signal. The mortality difference appears to be disease progression, or lack of efficacy rather than a specific toxicity. A phase I study (9766-CL-0038) was performed to specifically evaluate PK parameters in Chinese individuals. Chinese subjects had approximately 50% higher isavuconazonium exposure as compared to Western subjects due to reduced total

systemic clearance, but the drug exposure-response profile was flat. Please refer to the Clinical Pharmacology review by Dr. Dakshina Chilukuri.

Ethnicity
There were relatively few Hispanic or Latino patients in both the isavuconazonium group (22/257) and the voriconazole groups (9/259), therefore, a meaningful analysis of safety among ethnic groups is not possible.

Body Mass Index (BMI)
In the Phase 3 Controlled Population, when analyzed by BMI, the pattern of TEAEs was similar to the overall analysis. A total of 49 subjects had a BMI ≥ 30 kg/m^2 (Table 86)

Table 86: Overview of Serious TEAEs, TEAEs Leading to Discontinuations and Deaths by BMI in the Phase 3 Controlled Population

	< 25		≥ 25 to < 30 kg/m^2		≥ 30	
	Isavuconazonium (n = 153)	**Voriconazole (n = 169)**	**Isavuconazonium (n = 70)**	**Voriconazole (n = 59)**	**Isavuconazonium (n = 27)**	**Voriconazole (n = 22)**
All TEAEs	**146 (95.4%)**	**166**	**68 (97.1%)**	**58 (98.3%)**	**26 (96.3%)**	**22**
Serious TEAEs	79 (51.6%)	93 (55.0%)	39 (55.7%)	34 (57.6%)	13 (48.1%)	13 (59.1%)
TEAEs Leading to Discontinuation of Study Drug	23 (15.0%)	31 (18.3%)	10 (14.3%)	19 (32.2%)	4 (14.8%)	5 (22.7%)
TEAEs Leading to Death	44 (28.8%)	42 (24.9%)	14 (20.0%)	20 (33.9%)	2 (7.4%)	4 (18.2%)

Source: Adapted from Applicant Summary of Clinical Safety, Table 71

MO Comment: I agree that BMI has no clinically meaningful effect on serious TEAEs, TEAEs leading to discontinuation of study drug, and TEAEs leading to death between treatment goups.

7.5.4 Drug-Disease Interactions

The treatment differences between isavuconazonium and voriconazole observed for the overall analysis of TEAEs, serious TEAEs, TEAEs leading to discontinuation of study drug, and TEAEs leading to death in the Phase 3 Controlled Population were consistent by hematologic malignancy status, baseline neutropenic status, and uncontrolled malignancy status.

7.5.5 Drug-Drug Interactions

Please refer to Dr. Dakshina Chilukuri's clinical pharmacology review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Please refer to Dr. Owen McMaster's toxicology review.

7.6.2 Human Reproduction and Pregnancy Data

Because pregnant subjects were excluded from isavuconazonium studies, there are no data on human pregnancies exposed to isavuconazonium. There were also no studies todetermine the presence of isavuconazonium in human milk.

Isavuconazonium has been shown to pass through the placenta in rats. In both rats and rabbits, isavuconazonium administration during pregnancy at doses below the 200 mg/kg/day maintenance dose was associated with skeletal anomalies consistent with azole-class anti-fungal drugs. Please refer to Dr. Owen McMaster's toxicology review for more information.

7.6.3 Pediatrics and Assessment of Effects on Growth

Isavuconazonium trials enrolled subjects of at least 18 years of age, so there are no significant human safety data on the pediatric population, with the exception of one subject (WSAC004-3204-29) who was 17 years old and mistakenly enrolled. He received 2 days of Isavuconazonium, but invasive fungal disease was not confirmed (violation of selection at entry), resulting in the discontinuation of therapy.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

During clinical studies, total daily isavuconazonium doses higher than the recommended dose regimen were associated with an increased rate of adverse events. At supratherapeutic doses (isavuconazonium 600 mg/day maintenance dose) evaluated in a Thorough QT study, there were proportionally more TEAEs than in the therapeutic dose group (isavuconazonium 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. TEAEs leading to discontinuation of study drug occurred in 17.9% (7/39) of subjects in the isavuconazonium 600 mg treatment group, and 2% (9/490) in the 200 mg treatment group, as discussed in Section 7.3.3.

Isavuconazonium is not removed by hemodialysis. There is no specific treatment for Isavuconazonium overdose other than supportive care.

Isavuconazonium is not a drug with abuse potential.

7.7 Additional Submissions / Safety Issues

No safety issues in addition to those described in this review have been identified.

8 Postmarket Experience

None.

9 Appendices

9.1 Literature Review/References

The references are included as footnotes.

9.2 Labeling Recommendations

Warnings on the possibility of drug induced liver injury associated with isavuconazonium use and drug particulate formation within the IV formulation are being considered for inclusion on the package insert. The language of the warnings, as well as other labeling recommendations, has not yet been finalized at the time of completion of this review.

9.3 Advisory Committee Meeting

An advisory committee meeting is scheduled on January 22, 2015, i.e. in approximately six weeks after the completion of this review.

9.4 Criteria for Categorizing the Presence of IFD, Adapted from The European Organization for the Research and Treatment of Cancer/Mycoses Study Group Definitions, 2008

Proven: Positive culture from a normally sterile site or microscopy (cytology/histology) showing hyphal forms with evidence of associated tissue damage; OR positive blood culture in the context of a compatible infectious disease process

Probable: At least one host factor, one clinical feature and one mycological criterion

Possible: At least one host factor and one clinical feature

In detail: ProvenInvasiveFungalDisease[Appliestofilamentousfungi(molds)]

Patients with a positive diagnostic test obtained within the 7 days after the first administration of study medication:

- Either 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)

OR

- Recovery of a mold 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.

OR

- Blood culture that yields a mold (e.g., *Fusarium* species) in the context of a compatible infectious disease process.

Host factors and clinical features are not required for patients with proven IFD. However, if such host factors and clinical features are present at baseline, they will be recorded in the eCRF.

OtherProven InvasiveFungal Disease

DEEP TISSUE DISEASE OR FUNGEMIA

Non-*Candida* Yeasts

Histopathologic or cytopathologic examination of a needle aspiration or biopsy specimen from a normally sterile site excluding mucous membranes showing yeast cells;

OR

Recovery of a yeast by culture from a sample obtained by a sterile procedure (including a freshly [< 24 hours] placed drain) from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process.

CRYPTOCOCCOSIS

Cryptococcal meningitis documented by a cerebrospinal fluid (CSF) culture positive for *Cryptococcus.* Antigen titers are acceptable only as supportive evidence and for response and outcome assessment. Patients may enroll on the basis of positive India ink or other histopathology diagnostic for *Cryptococcus.*

ENDEMIC FUNGAL DISEASE

Histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, and infection due to *Penicillium marneffei*.

Disseminated and/or pulmonary disease

Must be proven by recovery in culture from a specimen obtained from the affected site, in a host with a temporally related illness consistent with a fungal infectious disease process;

OR

If a culture is negative or not obtained, histopathologic or direct microscopic demonstration of appropriate morphological forms is considered adequate for dimorphic fungi having truly distinctive appearance;

OR

Positive blood culture.

Additionally:

For histoplasmosis, a diagnosis of disseminated disease may be established by

- a positive *Histoplasma* antigen test on CSF, urine or serum by enzyme immunoassay in sites with access to laboratories were the assays have been validated,

OR

- the presence of characteristic intracellular yeast forms in a peripheral blood smear or in bone marrow.

For coccidioidomycosis, a diagnosis of disseminated disease may be established by demonstration of coccidioidal antibody in CSF, or a two-dilution rise measured in two consecutive blood samples tested concurrently in the setting of a temporally related infectious disease process.

ProbableInvasiveFungalDisease[Appliestofilamentousfungi(molds)]

	At least one host factor (a) as below
PLUS	**At least one clinical feature (b)** as below
PLUS	**At least one mycological criterion (c)** as below

a. HOST FACTORS:

- Either recently resolved or ongoing neutropenia (neutropenia defined as absolute neutrophil count < 0.5 x 10^9/L [< 500 / mm^3] for ≥ 10 days), temporally related to the onset of fungal disease;
- Or receipt of an allogeneic hematopoietic stem cell transplant (bone marrow transplantation [BMT]);
- Or treatment with other recognized T-cell immune suppressants (such as cyclosporine, tacrolimus, monoclonal antibodies or nucleoside analogues) during the past 90 days (patients whose underlying condition is rheumatologic in nature are not eligible for enrollment);
- Or inherited immunodeficiency (e.g. chronic granulomatous disease, severe combined immunodeficiency).

b. CLINICAL FEATURES:

Lower Respiratory Tract Disease (LRTD)

The medical history must be established to exclude alternative etiologies and to distinguish between an acute or subacute presentation rather than a chronic pulmonary infection. Onset of clinical symptoms and/or physical findings within approximately 2 weeks prior to the first administration of study medication defines an acute or subacute pulmonary infection.

The presence of **at least one** of the following **"specific" imaging signs on computed tomography (CT), high resolution computed tomography (HRCT) or magnetic resonance imaging (MRI)**:

- Well defined nodule(s) with or without a halo sign
- Air crescent sign
- Cavity

OR

Allogeneic HSCT/BMT or neutropenic patients who have non-specific focal infiltrates, on CT scan (or HRCT) or MRI, must have mycological evidence of disease at the time of study entry and will be classified as probable. Otherwise, patients with non-specific focal infiltrates are not eligible.

Non-Lower Respiratory Tract Disease (NLRTD)

See Table below for a summary of status of invasive fungal disease at baseline for patients with NLRTD.

- **Sino-nasal infection:**
- CT scan 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 or
- Meningeal enhancement on CT or MRI.

c. MYCOLOGICAL CRITERIA (cytology, direct microscopy, culture from non- sterile sites, serum)

- Either sputum, BAL, bronchial brush samples, or sinus cavity specimen demonstrating the presence of fungal elements either by recovery by culture of a mold or detection by cytology or direct microscopy of hyphal forms;
- Or skin ulcers, draining soft tissue lesions, or fissures for which both microscopy and (fungal) culture are required;

Status of Invasive Fungal Disease at Day 7 for Patients with Filamentous Fungi Lower Respiratory Tract Disease (LRTD)			
HOST FACTORS	**CLINICAL FEATURES "Lower Respiratory Tract Disease"**	**Positive culture or microscopy (cytology/histology) of hyphal forms**	
		Non-sterile site (i.e., sputum, BAL, bronchial brushing, or sinus cavity specimen)	**Sterile site (i.e., transbronchial biopsy or open-lung biopsy) or with associated tissue damage**
Neutropenia (ANC < 0.5×10^9/L [< 500/mm^3]) temporally related to the onset of fungal disease **OR** Receipt of an allogeneic hematopoietic stem cell transplant **OR**	Presence of at least one imaging sign on CT scan (or HRCT) or MRI: Well defined nodule(s) with or without a halo sign Air crescent sign Cavity **OR** Presence of new "non-specific" imaging findings on CT scan	Probable	Proven

HOST FACTORS	**CLINICAL FEATURES "Lower Respiratory Tract Disease"**	**Positive culture or microscopy (cytology/histology) of hyphal forms**	
		Non-sterile site (i.e., sputum, BAL, bronchial brushing, or sinus cavity specimen)	**Sterile site (i.e., transbronchial biopsy or open-lung biopsy) or with associated tissue damage**

Treatment with other recognized T-cell immunosuppressants, TNF-α blockers, monoclonal antibodies, nucleoside analogs during the past 90 days **OR** Inherited severe immunodeficiency	(or HRCT) or MRI[1]		
No host factors	Ineligible		

TNF: tumor necrosis factor

1. Only allogeneic HSCT/BMT or neutropenic patients who have non-specific focal infiltrates, confirmed by CT scan (or HRCT) or MRI, and have mycological evidence of disease at the time of study entry may be enrolled and will be classified as probable.

Status of Invasive Fungal Disease at Day 7 for Patients with Filamentous Fungi Non-Lower Respiratory Tract Disease (NLRTD)			
HOST FACTORS	**CLINICAL FEATURES Sino-Nasal Infection CNS Infection**	**Positive culture or microscopy (cytology/histology) of hyphal forms**	
		Non-sterile site	**Sterile site (i.e., brain biopsy or blood culture) or with associated tissue damage**

Neutropenia (ANC < 0.5×10^9/L [< 500/mm^3]) temporally related to the onset of fungal disease **OR** Receipt of an allogeneic hematopoietic stem cell transplant **OR** Treatment with other recognized T-cell immunosuppressants, TNF-α blockers, monoclonal antibodies, nucleoside analogs during the past 90 days **OR** Inherited severe immunodeficiency	**Sino-Nasal Infection** 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 or - Meningeal enhancement on CT or MRI.	Probable	Proven[1]
No host factors	Ineligible		

TNF: tumor necrosis factor

1. Blood cultures that yield a mold (e.g., *Fusarium* species) in the context of a compatible infectious disease process.

9.5 Data Review Committee Criteria for Determining Treatment Outcome, Reprinted from the Charter

(b) (4)

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9.7 Clinical Investigator Financial Disclosure Form

Clinical Investigator Financial Disclosure Review Template

Application Number: 207500 and 207501

Submission Date(s): 7/8/2014

Applicant: Astellas

Product: Isavuconazonium sulfate

Reviewer: Edward Weinstein, M.D., Ph.D.

Date of Review: 12/08/2014

Covered Clinical Study (Name and/or Number): 9766-CL-0103 and 9766-CL-0104

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 116 Principle Site Investigators for 9766-CL-0104 (Study Report Appendix 13.4.2); 38 Principle Site Investigators for 9766-CL-0103 (Study Report Appendix 13.4.2)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA		

3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: $0 Significant payments of other sorts: $125,000 Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator in sponsor of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3)		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[19] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

[19] See [web address].

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Discussion: The Applicant submitted form 3454 certification of financial interest in accordance with 21 CFR part 54 for each of the phase 3 clinical studies. The applicant identified a participating investigator in both studies, (b) (6) who was reimbursed $30,000 for his participation on the DRC for Study WSA-CS-003 and $1,000 for consulting fees. In addition, for assistance with the Fungiscope database, an additional $94,000 is expected to be paid to (b) (6)

(b) (6) was the investigator for site (b) (6). The site randomized (b) (6) subjects for study 9766-CL-0104, with an enrollment of (b) (6) subjects to the Isavuconazonium arm, and (b) (6) subjects to the voriconazole arm. The 42 day all-cause mortality at this site was 60% ((b) (6) enrolled) for isavuconzole, and 50% (b) (6) enrolled) for voriconazole. The site efficacy for the primary end point appeared to be balanced between the study arms. A single subject was enrolled for study 9766-CL-0103 who did not survive to day 42.

Comment: A limited number of patients were enrolled by (b) (6) in the phase 3 studies and the Fungiscope database existed before Astellas contracted with (b) (6). The results of the site do not appear to be irregular, and it is unlikely that the Fungiscope arrangement would invalidate the results of these studies.

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/s/

EDWARD A WEINSTEIN
12/12/2014

ELIZABETH M OSHAUGHNESSY
12/12/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 207500, 207501 **Applicant: Astellas** **Stamp Date: July 8, 2014**

Drug Name: Cresemba **NDA/BLA Type: 505(b)(1)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			Draft labeling proposed in PLR format (Module 1.14.1)
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Module 2.7.4 and CTD Module 5.3.5.3
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Module 2.7.3: Summary of Clinical Efficacy
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Present within the discussion section of the individual studies
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: WSA-CS-001 (9766-CL-0101) Study Title: A Phase II, Randomized, Multicenter, Double-Blind Study to Investigate the Efficacy and Safety	X			

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	Content Parameter	Yes	No	NA	Comment
	of Three Dosing Regimens of Water Soluble Azole BAL8557 Compared to Fluconazole in the Treatment of Patients With Uncomplicated Esophageal Candidiasis Sample Size: 160 Arms: 4 Location in submission: Module 5.3.3.2 Study Number: WSA-CS-002 (9766-CL-0102) Study Title: Open-Label, Multi-Center, Sequential Group, Clinical Study to Determine the Safety and Efficacy of Escalating Dosing Regimens of Intravenous or Oral BAL8557 in the Prophylaxis of Patients Undergoing Chemotherapy for Acute Myeloid Leukemia Sample Size: 23 Arms: 2 Location in submission: Module 5.3.3.2				
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: 9766-CL-0104 Indication: Invasive Aspergillosis Randomized, double-blind, noninferiority, comparative group study of 516 adult patients with suspected invasive fungal disease (IFD) caused by Aspergillus species or other filamentous fungi. Pivotal Study #2: 9766-CL-0103 Indication: Invasive Mucormycosis Open-label, multicenter, single arm study from a subpopulation of patients enrolled in the phase 3 Study 9766-CL-0103, who were confirmed to have proven or probable invasive mucormycosis.	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Agreement was reached on the primary study endpoint of all-cause mortality at day 42 in the intent-to-treat (ITT) population, and the associated 10% noninferiority margin.
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
21.	Has the applicant presented the safety data in a manner	X			

	Content Parameter	Yes	No	NA	Comment
	consistent with Center guidelines and/or in a manner previously requested by the Division?				
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			Study 9766-CL-0004, "QTc Measurements and Pharmacokinetics of Placebo- and Active-Controlled Multiple Dose Study of 2 Different Dosing Regimens of Isavuconazonium in Healthy Male and Female Volunteers" Study 9766-CL-0017, "Phase 1, Randomized, Double-Blind, Placebo and Active Controlled, Parallel Study to Evaluate the Effect of Repeat Doses of Isavuconazole on Cardiac Repolarization in Healthy Adult Subjects."
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	Not proposed to be a chronically administered drug, however amendment 4 of study WSA-CS-003 allowed treatment beyond 180 days on a compassionate basis.
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			Module 5.3.5.3
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and	X			Attachment 1

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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	Content Parameter	Yes	No	NA	Comment
	adverse dropouts (and serious adverse events if requested by the Division)?				narratives on study reports include deaths, SAEs, discontinuations, and events of interest (torsades, pancreatitis, nephrotoxicity and hepatotoxicity)
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Module 5.2 Study listing table
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Orphan Drug Status
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			EORTC/MSG 2008 Guidelines used
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?			X	Data standards (Eileen Navarro) will do data fitness
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			Please refer to note on question 28.
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			Module 1.3 Note: (b) (6) participated in both phase 3 studies, has been reimbursed $30,000 for his participation on the

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	Content Parameter	Yes	No	NA	Comment
					DRC for Study WSA-CS-003 and $1,000 for consulting fees, and $94,000 for fungiscope assistance
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			Study reports contain ethics sections verifying GCP, IRB and IC

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __YES_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Edward Weinstein, MD, PhD	8/12/2014
Reviewing Medical Officer	Date
Elizabeth O'Shaugnessy, MD	8/12/2014
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EDWARD A WEINSTEIN
08/12/2014

ELIZABETH M OSHAUGHNESSY
08/12/2014