

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207500Orig1s000 / 207501Orig1s000**

**SUMMARY REVIEW**

## Division Director Memo

<b>Date</b>	(electronic stamp)
<b>From</b>	Sumathi Nambiar MD MPH
<b>Subject</b>	Division Director Memo
<b>NDA # s</b>	207500, 207501
<b>Applicant Name</b>	Astellas Pharma US, Inc.
<b>Date of Submission</b>	July 08, 2014
<b>PDUFA Goal Date</b>	March 08, 2015
<b>Established (USAN) Name</b>	Isavuconazonium sulfate
<b>Trade Name</b>	CRESEMBA
<b>Dosage Forms / Strength</b>	Capsules, 186 mg isavuconazonium sulfate Powder for Injection 372 mg isavuconazonium sulfate/vial
<b>Proposed Indications</b>	Treatment of the following in patients 18 years of age and older <ol style="list-style-type: none"> <li>1. Invasive aspergillosis</li> <li>2. Invasive mucormycosis</li> </ol>
<b>Recommended Action:</b>	Approval

<b>Material Reviewed/Consulted</b>	<b>Names of Discipline Reviewers</b>
Action Package including:	
Cross-Discipline Team Leader Review	John Alexander MD MPH
Pharmacology Toxicology Review	Owen McMaster PhD
Chemistry Manufacturing and Controls Review	Nina Ni PhD, Yichun Sun PhD, Gene Holbert PhD
Biopharmaceutics Review	Banu Zolnik PhD
Medical Officer Review	Edward Weinstein MD PhD
Statistical Review	Cheryl Dixon PhD
Risk Management	Carolyn Yancey MD
Product Quality Review	Vinayak Pawar PhD
Microbiology Review	Shukal Bala PhD
Clinical Pharmacology Review	Dakshina Chilukuri PhD
Office of Scientific Investigations	Antoine El-Hage PhD
Division of Medication Error Prevention and Analysis	Jacqueline Sheppard Pharm D
Thorough QT Study Review	Interdisciplinary Review Team
Labeling Reviews	Christine Corser Pharm D Shawna Hutchins MPH BSN RN

## 1.0 Introduction

NDA 207500 and 207501, isavuconazonium sulfate capsules and sterile lyophilized powder for injection respectively, were submitted by Astellas Pharma Global Development, Inc. on behalf of Astellas Pharma US, Inc. on July 08, 2014 for treatment of invasive aspergillosis and treatment of invasive mucormycosis. Isavuconazonium sulfate is a prodrug of isavuconazole and is a member of the azole class of antifungal drugs. The currently approved therapies for invasive aspergillosis include different formulations of amphotericin B, itraconazole, voriconazole, and caspofungin. Mucormycosis refers to a group of opportunistic mycoses that occur in immunocompromised or diabetic patients and are caused by the ubiquitous filamentous fungi of the Mucorales order of the class Zygomycetes.<sup>1</sup> The more common species include *Rhizopus*, *Lichtheimia* (formerly known as *Absidia*), *Rhizomucor*, *Mucor*, and *Cunninghamella*. The only drug approved for the treatment of invasive mucormycosis (zygomycosis) is amphotericin B.

## 2.0 Background

The Investigational New Drug (IND) application for the intravenous formulation was submitted by Basilea Pharmaceutica International Ltd. in June 2005. In March 2010, the sponsorship of the IND was changed to Astellas Pharma Global Development, Inc. Astellas Pharma Global Development, Inc. submitted the IND for the oral formulation in August 2013. In 2013, isavuconazonium sulfate capsules and injection received orphan drug designation for both invasive aspergillosis and invasive mucormycosis. In November 2013, the products received qualified infectious disease product (QIDP) designation for the treatment of invasive aspergillosis and in February 2014, for the treatment of invasive mucormycosis.

Under the provisions of Generating Antibiotic Incentives Now (GAIN) [Title VIII of FDASIA], NDAs for products with a QIDP designation receive a priority review. As isavuconazonium sulfate has QIDP designation for the submitted indications, these NDAs received a priority review. These NDAs are eligible for five additional years of marketing exclusivity under GAIN. These NDAs are PDUFA V 'Program' applications as well.

The clinical development program includes two Phase 3 clinical trials, one in patients with invasive aspergillosis, and the other in patients with invasive fungal disease including invasive mucormycosis. Two Phase 2 trials have also been conducted, one in patients with esophageal candidiasis and the second as prophylaxis in patients with acute myeloid leukemia. Safety data

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<sup>1</sup> Petrikos G, Skiada A, Lortholary A et al. Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis 2012;54(S1):S23–34

from these Phase 2 trials were included in the safety analysis. The efficacy data from the Phase 2 trials were not directly relevant to the two proposed indications as the patient populations and clinical conditions studied were different.

The review team has completed their reviews of these applications. For a detailed discussion of NDAs 207500 and 207501, please refer to the discipline specific reviews and the Cross-Discipline Team Leader review.

### 3.0 Product Quality

The Chemistry Manufacturing and Controls (CMC) reviewers for NDA 207500 are Yichun Sun, PhD and Gene Holbert, PhD. The CMC reviewer for NDA 207501 is Nina Ni, PhD. The Product Quality Microbiology reviewer is Vinayak Pawar, PhD and the Biopharmaceutics reviewer is Banu Zolnik, PhD.

#### Isavuconazonium Sulfate Capsules (NDA 207500)

Isavuconazonium sulfate (BAL8557-002) is a water-soluble triazole prodrug which is hydrolyzed to the active moiety isavuconazole (BAL4815) and the inactive cleavage product (BAL8728). Isavuconazonium sulfate is an amorphous, white to yellowish white powder. It is highly soluble in water, (b) (4). The drug substance is moisture (b) (4) sensitive and hygroscopic. As isavuconazonium sulfate is a moisture-sensitive drug substance, (b) (4) of its manufacturing process. The proposed acceptance criteria for the potentially genotoxic impurities were deemed acceptable. Stability studies for three primary stability batches have demonstrated that the drug substance is stable under long term storage conditions of (b) (4) months.

The drug product, isavuconazonium sulfate capsules have a Swedish Orange (reddish-brown color) body and a white cap. Each capsule contains 186.3 mg isavuconazonium sulfate, equivalent to 100 mg isavuconazole. The inactive ingredients include magnesium citrate, microcrystalline cellulose, talc, colloidal silicon dioxide, and stearic acid. All excipients used in the drug product are of compendial grades. The capsules are prepared by (b) (4). The steps in the manufacturing process of the drug product include (b) (4). The capsules are packaged in aluminum blisters with desiccant. The drug product specifications were found acceptable. The proposed expiration dating period of 30 months is supported by 18-month long-term and 6-month accelerated stability data. The drug product needs to be protected from (b) (4) humidity.

Dr. Pawar noted that the microbial limits specification was acceptable and recommended approval of NDA 207500 from a product quality microbiology standpoint. Dr. Zolnik noted that

the dissolution method and acceptance criterion for isavuconazonium sulfate capsules were acceptable for batch release and stability testing and recommended approval of NDA 207500 from a biopharmaceutics perspective.

In a review dated January 06, 2015, Drs. Sun and Holbert concluded that the Applicant had provided sufficient CMC information to assure the identity, purity, strength and quality of the drug product. However, as the Office of compliance has not made a final “Acceptable” recommendation on the facilities and labeling issues have not been resolved, the NDA cannot be approved.

On March 03, 2015, the Office of Process and Facilities provided an overall recommendation of “Acceptable” for the facilities for both NDAs.

In an addendum dated March 04, 2015, Dr. Sun noted that all outstanding CMC issues have been addressed satisfactorily and recommended approval of NDA 207500.

#### Isavuconazonium Sulfate for Injection (NDA 207501)

For the drug substance, the Applicant has referenced NDA 207500. Dr. Holbert has reviewed the drug substance section for NDA 207500 and found it adequate to support both NDAs. The drug product, isavuconazonium sulfate for injection is a sterile, lyophilized product containing 372.6 mg of isavuconazonium sulfate, equivalent to 200 mg isavuconazole per vial. The inactive ingredients include mannitol as a bulking agent and sulfuric acid for pH adjustment. All excipients are of compendial grade.

The manufacturing process of isavuconazonium sulfate for injection consists of the following steps: (b) (4)

The proposed in-process controls were deemed adequate. The proposed drug product specification including description, identification, pH, related substances, BAL4815, 2-butenal, water content, bacterial endotoxins, uniformity of dosage units, foreign matter, particulate matter, sterility, and assay was acceptable. The to-be-marketed formulation is the same formulation used in Phase 3 clinical trials. The container closure system for the drug product consists of 10 mL vial, 20 mm stopper, and 20 mm aluminum/flip-off seal. The compatibility, suitability, functionality, and safety of the primary and in-use container closure system with the drug product have been demonstrated.

When the reconstituted solution is mixed with saline and 5% dextrose solution (D5W), a white precipitate is formed. Although this precipitate was observed throughout the compatibility study, the assay and impurity values were consistent. The precipitate has been identified as BAL4815, the active moiety present in the lyophilized drug product and does not result from hydrolysis of the product in the infusion solution as the precipitates are formed immediately. Dr. Ni notes that

BAL4815 (isavuconazole) levels in the drug substance and drug product cannot be lowered any further due to the poor solubility of BAL4815 in aqueous media. Dr. Ni also notes that neither the precipitate nor the removal of the precipitate with an inline filter will affect the efficacy of the drug product based on the acceptable assay values seen at maximum in-use storage times and after filtration. The Applicant provided data to demonstrate that there was (b) (4) with filters of two sizes (0.2 µm and 1.2 µm). Compatibility was also demonstrated between the drug product and two different types of in-line filters. The Dosage and Administration section (2.0) of the package insert includes a statement that the product should be administered using an inline filter. The Warnings and Precautions section of the package insert includes a warning regarding particulates and states that the product is to be administered through an in-line filter.

The drug product is to be administered by intravenous infusion after reconstitution with 5.0 mL of water for injection and further dilution with 0.9% sodium chloride (saline) solution or 5% dextrose solution (D5W). The prepared infusion solution should be kept for no more than 6 hours at room temperature [20°C to 25°C (68°F to 77°F)] or 24 hours refrigerated at 2° to 8°C.

Stability data up to 18 months were submitted for three registration batches. The drug product is physically and chemically stable with no significant change when stored in a refrigerator for up to 18 months and support the proposed shelf life of 24 months when stored in a refrigerator. All three batches were manufactured at the intended commercial manufacturing site, (b) (4) with the intended commercial manufacturing process on commercial scale, and packaged in the commercial packaging components.

For NDA 207501, reference was made to (b) (4) DMF (b) (4) for (b) (4). The information submitted was found to be adequate and Dr. Pawar recommended approval of NDA 207501, from a product quality microbiology perspective.

In a review dated 12/12/2014, Dr. Ni concluded that the applicant had provided sufficient CMC information to assure the identity, purity, strength and quality of the drug product. However, as the Office of Compliance has not made a final “Acceptable” recommendation on the facilities and labeling issues have not been resolved, the NDA cannot be approved.

In an addendum dated March 04, 2015, Dr. Ni recommended approval of NDA 207501.

I concur with the recommendations made by the product quality review team.

#### **4.0 Pharmacology/Toxicology**

The pharmacology/toxicology reviewer for these NDAs is Owen McMaster, PhD. Nonclinical studies were conducted in rats, mice, hamsters, rabbits, guinea pigs and monkeys. The effects of

oral isavuconazonium sulfate and/or chloride administration were evaluated for up to 39 weeks in monkeys, 26 weeks in rats and 13 weeks in mice and the effects of intravenous isavuconazonium sulfate were evaluated in rats and monkeys for up to 6 weeks. Intravenous administration was associated with hemorrhage, vasculitis/perivasculitis, necrosis and/or thrombosis at the injection site; otherwise no new toxicities were noted when compared to oral dosing.

In repeat- dose toxicology studies in monkeys, mice and rats, reversible increases in liver weights and/or hepatocellular hypertrophy were seen. As isavuconazole induces CYP3A and/or CYP2B, the hepatocellular hypertrophy is considered an adaptive response to the increase in activity of the hepatic microsomal drug metabolizing enzymes. There was no evidence of hepatocellular damage and the findings were reversible at the end of a four-week treatment free period. In rats, repeated administration of isavuconazonium sulfate was associated with an increase in thyroid weights and thyroid follicular cell hypertrophy/hyperplasia. These effects were not observed in monkeys. Dr. McMaster noted that rats handle thyroid hormones differently from humans and that the rat thyroid findings do not indicate a risk to humans. Repeated administration of isavuconazonium sulfate to monkeys resulted in increases in adrenal weights and/or vacuolation/hypertrophy of adrenocortical cells. There were no atrophic or necrotic lesions and the changes were reversible. Dr. McMaster noted that the clinical significance of these adrenal findings is unclear.

Isavuconazonium chloride administration was associated with dose-related increases in the incidence of skeletal abnormalities (rudimentary cervical ribs), in rats and rabbits at 30 and 45 mg/kg, respectively, doses equivalent to about one fifth and one tenth of the clinical exposures based on AUC comparisons. In rats, dose-related increases in the incidence of zygomatic arch fusion and supernumerary ribs/rudimentary supernumerary ribs were also noted at doses of 30 mg/kg and above, equivalent to one fifth the clinical dose based on AUC comparisons. Bone abnormalities have also been associated with the administration of other azole antifungal drugs such as ketoconazole and fluconazole to pregnant dams. The Warnings and Precautions section of the package insert (5.4) includes a warning about embryo-fetal toxicity and states that fetal harm may occur when administered to a pregnant woman. In dams dosed orally during pregnancy and through the weaning period, an increase in perinatal mortality among rat pups was seen. Isavuconazole was detected in the milk of lactating dams at levels up to 17 times higher than plasma levels. The Nursing Mothers subsection of the package insert (8.3), states that mothers should not breast-feed children while taking isavuconazonium sulfate. Oral administration of isavuconazonium sulfate did not affect the fertility in male or female rats treated at doses up to 90 mg/kg/day (less than half the clinical dose based on AUC comparisons).

The products are being labeled as pregnancy category C and are to be used during pregnancy only if the potential benefit to the patient outweighs the risk to the fetus. Subsection 8.1

(Pregnancy) of the package insert states that based on animal data, there is a potential for increasing the risk of adverse developmental outcomes above background risk.

Bone fractures were increased in (3/8) juvenile monkeys dosed with isavuconazonium sulfate for 39 weeks at doses similar to clinical exposures. Although one high-dose female rat showed a diaphysis fracture of the femur in the 26-week study in adult rats, it is not clear that this fracture was drug-related. This finding may relate to the effects of isavuconazonium sulfate on calcium homeostasis. The drug is not indicated for patients below 18 years of age.

No carcinogenicity studies were conducted and the Applicant stated that as other azoles have shown to be carcinogenic, this could be addressed in labeling. As the product could potentially be used for longer than six months, Dr. McMaster recommends that the Applicant conduct a two-year carcinogenicity study in rats and one other abbreviated carcinogenicity evaluation (such as the Tg-rasH2 mouse). The Applicant has agreed to conduct two-year mouse and rat carcinogenicity studies and these studies will be postmarketing requirements (PMRs). No mutagenic or clastogenic effects were detected in the in vitro bacterial reverse mutation assay and the in vivo bone marrow micronucleus assay in rats.

Dr. McMaster recommends approval of these NDAs from a pharmacology/toxicology perspective. I agree with his assessment.

## 5.0 Clinical Microbiology

The clinical microbiology reviewer for these NDAs is Shukal Bala, PhD. Similar to other azoles, isavuconazole acts by inhibiting the enzyme cytochrome P450 sterol 14  $\alpha$ -demethylase, thereby interfering with the synthesis of ergosterol. Depletion of ergosterol disrupts the structure and function of the fungal membrane leading to inhibition of fungal growth.

The activity of isavuconazole was measured in vitro against different species of *Aspergillus* and Mucorales. In surveillance studies, the MIC<sub>90</sub> for most *Aspergillus* species was  $\leq 2$  mcg/mL, with the exception of *A. niger* which had an MIC<sub>90</sub> of 4 mcg/mL. In clinical trial isolates, the MIC<sub>90</sub> for *A. niger* was 8 mcg/mL and  $\leq 4$  mcg/mL for the other *Aspergillus* species. The Epidemiologic Cut-off Values (ECV) for *A. fumigatus*, *A. flavus*, and *A. terreus* was established at 1 mcg/mL and for *A. niger* at 4 mcg/mL.

The activity of isavuconazole against Mucorales [*Lichtheimia (Absidia)*, *Cunninghamella*, *Mucor*, *Rhizomucor*, and *Rhizopus* species] was variable. For Mucorales, the MIC<sub>90</sub> ranged from 4-32 mg/L. No ECVs were established for Mucorales. The Quality Control (QC) strains and the minimum inhibitory concentration (MIC) range selected for in vitro susceptibility testing against filamentous fungi were found to be acceptable.

The activity of isavuconazole was studied in various animal models of disseminated aspergillosis and pulmonary aspergillosis. Activity of isavuconazole was demonstrated by improved survival and/or reduction in fungal burden in animals infected with *A. flavus* or *A. fumigatus*. In *A. terreus* infected mice, isavuconazole was not effective under the experimental conditions tested.

The activity of isavuconazole was studied in neutropenic and diabetic ketoacidotic (DKA) mice in intratracheal mucormycosis and hematogenous disseminated mucormycosis infection models with a strain of *Rhizopus oryzae*. In the pulmonary infection model, isavuconazonium sulfate 215 mg/kg (highest dose tested), administered 8 hours following exposure with  $4.1 \times 10^3$  spores, improved survival of neutropenic mice but not in DKA mice. In another experiment in DKA mice challenged with a lower inoculum ( $2.4 \times 10^3$  spores), a trend towards increased survival was observed after treatment with isavuconazonium sulfate at a dose of 110 mg/kg three times daily compared to placebo-treated mice. The activity of isavuconazonium sulfate was similar to high-dose liposomal amphotericin B in neutropenic mice with intratracheal mucormycosis infection. Isavuconazonium sulfate did not demonstrate a survival benefit in hematogenously disseminated mucormycosis infection model in DKA or neutropenic mice. Activity was not assessed against Mucorales other than *R. oryzae*.

The pharmacodynamic (PD) marker that correlated with antifungal activity varied among the studies. In the *A. fumigatus* neutropenic and non-neutropenic murine models, AUC/MIC was considered to be the driver of efficacy. In one study of non-neutropenic model of disseminated aspergillosis, the target attainment based on AUC/MIC for 14-day survival was 50.48. However, in an immunocompromised pulmonary aspergillosis model, the target attainment based on AUC/MIC using a PD marker of a one-log reduction in fungal burden on Day 7, by PCR, was 503. In an immunocompromised rabbit model of pulmonary aspergillosis, doses equivalent to isavuconazole 40 or 60 mg/kg/day, were associated with prolonged survival, lower pulmonary fungal burdens and reduced lung injury compared with untreated controls. In one study in neutropenic mice infected with *A. fumigatus*,  $T > MIC$ , rather than AUC, was thought to be the parameter that best described the in vivo antifungal activity of isavuconazole.

In the Phase 3 trial, there were very few isolates of *Aspergillus* species other than *A. fumigatus*, *A. flavus*, and *A. niger*. There were very few isolates of Mucorales other than *R. oryzae* and Mucormycetes. No correlation between the MICs of the baseline pathogen and clinical or microbiological response could be demonstrated and may be due to the small number of baseline isolates.

There is a potential for development of resistance to isavuconazole. Potential mechanisms include substitutions in the target cyp51 gene, changes in sterol profile, and/or elevated efflux pump activity. Isavuconazole MICs were higher against strains of *A. fumigatus* with reduced susceptibility to other azoles suggesting cross-resistance. The Applicant had proposed

susceptibility test interpretive criteria for *A. fumigatus* based on evaluation of the epidemiological cut-off values, PK-PD modeling, patient outcome by MIC, and exposure-response analysis based on the Phase 3 trial.

Target attainment analysis was performed in three different models: in vitro dynamic model, non-neutropenic murine model of disseminated aspergillosis and immunocompromised murine model of pulmonary aspergillosis. Each model utilized different endpoints to estimate the PD target required for exposure-response relationship. In the in vitro model, a reduction in galactomannan was used as the PD endpoint. The PD endpoint in the non-neutropenic murine model was 14-day survival and in the immunocompromised murine model, the PD endpoint was 1-log reduction in lung fungal burden by PCR on Day 7. The appropriate model and PD endpoint for predicting clinical response is unclear. Additionally, the murine models are limited by the half-life of isavuconazole which is much shorter than that seen in humans. The Applicant proposed susceptibility test interpretive criteria based on the target of 50.48 from the non-neutropenic *A. fumigatus* disseminated aspergillosis murine model using 14-day survival as the endpoint. Using this target, the Applicant had concluded that greater than 90% of patients achieve the PD target after administration of the recommended dosing regimen of isavuconazonium sulfate to treat *A. fumigatus* with MIC values of 1 mg/L.

(b) (4)

Dr. Bala recommends that the Applicant conduct surveillance studies and collect MIC data for all Aspergillus and Mucorales species for at least five years postmarketing to evaluate if there is a shift in wild-type population and ECVs. The Applicant has agreed to conduct this study as a postmarketing requirement. I agree with Dr. Bala's assessment that the NDA can be approved.

## 6.0 Clinical Pharmacology

The clinical pharmacology reviewer for these NDAs is Dakshina Chilukuri, PhD. Isavuconazonium sulfate is rapidly hydrolyzed in the blood to isavuconazole by esterases, predominantly butyrylcholinesterase. Following oral administration of radio-labeled isavuconazonium sulfate to healthy volunteers, 46.1% of the radioactive dose was recovered in the feces and 45.5% was recovered in the urine. The inactive cleavage product is primarily eliminated by metabolism and subsequent renal excretion. Following IV administration of radio-labeled cleavage product, 95% of the total radioactive dose was excreted in the urine.

Isavuconazole is a sensitive CYP3A substrate, an inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 and an inducer of CYP3A4/5, CYP2B6, CYP2C8, and CYP2C9. Isavuconazole is an inhibitor of P-gp, BCRP and OCT2-mediated drug transporters.

The pharmacokinetics (PK) of isavuconazole was dose-proportional in the dose range equivalent to 100 to 600 mg of isavuconazole. Isavuconazole has a steady state volume of distribution ( $V_{ss}$ ) of approximately 450 L after IV administration. Isavuconazole is > 99% protein bound, primarily to albumin. In healthy volunteers, after single or multiple oral doses of isavuconazonium sulfate capsules, maximum plasma concentrations ( $C_{max}$ ) were achieved in 2 to 3 hours. No significant concentrations of the prodrug or inactive cleavage product were detected in plasma after oral administration. Following IV administration of isavuconazonium sulfate, concentrations of the prodrug and inactive cleavage product were detectable during infusion and declined rapidly following the end of administration. The prodrug was below the level of detection by 1.25 hours after the start of a 1-hour infusion. The inactive cleavage product was quantifiable in some subjects up to 8 hours after the start of infusion. The mean half-life of isavuconazole was approximately 130 hours for both routes of administration across a range of doses, suggesting that elimination is not dependent on dose or route of administration. The absolute oral bioavailability of isavuconazonium sulfate was 98%. Oral isavuconazonium sulfate can be taken with or without food.

There were no clinically meaningful differences in isavuconazole AUC and  $C_{max}$  in subjects with mild, moderate and severe renal impairment. No dose adjustment is necessary in patients with renal impairment. Isavuconazole is not readily dialyzable and dose adjustment is not needed in patients with end stage renal disease. No dose adjustment is required in patients with mild to moderate hepatic disease. Isavuconazonium sulfate has not been studied in patients with severe hepatic disease (Child-Pugh Class C). In a two-compartment population PK model, clearance was lower in Chinese subjects compared to Western subjects and hence AUCs were approximately 50% higher. Body mass index (BMI) did not play a role in the observed differences. No dose adjustment is recommended for Chinese patients. No dose adjustment is required based on age and gender.

In the Phase 3 trial in invasive aspergillosis, no exposure-response relationship was seen for certain adverse events of interest. A trend towards an exposure-response relationship was seen for the endpoints of mortality at Day 42 and Day 84, with higher mortality in the fourth quartile for drug exposure. This observation was confounded by subjects of Asian race or subjects enrolled in Asian countries. In the highest exposure quartile, there were ~47% Asians compared to 2-10% in the lower quartiles. Several analyses were performed to explore this issue further and it was determined that no specific dosing recommendations are required for the Asian population.

Dr. Chilukuri noted that the Applicant had proposed

(b) (4)

The basis for the dosing regimen used in the Phase 3 trials was to ensure rapid achievement of trough exposures above the ECVs for *Aspergillus* species (1 to 2 mg/L). From the multiple ascending dose concentration time profile, it was determined that a loading dose regimen would be required to ensure rapid attainment of target trough concentrations. For invasive mucormycosis, in vivo PD models are not available to guide target exposures and dose selection and MIC values have not been found to be helpful in guiding therapy. Hence, the same dose regimen selected for invasive aspergillosis was utilized for the treatment of invasive mucormycosis. Dr. Chilukuri agrees with the following dosing regimen:

Loading Dose: 372 mg isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) every 8 hours for 6 doses via oral or intravenous administration

Maintenance Dose: 372 mg isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) once daily via oral or intravenous administration starting 12 to 24 hours after the last loading dose.

Dr. Chilukuri recommends approval of the NDA and I agree with his recommendation.

## **7.0 Clinical Efficacy and Safety**

The clinical reviewer for these NDAs is Edward Weinstein, MD PhD and the statistical reviewer is Cheryl Dixon, PhD.

### **Efficacy**

#### Invasive Aspergillosis

Study 9766-CL-0104 was a randomized, double-blind, noninferiority trial comparing the efficacy and safety of isavuconazonium sulfate to voriconazole. The pre-specified noninferiority (NI) margin was 10%. The primary efficacy endpoint was all-cause mortality through Day 42. A key secondary efficacy endpoint was the Data Review Committee (DRC) assessment of overall response at the end of treatment (EOT). The NI margin for all-cause mortality through day 42 was justified based on a trial demonstrating superiority of voriconazole over amphotericin B and literature to derive historical estimates of mortality with placebo (no treatment) and amphotericin B. An estimate of the effect of voriconazole over placebo (M1) was estimated to be 58%, and an NI margin of 10% was considered acceptable, based on clinical judgment.

Patients  $\geq$  18 years of age with proven, probable, or possible invasive fungal disease (IFD) per the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) 2008 criteria<sup>2</sup> were enrolled and randomized 1:1 to receive either isavuconazonium sulfate or voriconazole. Patients with renal impairment (creatinine clearance less than 50 mL/min) were excluded. Patients were stratified by geographic location (United States/Canada, Western Europe/Australia/New Zealand, and Other Regions), whether or not they underwent an allogeneic bone marrow transplant (BMT), and whether or not they had uncontrolled malignancy at baseline.

Patients randomized to isavuconazonium sulfate were to receive a loading dose equivalent to 200 mg of isavuconazole IV three times a day for two days followed by a maintenance dose equivalent to 200 mg of isavuconazole IV or oral once a day. Patients randomized to receive voriconazole were to receive a loading dose of 6 mg/kg q12h IV in the first 24 hours followed by a maintenance dose of 4 mg/kg q12h IV or 200 mg q12h orally. Switch to oral therapy was allowed from Day 3. Patients were to receive treatment for a minimum of 7 days after resolution of all clinical signs and symptoms or for a maximum of 84 days. Survival status was recorded at EOT, Day 42, Day 84, and at the post-treatment follow-up visit.

An independent DRC consisting of experts in infectious diseases was established to adjudicate the categorization of each patient's IFD at enrollment and to evaluate clinical, mycological, radiological, and overall response at EOT, Day 42, and Day 84, as well as to assess attributable mortality. The patient profile data reviewed by the DRC did not include the investigator's assessments of baseline mycological criteria or response, or any adverse events that could potentially unblind the DRC. Independent radiology experts provided a qualitative assessment of radiology images as well as an overall outcome assessment of percent improvement from baseline at EOT, Day 42, and Day 84.

The DRC categorized each patient's IFD at enrollment as proven, probable, possible, or no IFD/no invasive mold infection based on host factors, radiologic and clinical features, and mycological evidence from histopathology, culture, and/or galactomannan (GM) per the EORTC/MSG 2008 criteria.

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<sup>2</sup> DePauw, B., Walsh, T.J., Donnelly, J.P., et al. Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/ Invasive Fungal Infections Cooperative Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008;46(12):1813-21.

The DRC assessed clinical response as follows:

- Success- Complete or partial resolution of all attributable clinical symptoms and physical findings
- Failure- No resolution of any attributable clinical symptoms and physical findings and/or worsening
- Not applicable- No attributable signs and symptoms present at baseline and no symptoms attributable to IFD developed post baseline
- Not done

Mycological response was assessed by the DRC as a success in a patient with eradication or presumed eradication. Radiological response was assessed by the DRC as success if there was improvement of at least 25% from baseline if assessment was made prior to Day 42 or at least 50% from baseline if the assessment was made after Day 42.

The intent-to-treat (ITT) population included all randomized patients who received at least one dose of study drug. The modified ITT (mITT) population included ITT patients who had proven or probable IFD as determined by the DRC. Per the protocol, the DRC could assess a probable case of aspergillosis based on two consecutive serum GM values of  $\geq 0.5$  or a single serum GM value of  $\geq 0.7$ . The draft guidance on qualification of GM in studies of treatments of invasive aspergillosis defines probable aspergillosis as two consecutive serum GM values  $\geq 0.5$  or a single serum or bronchoalveolar lavage (BAL) GM value  $\geq 1.0$ .<sup>3</sup> Based on this definition, a single serum GM value between 0.7 and 1.0 would be considered possible aspergillosis. In the mITT-FDA population, the GM criteria used to define probable IFD was two consecutive serum GM values  $\geq 0.5$  or at least one serum or BAL GM value  $\geq 1.0$ . The mycological ITT (myITT) population included mITT patients with proven or probable invasive aspergillosis based on cytology, histology, culture, or GM values per the protocol.

The trial enrolled 527 patients at 102 centers globally. Eleven patients were randomized but did not receive any dose of study medication. The ITT population consisted of 516 patients (258 in each treatment group). The mITT population consisted of 143 isavuconazonium-treated patients and 129 voriconazole-treated patients; 244 patients were excluded from the mITT population because the DRC assessed the patient as having either possible or no IFD at baseline. The myITT population included 123 isavuconazonium-treated patients and 108 voriconazole-treated patients who had proven or probable invasive aspergillosis. At least one *Aspergillus* species was

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<sup>3</sup> Draft Guidance on Qualification of Biomarker - Galactomannan in studies of treatments of invasive Aspergillosis. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM420248.pdf>; accessed February 15, 2015

identified in 30% of the subjects; *A.fumigatus* and *A. flavus* were the most common pathogens identified. Other *Aspergillus* species (*A. niger*, *A. sydowi*, *A. terreus*, and *A. westerdijkiae*) was identified in less than seven patients.

The following table summarizes the various analysis populations. Most cases were considered as probable IFD and the majority of those were on the basis of positive serum GM.

**Table 1: Analysis Populations**

	<b>Isavuconazonium*</b>	<b>Voriconazole</b>
<b>ITT</b>	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)
<b>mITT</b>	143	129
<i>Aspergillus</i> species only	49 (34.3)	39 (30.2)
<i>Aspergillus</i> species plus other mold species	3 (2.1)	1 (0.8)
<i>Non-Aspergillus</i> species only	5 (3.5)	6 (4.7)
Mold species not otherwise specified (NOS)	14 (9.8)	15 (11.6)
No pathogen identified*	72 (50.3)	68 (52.7)
<b>myITT</b>	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)

Source: Table 4, Statistics Review; \* isavuconazonium sulfate

Overall, 60% of the study population was male, 78% was White, and the mean age was 51 years. The majority of patients had hematologic malignancy as their underlying condition. Distribution by geographic region was 11% US/Canada, 41% Western Europe/Australia/New Zealand, and 48% all other regions. Approximately 20% of patients had a prior allogeneic BMT and 70% of patients had an uncontrolled malignancy at baseline. Approximately 66% of patients were neutropenic at baseline. The median duration of IV and oral dosing was 5 days and 60 days respectively.

All-cause mortality rates through Day 42 are presented in Table 2 for the various ITT-related populations. In the various analysis populations, the mortality rates were lower in isavuconazonium-treated patients. The upper bounds of the 95% confidence interval (CI) around the adjusted treatment difference ranged from 5.9% to 8.2%. As the upper bound of the 95% CI was less than the pre-specified NI margin of 10%, noninferiority of isavuconazonium sulfate relative to voriconazole was demonstrated with respect to all-cause mortality through Day 42.

**Table 2: Day 42 All-cause Mortality**

Population	Isavuconazonium <sup>§</sup>	Voriconazole	Treatment difference and 95% CI*
ITT**	48/258 (18.6)	52/ 258 (20.2)	-1.0 (-8.0, <b>5.9</b> )
mITT	28/143 (19.6)	30/129 (23.3)	-2.6 (-12.6, <b>7.3</b> )
mITT-FDA	28/147 (19.0)	28/128 (21.9)	-2.1 (-11.9, <b>7.7</b> )
myITT	23/123 (18.7)	24/108 (22.2)	-2.7 (-13.6, <b>8.2</b> )

Source: Table 7, Statistics Review; § isavuconazonium sulfate

\*adjusted difference (Isa- Vori) and CI calculated using stratified CMH method using the strata of geographic region, allogeneic BMT status, and uncontrolled malignancy status

\*\*survival status unknown for 3 isavuconazole and 2 voriconazole ITT subjects imputed as deaths

The all-cause mortality rate in the ITT population through Day 84 was 29.1% in the isavuconazonium sulfate arm and 31.0% in the voriconazole arm [(treatment difference -1.4, 95% CI (-9.2, 6.4)]. Survival status at Day 84 was known for all but three ITT patients in the isavuconazonium sulfate arm and five in the voriconazole arm and was imputed as deaths in the analysis. In the mITT population, the DRC-assessed overall response rates at EOT were similar between the two treatment groups [(treatment difference -1.6, 95% CI (-12.8, 9.6)]. In the myITT population, DRC-assessed overall response at EOT was slightly higher in the voriconazole arm compared to the isavuconazonium sulfate arm.

**Table 3: DRC- Assessed Overall Response at EOT**

Outcome	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)	
mITT-FDA - Success	52/147 (35.4)	47/128 (36.7)	-1.8 (-12.9, 9.3)
Complete	19 (12.9)	14 (10.9)	
Partial	33 (22.5)	33 (25.8)	
Stable	43 (29.3)	34 (26.6)	
Progression	52 (35.4)	47 (36.7)	
myITT- 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)	

Source: Table 9, Statistics Review; \* Isavuconazole sulfate

\*\*adjusted difference (Isa-Vori) and CI calculated using stratified CMH method with the strata of geographic region, allogeneic BMT status, and uncontrolled malignancy status

In Trial 9766-CL-0103, an open label, multi-center, non-comparative trial that included patients with renal impairment, there were 24 patients assessed by the DRC as having invasive aspergillosis only and 20 of these had renal impairment. The all-cause mortality rate through Day 42 was 12.5% for all patients with invasive aspergillosis only and 15% for those with

invasive aspergillosis only and renal impairment. The DRC-assessed overall response at EOT was 34.8% for patients with IA only and 30.0% for those IA only patients with renal impairment.

### Invasive Mucormycosis

Trial 9766-CL-0103 was an open-label, Phase 3 trial conducted to evaluate the safety and efficacy of isavuconazonium sulfate for the primary treatment of IFD caused by *Aspergillus* species in patients with renal impairment, or caused by rare filamentous fungi. The trial was conducted at 34 centers globally from April 2008 to January 2014. The dosing regimen was similar to that used in the Phase 3 trial in invasive aspergillosis.

Survival status was recorded at Day 42, Day 84 and 4 weeks after the last dose of study drug. Baseline mycological assessment (screening through Day 7) of the patient's IFD status was performed using suitable samples for fungal culture and specimens from the infected site for histology and cytology. Baseline radiological assessments were performed during the screening period. The EORTC/MSG 2008 definitions of IFD were used for diagnosis. Clinical, mycological and radiological assessments were performed at Day 42, Day 84 and EOT. 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. The DRC also assessed location of disease, therapy status (i.e., primary, refractory or intolerant) and attributable mortality.

DRC-assessed overall response was specified as the primary endpoint in the protocol. However, both the Applicant and the FDA agreed that 42-day mortality was the most relevant primary endpoint because it was consistent with trials of other antifungal drugs and allowed for comparison with historical controls. DRC-assessed overall response at EOT was analyzed as a secondary endpoint.

The ITT population consisted of all enrolled patients who received at least one dose of study drug. The mITT population consisted of ITT patients who had proven or probable IFD as determined by the DRC. The mITT-Mucorales population included patients classified by the DRC as having infection due to Mucorales only.

Of the 149 patients enrolled in the trial, 146 patients received at least one dose of study drug and were included in the ITT population. The mITT- Mucorales population consisted of 37 patients identified as having infection due to Mucorales only. The mITT- Mucorales population was further divided into primary, refractory, or intolerant subgroups. The primary treatment group consisted of patients who received isavuconazonium sulfate as initial antifungal therapy, and the refractory or intolerant groups were considered to have received salvage therapy. The refractory treatment group had progression of disease while on antifungal therapy at enrollment, and the

intolerant treatment group had either failed to achieve therapeutic drug levels or experienced significant drug related adverse reactions. The various analysis populations are shown in Table 4.

**Table 4: Analysis Populations**

	<b>Renally Impaired</b>	<b>Not Renally Impaired</b>	<b>Total</b>
Enrolled	59	90	149
ITT/Safety	59	87	146
mITT	54	86	140
mITT-Mucorales	11	26	37
mITT- <i>Aspergillus</i>	20	4	24
mITT-Other filamentous fungi (not <i>Aspergillus</i> or Mucorales)	9	8	17
mITT- Mold species NOS	5	2	7
mITT- Dimorphic fungi	2	27	29
mITT- <i>Non-Candida</i> yeast	4	7	11
mITT- mixed infection	3	12	15

Source: Table 13, Statistics Review

In the mITT- Mucorales population, 21 cases were considered primary, 11 refractory, and five intolerant. The median age of patients was 50 years, 81% were male, and 68% were White. The majority of patients were in the primary therapy group. The proportion of patients with hematologic malignancy (59%) at baseline was greater than that reported by Skiada et al. (44%) and Roden et al. (17%).<sup>4,5</sup> The number of patients who had received bone marrow transplant was also higher (35%) compared to 9% and 5% in the Skiada and Roden studies, respectively. No patient had burn/trauma as the underlying host factor in this trial compared to ~20% in the Skiada and Roden studies. Overall, a third of patients had disseminated disease. The site of infection was comparable in this trial and in the Skiada study.

The DRC assessed site of infection is summarized in Table 5.

<sup>4</sup> Roden, M.M., Zaoutis, T.E., Buchanan, W.L., et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis.* 2005; 41:634-53

<sup>5</sup> Skiada A., Pagano L., Groll A., et al. 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

**Table 5: DRC Assessment of IFD Locations at Baseline**

	<b>Primary (n = 21)</b>	<b>Refractory (n = 11)</b>	<b>Intolerant (n = 5)</b>	<b>Total (n = 37)</b>
<b>Disseminated Disease</b>				
Yes	8 (38%)	2 (18%)	1 (20%)	11 (30%)
No	13 (62%)	9 (82%)	4 (80%)	26 (70%)
<b>Location</b>				
LRTD * Only	1 (5%)	5 (45%)	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%)
<b>Non-LRTD Location</b>				
Sinus	13 (62%)	3 (27%)	0	16 (43%)
Eye	7 (33%)	0	0	7 (19%)
CNS	6 (29%)	0	0	6 (16%)
Bone	4 (19%)	0	1 (20%)	5 (14%)
Other**	10 (48%)	2 (18%)		12 (32%)

\*Lower Respiratory Tract Disease; \*\* Other locations include deep soft tissue, gastrointestinal tract, kidneys, liver, skin and spleen  
Source: Table 30, MO Review

Overall, the three most commonly reported baseline pathogens, as assessed by the DRC, were Mucormycetes NOS (35%), Mucor NOS (19%) and *R. oryzae* (19%). In the primary therapy group, the three most commonly reported baseline pathogens, as assessed by the DRC, were Mucor NOS (33%), Mucormycetes NOS (29%) and *R. oryzae* (19%).

In the mITT- Mucorales population, all-cause mortality at Day 42 was 38% and at Day 84 was 43%. In the primary treatment group, all-cause mortality at Day 42 was 33% and at Day 84 was 43%. In the mITT-Mucorales population, 31% of patients were assessed as success, with 14% judged to be complete success and 17% assessed to be partial success.

**Table 6: All-Cause Mortality through Day 42 and Day 84 (mITT-Mucorales Population)**

<b>Outcome</b>	<b>Primary (n = 21)</b>	<b>Refractory (n = 11)</b>	<b>Intolerant (n = 5)</b>	<b>Total (n = 37)</b>
<b>By Day 42</b>				
<b>All-Cause Mortality†</b>	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%)
<b>By Day 84</b>				
<b>All-Cause Mortality‡</b>	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: Table 34, MO Review

The review team identified three epidemiologic reports that provided natural history data for untreated invasive mucormycosis. In a review of 929 cases, Roden and colleagues noted a mortality rate of 97% (233/241) in those who received no treatment.<sup>6</sup> However, many of the cases were identified post-mortem. Of the 241 patients who received no treatment, 8 (3%) survived. The review team contacted the authors to ascertain the number of patients diagnosed with mucormycosis prior to death. Of the 233 patients who died, 18 (8%) were diagnosed pre-mortem and 215 (92%) were diagnosed post-mortem.

Skiada and colleagues noted that 21/22 (95%) untreated patients did not survive.<sup>7</sup> While only 10 cases (4%) were diagnosed post-mortem, information is lacking on how these cases were distributed among the treatment groups, the presence of underlying medical conditions, and the duration of the follow up from the time of diagnosis.

In a study by Chamilos et al., 84-day mortality was assessed in 70 consecutive patients with hematologic malignancy and mucormycosis.<sup>8</sup> The diagnostic criteria used in this study were similar to that used in Trial 9766-CL-0103. Of the 70 patients, 45 were definite cases and 25 were probable cases; 32 had received hematopoietic stem cell transplant. Most patients (70%) had either sinopulmonary or disseminated mucormycosis. The overall mortality rates at 4 and 12 weeks after diagnosis were 47% (33/70) and 66% (46/70), respectively. All patients who died had active mucormycosis at the time of death. Using classification and regression tree (CART) analysis, the authors identified the mortality breakpoint between early and delayed amphotericin-B based therapy as six days after the onset of symptoms.

Thirty-five patients received amphotericin B-based therapy  $\geq$  six days after symptom onset. In the group that received early treatment, 84 day-mortality was 48.6%. A delay of six days or more in initiating amphotericin B-based therapy resulted in a two-fold increase in 84 day-mortality (82.9%, 95% CI [68.9, 96.8]). The 84-day mortality approached 100% at 84 days with further delays in treatment. The review team contacted the authors to obtain patient level data. However, these data were not available.

The Applicant also provided data on patients with untreated invasive mucormycosis from the Fungiscope Registry. The Fungiscope Registry is a global database, coordinated from the Clinical Trials Centre at the University of Cologne, Germany and contains information on rare fungal infections, including more than 150 cases of invasive mucormycosis diagnosed and

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<sup>6</sup> Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis* 2005;41(5):634-53

<sup>7</sup> Skiada A, Pagano L, Groll A, et al. 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; 17(12):1859-67

<sup>8</sup> 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;47(4):503-9.

treated between 2003 and 2013. Of the 136 cases of invasive mucormycosis with available survival data through Day 42, 29 did not receive treatment and all 29 died. Most of the untreated patients were diagnosed post-mortem or shortly before death, similar to the studies by Roden et al. and Skiada et al.

The mortality rate and 95% CI for patients with proven or probable invasive mucormycosis from Study 9766-CL-0103 are presented in Table 7 in comparison to the 6-day delayed therapy group from the study by Chamilos et al. In the mITT-Mucorales population and in the primary treatment subgroup, the upper limit of the 95% CI for mortality in patients treated with isavuconazonium sulfate is below the lower limit of the 95% CI for the 6-day delayed treatment group. In the subgroup of patients with hematologic malignancy treated with isavuconazonium sulfate, 84-day mortality was 41% (9/22) (95% CI [20.4, 61.5]) compared to 82.9% in the Chamilos et al. study.

**Table 7: Mortality Rates in Isavuconazonium-Treated Patients and Patients with 6-day delayed treatment**

Timepoint	All-Cause Mortality <sup>1</sup> All Mucor (%) [95% CI] <sup>2</sup>	All-Cause Mortality Primary Therapy (%) [95% CI] <sup>2</sup>	All-Cause Mortality 6-day delay Chamilos et al. (%) [95% CI] <sup>2</sup>
Day 42	14/37 (37.8%) [22.5, 55.2]	7/21 (33.3%) [14.6, 57.0]	82.9% [68.9, 96.8]
Day 84	16/37 (43.2%) [27.1, 60.5]	9/21 (42.9%) [21.8, 66.0]	

<sup>1</sup> 1 patient with unknown survival status at day 42 was assumed to be dead

<sup>2</sup> Confidence intervals were calculated using exact binomial method

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

The treatment effect seen with isavuconazonium sulfate treatment relative to a six-day delay of amphotericin B treatment is a conservative estimate of a treatment effect over placebo and is likely to be greater relative to no treatment.

The Applicant also compared the outcomes in patients treated with isavuconazonium sulfate in this trial to the current standard of care, amphotericin B-based therapy using data from the Fungiscope Registry (Table 8). Patients from Study 9766-CL-0103 were matched with up to three controls from the Fungiscope Registry Database who received primary therapy with amphotericin B for proven or probable invasive mucormycosis, using three primary criteria:

- Severe disease, defined as CNS involvement or disseminated disease, with the latter defined as a disease involving more than one 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.

**Table 8: Observed All-Cause Mortality Compared to Matched Fungiscope Controls**

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

Source: Table 43: MO Review

### Safety

The safety database of 1692 subjects exposed to isavuconazonium sulfate includes 1145 healthy volunteers from 40 Phase 1 studies, 144 patients in the Phase 2 trials, and 403 patients in the Phase 3 trials. Mean duration of exposure was 59.9 days; 309/547 (56.5%) received isavuconazonium sulfate for at least 21 days, 276/547 (50.5%) for at least 28 days, 144/547 (26.3%) for at least 84 days, and 52/547 (9.5%) for at least 180 days.

In Trial 9766-CL-0104, a total of 81 deaths (31.5%) were reported in isavuconazonium-treated patients and 87 deaths (33.6%) in voriconazole-treated patients. The common System Organ Class (SOC) for Treatment Emergent Adverse Events (TEAEs) leading to death were infections and infestations, neoplasms, respiratory, thoracic and mediastinal disorders. The TEAEs leading to death that occurred in  $\geq 2\%$  of patients in the isavuconazonium sulfate or voriconazole arms, 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%). In the Phase 2 trials, there were three deaths 3/144 (2%) in the isavuconazonium-treated patients, consistent with the lower mortality seen in the patient population studied. In the Phase 2 and 3 trials combined, there were 107 deaths in isavuconazonium-treated patients through 28 days after the last dose of study drug.

The incidence of serious adverse events (SAEs) in Trial 9766-CL-0104 was 134/257 (52.1%) in the isavuconazonium sulfate arm and 149/259 (57.5%) in the voriconazole arm. Most SAEs were reported more frequently in the voriconazole arm with the exception of the following three SOCs: Blood and lymphatic system disorders, nervous system disorders, and skin and subcutaneous tissue disorders. Dr. Weinstein reviewed the SAEs reported in the nervous system disorders SOC and noted that there were more serious, non-fatal convulsive adverse events

(convulsion, epilepsy, febrile convulsion, and grand mal convulsion) in the isavuconazonium sulfate arm when combining these preferred terms, (7 events in 6 subjects) than in the voriconazole arm (3 events in 3 subjects). Each case was confounded by underlying conditions and/or exposure to other medications with seizure potential. All patients recovered from the seizures. Overall, in the Phase 2 and 3 trials, SAEs occurred in 42.0% of patients. In the Phase 1 studies, 4/1001 (0.4%) subjects experienced SAEs; one received a single dose of isavuconazonium sulfate and three received multiple doses. The four SAEs were elevation in liver enzymes, Guillain-Barre Syndrome and meningoencephalitis, gastritis and gastroesophageal reflux, and numbness. In Dr. Weinstein's assessment, the case of Guillain-Barre Syndrome and meningoencephalitis was probably not related to the drug, while in the other three cases the contribution of isavuconazonium sulfate could not be ruled out.

In Trial 9766-CL-0104, one or more TEAEs were reported by 96.1% of isavuconazonium-treated patients and 98.5% of voriconazole-treated patients. The most common adverse events (AEs) in the isavuconazonium sulfate arm were nausea, vomiting and diarrhea. For the following SOCs, the frequency of AEs was higher in the voriconazole arm: 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%), and cardiac disorders (16.7% vs 22.0%). In the Phase 1 studies, the highest incidence of TEAEs occurred in the 600 mg group (34/39, 87.2%).

In Trial 9766-CL-0104, hepatic TEAEs were reported in 23/257 (8.9%) isavuconazonium-treated patients compared to 42/259 (16.2%) voriconazole-treated patients. The three SAEs reported in the isavuconazonium sulfate arm were hepatitis, acute hepatitis, and cholecystitis. In one patient in the isavuconazonium sulfate arm who developed acute hepatitis and had a fatal outcome, no other etiology for the hepatitis was identified. The second patient with a fatal outcome had a suspected drug-related hepatic adverse reaction of acute hepatic failure. This patient had other confounding factors including activation of chronic hepatitis C, sepsis, AML progression, GVHD, and was on potentially hepatotoxic concomitant medications. In the combined Phase 2 and 3 trials, eight SAEs were reported in the hepatobiliary disorders SOC with the following preferred terms (PTs): cholecystitis, cholangitis, cholelithiasis, liver disorder, acute hepatic failure, hepatitis, and acute hepatitis. In the controlled Phase 3 trial, there were a total of 24 hepatobiliary AEs in the isavuconazonium sulfate arm and 44 in the voriconazole arm. In the combined Phase 2 and Phase 3 safety population, 5/535 (0.9%) isavuconazonium-treated patients satisfied the laboratory criteria for Hy's Law. All cases had alternative etiologies such as concurrent sepsis, multi-organ failure, and concurrent use of hepatotoxic drugs. Dr. Weinstein noted that administration of isavuconazonium sulfate was temporally related in each case and the contribution of isavuconazonium sulfate to liver injury could not be excluded.

Twenty-one patients in Trial 9766-CL-0104 and six patients in Trial 9766-CL-0103 were inadvertently administered intravenous isavuconazonium sulfate without an in-line filter. No embolic or thromboembolic AEs were reported in these patients.

In Trial, 9766-CL-0104, potential anaphylaxis and severe cutaneous reactions were reported in 1.9% of patients in both treatment arms. Infusion-related reactions were defined as serious adverse reactions that occurred during or within two days following IV dosing. In Trial 9766-CL-0104, potential infusion-related serious TEAEs were reported in 10.1% of patients in the isavuconazonium sulfate arm compared to 6.9% in the voriconazole arm.

Hepatic adverse drug reactions, infusion-related reactions, hypersensitivity reactions, and the need to administer isavuconazonium sulfate through an in-line filter are included as warnings in the Warnings and Precautions section of the package insert.

No significant prolongation of QTc was seen in the thorough QT (TQT) study. The largest upper bounds of the 2-sided 90% CI for the mean difference between isavuconazonium sulfate (equivalent to 200 mg and 600 mg of isavuconazole) and placebo were below 10 ms. The TQT study was a randomized, double-blind, placebo and active-controlled study in which 160 subjects received oral isavuconazonium sulfate (equivalent to 200 mg and 600 mg of isavuconazole), placebo, and a single oral dose of moxifloxacin 400 mg. In the 600 mg group, there was no prolongation of the QT interval to any clinical relevant extent. A dose-and-concentration related shortening of the QTc interval was observed. In the 200 mg group, the least squares mean (LSM) difference from placebo was -13.1 ms at 2 hours post-dose [90% CI: -17.1, -9.1 ms]. In the 600 mg group, the LSM difference from placebo was -24.6 ms at 2 hours post-dose [90% CI: -28.7, -20.4]. The IRT agreed with the Applicant's assessment that this was likely due to a slight block of the calcium level. One patient in the isavuconazonium sulfate arm had a QT shortening TEAE with a QTcF of 378 ms, compared to none in the voriconazole arm. The adverse effect resolved the following day without treatment. No events of ventricular tachycardia or ventricular fibrillation were observed in either treatment arm. The Contraindications section (4) of the package insert includes a statement about QTc interval shortening and use of isavuconazonium sulfate is contraindicated in patients with Familial Short QT syndrome. No TQT studies were conducted with the IV formulation. The IRT noted that QT prolongation is unlikely with the IV formulation. A small effect on reducing the PR interval was also noted and assessed to be not clinically relevant.

Dr. Dixon concluded that there is adequate evidence to support the indication of treatment of invasive aspergillosis. Dr. Dixon also noted that while inferential testing to define the benefit of isavuconazonium sulfate treatment relative to no treatment or to treatment with another antifungal drug is not possible, the results in the subgroup of patients with invasive mucormycosis from Trial 9766-CL-0103 indicate some evidence of efficacy for

isavuconazonium sulfate in the treatment of invasive mucormycosis. In conjunction with the results of Trial 9766-CL-0104 in invasive aspergillosis, Dr. Dixon recommended that the results of Trial 9766-CL-0103 be considered adequate evidence to support the indication of treatment of invasive mucormycosis. Dr. Alexander noted that for the invasive mucormycosis indication, while there are limitations with the data, the risks are reasonable relative to the expected benefit and that isavuconazonium sulfate may provide an important option for treatment of patients with renal impairment in this indication. Drs. Weinstein and Alexander recommend approval of isavuconazonium sulfate for the treatment of invasive aspergillosis and invasive mucormycosis. I agree with their assessment.

## **8.0 Labeling**

Labeling recommendation from Jacqueline Sheppard, PharmD from the Division of Medication Error Prevention and Analysis (DMEPA), Christine Corser PharmD, from the Office of Prescription Drug Promotion (OPDP), and Shawna Hutchins, MPH, BSN, RN, from the Division of Medical Policy Programs have been incorporated in labeling. The proposed proprietary name of CRESEMBA was found acceptable.

To minimize the risk of medication errors and to inform prescribers that the product is an azole, the labeling will include information on the strength of isavuconazonium sulfate and the equivalent amount of isavuconazole and not include the strength of isavuconazonium. According to 21 U.S.C. 352(e)(1)(A)(ii), labeling needs to include the name and the amount of the drug substance (active ingredient). Per the USP Salt Policy, when an active ingredient (drug substance) in a drug product is a salt, the nonproprietary (established) name of the drug product should contain the name of the active moiety and not the name of the salt and the strength should be expressed in terms of the active moiety.<sup>9</sup> The Office of Product Quality (OPQ) supported an exception to the USP Salt Policy in this case due to concerns for medication errors and the implications on clinical use of the product. In addition, as isavuconazonium sulfate is an azole antifungal drug and has been referred to as isavuconazole in the medical literature, it is important to include information regarding the equivalent amount of isavuconazole in labeling.

The Dosage and Administration Section of the package insert provides the dosage regimen as shown in Table 9.

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<sup>9</sup> [http://www.usp.org/sites/default/files/usp\\_pdf/EN/USPNF/1121Nomenclature.pdf](http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/1121Nomenclature.pdf); accessed March 04, 2015

**Table 9: Dosage Regimen**

	<b>Loading Dose</b>	<b>Maintenance Dose<sup>c</sup></b>
<b>CRESEMBA for Injection</b> 372 mg <sup>a</sup> of isavuconazonium sulfate per vial	1 reconstituted vial (372 mg <sup>a</sup> ) intravenously every 8 hours for 6 doses (48 hours)	1 reconstituted vial (372 mg <sup>a</sup> ) intravenously once daily
<b>CRESEMBA Capsules</b> 186 mg <sup>b</sup> of isavuconazonium sulfate per capsule	2 capsules (372 mg <sup>a</sup> ) orally every 8 hours for 6 doses (48 hours)	2 capsules (372 mg <sup>a</sup> ) orally once daily

<sup>a</sup> 372 mg of isavuconazonium sulfate is equivalent to 200 mg of isavuconazole

<sup>b</sup> 186 mg of isavuconazonium sulfate is equivalent to 100 mg of isavuconazole

<sup>c</sup> Start maintenance doses 12 to 24 hours after the last loading dose

The Dose Forms and Strengths Section of the package insert states the following:

[Redacted text] (b) (4)

[Redacted text] (b) (4)

These recommendations were acceptable to reviewers from OPQ. Dr. Sheppard from DMEPA expressed concern that reference to dosing based on equivalent amounts of isavuconazole may promote prescribing based on isavuconazole and recommended that statements regarding isavuconazole equivalency be minimized. In addition, Dr. Sheppard noted that in the table above, reference to dosing based on package size or units (1 vial or 2 capsules instead of 372 mg) may promote prescribers to write for 1 vial or 2 capsules instead of the dose of isavuconazonium sulfate in milligrams. Dr. Sheppard recommended that isavuconazonium sulfate remain the primary expression of dosage and be placed first in applicable cells within the dosage table. In general, I agree with some of the concerns raised by Dr. Sheppard. However, the circumstances surrounding this product pose unique challenges based on information already available in the medical literature and the fact that the drug is an azole antifungal drug. Hence, it is important to include information about the equivalent amounts of isavuconazole in relevant sections of labeling. The reason for greater emphasis on dosing based on the reconstituted vial was to obviate any potential for administering a fraction of the vial based on isavuconazole doses and to emphasize that the entire contents of the single-dose vial should be administered. The first column in the table provides information that each vial contains 372 mg of isavuconazonium sulfate.

In my assessment, in the labeling as currently proposed, every effort has been made to minimize the potential for medication errors and to provide useful information to prescribers and pharmacists. If medication errors are reported postmarketing, labeling may need to be revised.

## **9.0 Pediatrics**

As both products have orphan drug designation for both indications, pediatric studies under the Pediatric Research Equity Act (PREA) are not required.

## **10.0 Other Regulatory Issues**

### **Clinical Site Inspections**

Antoine El-Hage, PhD provided the clinical inspections summary for these NDAs. Six clinical investigator sites were inspected. Regulatory violations were noted at four sites. The pending classification for four sites is Voluntary Action Indicated (VAI) and the pending classification for two sites is No Action Indicated (NAI). For the pending classifications, Dr. El-Hage noted that a summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Reports (EIRs). Overall, while regulatory deficiencies were observed, Dr. El-Hage noted that these findings are unlikely to have a significant impact on acceptability of data.

### **Advisory Committee Meeting**

These NDAs were discussed by the Anti-Infective Drugs Advisory Committee on January 22, 2015. The two questions and the committee votes are noted below:

Q1: Has the applicant demonstrated substantial evidence of safety and efficacy of isavuconazonium for the proposed indication of invasive aspergillosis?

- a. If yes, please provide any recommendations concerning labeling.
- b. If no, what additional studies/analyses are needed?

Vote: Yes: 11 No: 0 Abstain: 0

Q2: Has the applicant demonstrated substantial evidence of safety and efficacy of isavuconazonium for the proposed indication of invasive mucormycosis?

- a. If yes, please provide any recommendations concerning labeling.
- b. If no, what additional studies/analyses are needed?

Vote: Yes: 8 No: 2 Abstain: 1

## **11.0 Risk Management**

Carolyn Yancey, MD, was the reviewer from the Division of Risk Management. Dr. Yancey concluded that the risks that have emerged to date can be addressed in labeling and a Risk Evaluation and Mitigation Strategy (REMS) is not required at this time. I agree with Dr. Yancey's assessment that safety findings with isavuconazonium sulfate have been adequately addressed in labeling and that a REMS is not required at this time.

### **Post Marketing Requirements (PMRs) and Post Marketing Commitment (PMC)**

The Applicant has agreed to the following PMRs under 505(o):

1. Conduct a prospective study over a five-year period to determine if decreased susceptibility to Cresemba (isavuconazonium sulfate) is occurring in the target population of organisms that are in the approved Cresemba (isavuconazonium sulfate) label.
2. Conduct a two-year mouse carcinogenicity study.
3. Conduct a two-year rat carcinogenicity study.

The Applicant has agreed to the following PMC:

Establish a registry to collect and analyze clinical efficacy-related outcome data on patients treated with isavuconazonium sulfate who have invasive mucormycosis or infection with non-fumigatus aspergillus species.

The timelines proposed by the Applicant on March 03, 2015 were acceptable to the review team.

## **12.0 Recommended Regulatory Action**

The efficacy of isavuconazonium sulfate in the treatment of invasive aspergillosis was demonstrated in an adequate and well controlled noninferiority trial. Isavuconazonium sulfate was noninferior to voriconazole for the primary endpoint of 42-day all-cause mortality. The finding of noninferiority was consistent across various analysis populations. The safety profile of isavuconazonium sulfate was favorable relative to voriconazole and generally consistent with that of the azole antifungal drugs. I agree with the review team that the results of this trial provide adequate evidence to support the safety and effectiveness of isavuconazonium sulfate for the treatment of invasive aspergillosis in patients 18 years of age and older.

Efficacy in invasive mucormycosis was demonstrated against historical controls where mortality in patients who received amphotericin B after a delay of six or more days was considered as an estimate for mortality rates in untreated controls. This could represent a conservative estimate as

it is likely that mortality rates will be higher with further delays in treatment and/or with untreated disease.

The Code of Federal Regulations, 21 CFR 314.126 (b) recognizes historical controls as an acceptable option, where results of treatment with the test drug are compared with experience historically derived from adequately documented natural history of the disease or condition. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).<sup>10</sup>

Invasive mucormycosis is a serious and rare disease and active controlled clinical trial(s) in this indication are not feasible at this time. The only antifungal drug approved for this indication is amphotericin B, which can be associated with several adverse events and also has limitations with regard to use in patients with renal impairment. Based on the demonstration of treatment effect for mortality relative to historical controls, the severity of the illness, the inability to conduct larger clinical trials given the infrequent occurrence of the disease, the overall safety profile of the drug and the need for alternate treatment options, I conclude that the data are adequate to support the safety and effectiveness of isavuconazonium sulfate for the treatment of invasive mucormycosis in patients 18 years of age and older. I agree with the review team that there is adequate evidence to support the safety and effectiveness of isavuconazonium sulfate for the treatment of invasive mucormycosis in patients 18 years of age and older.

As provided in Section 115(a) of the Modernization Act, Section 505(d) of the Act was amended to allow data from one adequate and well-controlled clinical investigation to constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness.<sup>11</sup> The findings of efficacy in each of the indications, invasive aspergillosis and invasive mucormycosis provide independent substantiation of effectiveness for the other indication. While there are differences in the etiologic agents for the two indications, based on the similarities in the pathophysiology such as the angioinvasive nature of the disease, sites of infection, and the patient population affected by the disease, efficacy in one indication supports effectiveness in the second indication.

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<sup>10</sup> <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.126>

<sup>11</sup> Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm078749.pdf>

In summary, I agree with the review team that the Applicant has provided adequate information to support the safety and effectiveness of isavuconazonium sulfate for the treatment of invasive aspergillosis and invasive mucormycosis in patients 18 years of age and older. Major safety concerns are adequately addressed in labeling. I recommend approval of NDA 207500 and NDA 207501.

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/s/  
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SUMATHI NAMBIAR  
03/05/2015

## Memo to File

<b>Date</b>	(electronic stamp)
<b>From</b>	Sumathi Nambiar MD MPH
<b>Subject</b>	Memo to File
<b>NDA # s</b>	207500, 207501
<b>Applicant Name</b>	Astellas Pharma US, Inc.
<b>Date of Submission</b>	July 08, 2014
<b>PDUFA Goal Date</b>	March 08, 2015
<b>Established (USAN) Name</b>	Isavuconazonium sulfate
<b>Trade Name</b>	CRESEMBA
<b>Dosage Forms / Strength</b>	Capsules, 186 mg isavuconazonium sulfate Powder for Injection 372 mg isavuconazonium sulfate/vial
<b>Proposed Indications</b>	<ol style="list-style-type: none"> <li>1. Invasive aspergillosis</li> <li>2. Invasive mucormycosis</li> </ol>
<b>Recommended Action:</b>	Approval

<b>Material Reviewed/Consulted</b>	<b>Names of Discipline Reviewers</b>
Action Package including:	
Cross-Discipline Team Leader Review	John Alexander MD MPH
Pharmacology Toxicology Review	Owen McMaster PhD
Chemistry Manufacturing and Controls Review	Nina Ni PhD, Yichun Sun PhD, Gene Holbert PhD
Biopharmaceutics Review	Banu Zolnik PhD
Medical Officer Review	Edward Weinstein MD PhD
Statistical Review	Cheryl Dixon PhD
Risk Management	Carolyn Yancey MD
Product Quality Review	Vinayak Pawar PhD
Microbiology Review	Shukal Bala PhD
Clinical Pharmacology Review	Dakshina Chilukuri PhD
Office of Scientific Investigations	Antoine El-Hage PhD
Division of Medication Error Prevention and Analysis	Jacqueline Sheppard Pharm D
Thorough QT Study Review	Interdisciplinary Review Team
Labeling Reviews	Christine Corser Pharm D Shawna Hutchins MPH BSN RN

NDA 207500 and 207501, isavuconazonium sulfate capsules and sterile lyophilized powder for injection respectively, were submitted by Astellas Pharma Global Development, Inc. on behalf of Astellas Pharma US, Inc. on July 08, 2014 for treatment of invasive aspergillosis and treatment of invasive mucormycosis. Isavuconazonium sulfate is a prodrug of isavuconazole and is a member of the azole class of antifungal drugs. The currently approved therapies for invasive aspergillosis include different formulations of amphotericin B, itraconazole, voriconazole, and caspofungin. Mucormycosis refers to a group of opportunistic mycoses that occur in immunocompromised or diabetic patients and are caused by the ubiquitous filamentous fungi of the Mucorales order of the class Zygomycetes.<sup>1</sup> The more common species include *Rhizopus*, *Lichtheimia* (formerly known as *Absidia*), *Rhizomucor*, *Mucor*, and *Cunninghamella*. The only drug approved for the treatment of invasive mucormycosis (zygomycosis) is amphotericin B.

All primary reviews and the CDTL review have been completed. However, a final recommendation regarding the acceptability of the facilities is not yet available. Although, the CMC reviews concluded that the information provided was generally satisfactory to assure the identity, strength, purity, and quality of the drug substance and the drug products, because of the outstanding inspections of the facilities at the time the review was required to be completed [under the requirements of the Program (PDUFA V applications)], Drs. Sun, Holbert, and Ni did not recommend approval of the NDA.

I agree with the review team that the Applicant has provided adequate information to support the safety and effectiveness of isavuconazonium sulfate for the treatment of adults with invasive aspergillosis and invasive mucormycosis. However, I am unable to make a final recommendation on the regulatory action for these NDAs as the status of the facilities is still under review.

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<sup>1</sup> Petrikos G, Skiada A, Lortholary A et al. Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis 2012;54(S1):S23–34

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/s/  
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SUMATHI NAMBIAR  
02/27/2015