CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 207-500 and 207-501
Drug Name:	Cresemba (isavuconazonium sulfate) Capsules and Intravenous
Indication(s):	The treatment of invasive aspergillosis and invasive mucormycosis in patients 18 years of age and older
Applicant:	Astellas
Date(s):	Stamp date: July 8, 2014
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Review Priority:	Priority
Biometrics Division:	Division of Biometrics IV
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Keywords: clinical studies, invasive aspergillosis, invasive mucormycosis

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1 EXECUTIVE SUMMARY

In this submission, the Applicant is seeking the approval of Cresemba (isavuconazonium sulfate) the prodrug of isavuconazole for the indications of the treatment of invasive aspergillosis and the treatment of invasive mucormycosis. Two Phase 3 trials were conducted to provide support of the efficacy for these two indications. Study 9766-CL-0104 is entitled "A Phase III, Double-blind, Randomized Study to Evaluate Safety and Efficacy of BAL8557 (isavuconazole) Versus Voriconazole for Primary Treatment of Invasive Fungal Disease Caused by *Aspergillus* Species or Other Filamentous Fungi." Study 9766-CL-0103 is entitled "Open-label Study of Isavuconazole in the Treatment of Patients with Aspergillosis and Renal Impairment or of Patient with Invasive Fungal Disease Caused by Rare Molds, Yeasts, or Dimorphic Fungi."

For the indication of treatment of invasive aspergillosis, the primary evidence of efficacy for isavuconazole is based on a single Phase 3 trial. Study 9766-CL-0104 was a randomized, double-blind, non-inferiority, comparative group study which evaluated the efficacy and safety of isavuconazole compared to voriconazole. The primary objective of the trial was to assess non-inferiority of isavuconazole compared to voriconazole in all-cause mortality through Day 42. The primary efficacy endpoint was the crude rate of all-cause mortality through Day 42. A key secondary efficacy endpoint was the Data Review Committee (DRC) assessment of overall response at end of treatment (EOT). The primary analysis of all-cause mortality through Day 42 was based on the difference in the rate (isavuconazole-voriconazole) and corresponding 95% confidence interval calculated using the stratified Cochran-Mantel Haenszel (CMH) method. The stratification factors were Geographical Region, Allogeneic BMT Status, and Uncontrolled Malignancy Status. The upper bound of the 95% confidence interval was compared to a justified non-inferiority margin of 10%. If the upper bound was less than 10%, isavuconazole was considered non-inferior to voriconazole with respect to all-cause mortality through Day 42.

In Study 9766-CL-0104, 527 patients were randomized into the trial. The Intent-to-Treat (ITT) population consisted of 516 patients (258 in each treatment group). The modified ITT (mITT) population, which included ITT patients who had a proven or probable invasive fungal disease (IFD) as assessed by the DRC, consisted of 143 isavuconazole patients and 129 voriconazole patients. Of these, 123 isavuconazole patients and 108 voriconazole patients had proven or probable invasive aspergillosis and were included in the mycological ITT (myITT) population. All-cause mortality through Day 42 in the ITT population was 18.6% for isavuconazole and 20.0% for voriconazole. The adjusted difference between treatment groups was -1.0% with a corresponding 95% confidence interval of (-8.0%, 5.9%). Non-inferiority of isavuconazole compared to voriconazole was demonstrated with respect to all-cause mortality through Day 42 since the upper bound of the 95% confidence interval is less than 10%. The results are robust across the mITT and myITT populations. The adjusted treatment difference for the various populations with proven or probable IFD/aspergillosis ranged from -2.7% to -2.1%. The upper bound of the 95% confidence interval around the adjusted treatment difference across these populations ranged from 7.3% to 8.2% and is lower than the 10% non-inferiority margin. The key secondary endpoint of DRC-assessed overall response at EOT was similar between treatment groups across (35.0% for isavuconazole and 36.4% for voriconazole, mITT population). The adjusted difference between treatment groups was -1.6% with a corresponding 95% confidence

interval of (-12.8%, 9.6%). The results for the myITT population are similar with a slightly higher DRC-assess overall response at EOT for voriconazole patients as compared to isavuconazole patients.

Supportive data for the invasive aspergillosis indication comes from 24 patients in Study 9766-CL-0103 assessed by the DRC as having only an *Aspergillosis* infection. Twenty of these patients 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 all patients having only an *Aspergillosis* infection and 30.0% for those that were renally impaired. Although the number of patients is small, the results including those of renally impaired patients are similar to those observed in Study 9766-CL-0104.

For the indication of treatment of mucormycosis, the primary evidence to support the efficacy of isavuconazole for the treatment of invasive mucormycosis was based on the single open-label Phase 3 trial, Study 9766-CL-0103. This study enrolled 46 patients with mucormycosis, 37 were assessed by the DRC as having proven or probable invasive mucormycosis infection only, 1 was assessed as having possible Mucorales infection, and the remaining 8 patients had mixed infections. Of the 37 proven or probable invasive mucormycosis infection only patients, 21 received isavuconazole as primary therapy. The all-cause mortality rate through Day 42 was 37.8% with an exact 95% confidence interval of (22.5%, 55.2%) for those with proven or probable invasive mucormycosis infection only and 33.3% with an exact 95% confidence interval of (14.6%, 57.0%) in the primary therapy patients. The DRC assessed overall response at EOT was 31.4% with an exact 95% confidence interval of (16.9%, 49.3%) for those with proven or probable invasive mucormycosis infection only and 31.6% with an exact 95% confidence interval of (12.6%, 56.6%) in the primary therapy patients.

Based on the results from Study 9766-CL-0104 and supportive information from Study 9766-CL-0103 in the subset of patients with invasive aspergillosis and renal impairment, there is adequate evidence of efficacy to support the indication of the treatment of invasive aspergillosis with isavuconazole. While inferential testing to define the benefit of isavuconazole treatment relative to no treatment or even to another active anti-fungal is not possible in the treatment of mucormycosis, the results of the subset of patients with invasive mucormycosis from Study 9766-CL-0103 do indicate some evidence of efficacy for isavuconazole. In conjunction with the successful outcome of the larger randomized, comparative Study 9766-CL-0104 in invasive aspergillosis, another difficult to treat fungal infection, it is recommended that the results of Study 9766-CL-0103 be considered adequate evidence of efficacy to support the indication of treatment of invasive mucormycosis for isavuconazole. The final decision, however, is left to the Medical Division.

2 INTRODUCTION

2.1 Overview

These NDAs are for Cresemba (isavuconazonium). NDA 207-500 is for the hard gelatin capsules and NDA 207-501 is for the lyophilized powder formulation for intravenous administration of isavuconazonium. Isavuconazonium is a water-soluble triazole antifungal agent. Isavuconazole is the active moiety of isavuconazonium. The proposed indications for Cresemba are the treatment of invasive aspergillosis and the treatment of invasive mucormycosis in patients 18 years of age and older.

The clinical development program for isavuconazole consists of 40 Phase 1 studies, 2 Phase 2 studies, and 2 completed Phase 3 studies. Primary support of the efficacy of isavuconazole for the invasive aspergillosis indication is based on the Phase 3 trial, Study 9766-CL-0104. This was a randomized, double-blind, non-inferiority, comparative group study which evaluated the efficacy and safety of isavuconazole compared to voriconazole for the treatment of invasive aspergillosis. The indication is also supported by data from patients with invasive aspergillosis and renal impairment that were enrolled in the open-label Phase 3 trial, Study 9766-CL-0103. Study 9766-CL-0103 was an open-label, multicenter, single arm study of isavuconazole for the treatment of invasive aspergillosis in patients with renal impairment or in patients with invasive fungal disease (IFD) caused by rare molds, yeasts, or dimorphic fungi. The invasive mucormycosis indication is based on the data from a subpopulation of patients enrolled in Study 9766-CL-0103, who were confirmed to have proven or probable invasive mucormycosis as determined by an independent Data Review Committee (DRC). The mucormycosis results from Study 9766-CL-0103 are supplemented by a literature review as well as a matched-case control analysis using the Fungiscope Registry Database. The focus of this review will be the two Phase 3 efficacy trials.

Table 1
Listing of Studies Included in Review

Protocol	Phase and Design	Dosing Regimen	Dosing Duration	# of Subjects per Arm	Study Population
9766-CL-0104	Phase 3 double-blind, randomized, non-inferiority, active controlled	Loading dose: 200 mg q8h IV for 2 days Maintenance dose: 200 mg once per day IV or oral	Maximum 84 days	258 Isa 258 Vori	Patients with IFD caused by *Aspergillosis* or other filamentous fungi
9766-CL-0103	Phase 3 open label, noncomparative	Loading dose: 200 mg q8h IV or oral for 2 days Maintenance dose: 200 mg once per day IV or oral	Maximum 180 days. Could continue in certain cases if patient was deriving clinical benefit	146 Isa	Renally impaired patients with invasive aspergillosis and patients with IFD caused by other rare molds, yeasts, or dimorphic fungi

Isa: Isavuconazole, Vori: Voriconazole, IFD: Invasive Fungal Disease

In December 2005, an End-of-Phase 2 meeting was held with Basilea Pharmaceuticals, the original Sponsor of the isavuconazole IND. At this meeting, the Sponsor was encouraged to pursue a primary treatment indication in *Aspergillus* infection (b) (4) (b) (4) . In March 2010, the IND for isavuconazole was transferred from Basilea to Astellas. In April 2010, a type B meeting was held to discuss Protocol 9766-CL-0104 and other clinical development issues associated with the change in Sponsorship. The Sponsor proposed to change the primary endpoint in Protocol 9766-CL-0104 to all-cause mortality. As the trial was still fully blinded and interim results were unknown, the Division was in general agreement with this change provided a detailed non-inferiority margin justification was provided for this endpoint. Follow-up discussions were held in October 2010, August 2011, and finally October 2012 when the Division agreed that a 10% non-inferiority margin for 6 week all-cause mortality would be acceptable for assessing the primary endpoint in Protocol 9766-CL-0104. Isavuconazonium was granted an Orphan drug-designation for both of the proposed indications in 2013 and was designated as a Qualified Infectious Disease Product (2013 for Invasive Aspergillosis and 2014 for Invasive Mucormycosis).

Isavuconazole is also being studied for the treatment of candidemia and invasive candidiasis. A third Phase 3 trial evaluating the efficacy and safety of isavuconazole in the treatment of candidemia and other invasive *Candida* infections is still ongoing. (b) (4)

2.2 Data Sources

The data analyzed in this review comes from the Phase 3 trials submitted as the pivotal evidence to support the efficacy of isavuconazole. The final clinical study reports for 9766-CL-0104 and 9766-CL-0103 and datasets for the two trials provided in the electronic submission were reviewed. Additionally, the report for the matched-case analysis of primary mucormycosis patients from isavuconazole Study 9766-CL-0103 to patients from the Fungiscope registry database and the Sponsor's review of the natural history and efficacy of antifungal agents for mucormycosis were reviewed. These can all be found in the electronic submission located at: \\CDSESUB1\evsprod\NDA207500\0000.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The datasets submitted were of acceptable quality. Minimal programming was necessary to reproduce the results presented by the Applicant.

Reviewer's Comment: *Unless otherwise indicated, tables presented in this review are based on analyses conducted by this reviewer using the analysis datasets submitted by the Applicant and*

confirm the results of those presented by the Applicant in the 9766-CL-0104 and 9766-CL-0103 Study Reports.

3.2 Evaluation of Efficacy

3.2.1 Study 9766-CL-0104 (WSA-CS-004)

3.2.1.1 Study Design and Endpoints

9766-CL-0104 was a Phase 3, randomized, multicenter, double-blind, non-inferiority, comparative group study designed to evaluate the safety and efficacy of isavuconazole versus voriconazole for the primary treatment of invasive fungal disease (IFD) caused by *Aspergillus* species or other filamentous fungi. The trial was conducted at 102 centers in North America, South America, Europe, the Middle East, Africa, Southeast Asia, the Far East and Pacific regions. Eligible patients were male or female aged ≥ 18 years with proven, probable, or possible IFD based on diagnostic tests, the presence of host factors, radiological/clinical features, and mycological evidence. Enrolled subjects were randomized in a 1:1 ratio to receive treatment with either isavuconazole or voriconazole. 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 receive isavuconazole were to receive a loading dose of 200 mg tid IV the first 2 days of treatment followed by a maintenance dose of 200 mg qd IV or oral from Day 3 to end of treatment (EOT). Patients randomized to receive voriconazole were to receive a loading dose of 6 mg/kg q12h IV in the first 24 hours of treatment followed by a maintenance dose of 4 mg/kg q12h IV or 200 mg q12h oral from Day 2 to EOT. The switch from IV to oral was to be made as early as possible from day 3 but patients could remain on IV treatment for reasons such as inability to swallow, gastric suction, or concerns about adequate dosing. In order to maintain the blind, patients randomized to voriconazole received a placebo infusion during the loading dose phase and patients randomized to isavuconazole received a placebo infusion while staying on IV during the maintenance period. While on oral treatment, a double dummy was used so that patients received placebo capsules to match the treatment they were not randomized to. Patients were to receive treatment for a minimum of 7 days after resolution of all clinical symptoms and physical findings of infection or for a maximum of 84 days.

On-treatment study visits were to occur on Day 1, Day 2, Day 3, Day 7 (+1 day), Day 14 (± 3 days), Day 28 (± 7 days), Day 42 (± 7 days), Day 63 (± 7 days), Day 84 (± 7 days), and within 3 days of EOT. A post-treatment follow-up visit was conducted 4 weeks after EOT. Survival status was recorded at EOT, Day 42, Day 84, and at the post-treatment follow-up visit. An assessment of clinical symptoms and physical findings of IFD were performed at screening and at all subsequent visits from Day 3 onward including EOT, Day 42, Day 84, and post-treatment follow-up. The baseline mycological assessment (screening through day 7) of the patient's IFD status was performed according to best local practice based on samples for fungal culture and isolation and/or biopsy/biological fluid samples from the infected site for histology/cytology. Mycological assessments were also performed at EOT, Day 42, and Day 84. Additional

mycological assessments could be performed as clinically indicated and/or in line with standard clinical management. Baseline radiological assessments of IFD were performed during the screening period but assessments performed up to 7 days after the first administration of study drug may have been used to confirm the diagnosis of IFD. Radiological assessments of IFD were to be performed at EOT and on study Days 42 and 84 and additionally, on Days 14, 28 and follow-up, if clinically indicated. Patients were assessed for the occurrence of adverse events (AEs) on an ongoing basis during the course of the study and up to the follow-up visit (28 days after the last administration of study drug).

An independent Data Review Committee (DRC) was established to adjudicate the categorization of each patient's IFD at enrollment (including data up to Day 7 as relevant) and to evaluate clinical, mycological, radiological, and overall response at EOT, Day 42, and Day 84, as well as to assess attributable mortality. The DRC consisted of experts in infectious diseases. The patient profile data reviewed by the DRC did not include the Investigator's assessments of baseline mycological criteria or response, or any AEs that could potentially unblind the DRC. Independent radiology experts were responsible for providing a qualitative assessment of radiology images including an overall impression of the images that described the size, number and characteristics of the IFD for each time point, as well as an overall outcome assessment of percent improvement from baseline at EOT, Day 42, and Day 84. This information was provided to the DRC.

The DRC categorized each patient's IFD at enrollment as proven, probable, possible, or no IFD/no invasive mold infection based on the presence of adequate host factors, the presence of adequate radiologic and clinical features, and mycological evidence from histopathology, culture, and/or galactomannan (GM). Per the protocol, the DRC could assess a probable case of aspergillosis using GM if there were 2 consecutive serum GM values ≥ 0.05 or a single serum GM value ≥ 0.7. Current guidance from the Medical Division, is that a case can be assessed as probable aspergillosis of there are 2 consecutive serum GM values ≥ 0.05 or a single serum or bronchoalveolar lavage (BAL) GM value ≥ 1.0. Based on this guidance, a single serum GM value between 0.7 and 1.0 would only be considered as possible aspergillosis.

Overall response was assessed by the DRC as complete, partial, stable, failure, or not done. A patient with complete or partial overall response was considered a success. Clinical response was assessed by the DRC as:

- Success- Resolution of all attributable clinical symptoms and physical findings OR partial resolution of 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 eradication, presumed eradication, persistence, presumed persistence, no mycological evidence available at baseline, or not done. A patient with eradication or presumed eradication was considered a success. 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, failure, no post-baseline radiology available for patient with baseline evidence of radiologic disease, or radiology not applicable at baseline. An assessment of response was not made by the DRC if the DRC indicated that the patient had no IFD/no invasive mold infection at baseline.

The primary objective of the trial was to assess non-inferiority of isavuconazole compared to voriconazole in all-cause mortality through Day 42. The primary efficacy endpoint was the crude rate of all-cause mortality through Day 42. All-cause mortality through Day 84 and time-to-death were secondary endpoints. A key secondary efficacy endpoint was the DRC assessment of overall response at EOT. Additional secondary efficacy endpoints included DRC-assessed overall response at Day 42 and Day 84, as well as DRC-assessed rates at EOT, Day 42, and Day 84 of clinical response, mycological response, and radiological response individually.

3.2.1.2 Statistical Methodologies

The primary analysis of all-cause mortality through Day 42 was based on the difference in the rate (isavuconazole-voriconazole) and corresponding 95% confidence interval calculated using the stratified Cochran-Mantel Haenszel (CMH) method. The stratification factors were Geographical Region, Allogeneic BMT Status, and Uncontrolled Malignancy Status. The upper bound of the 95% confidence interval was compared to the justified non-inferiority margin of 10% (refer to Section 5.1 for a discussion of the justification of the non-inferiority margin). If the upper bound was less than 10%, isavuconazole was considered non-inferior to voriconazole with respect to all-cause mortality through Day 42. A patient with unknown survival status through Day 42 was included as a death in the calculation of the all-cause mortality rate through Day 42.

Analyses of the secondary endpoints related to rates were analyzed using the same method as the primary endpoint. A patient with unknown survival status through Day 84 was included as a death in the calculation of the all-cause mortality rate through Day 84. For the DRC-assessed endpoints, a patient that the DRC indicated as Not Done for a visit was considered as missing and was included as a failure for the visit.

The following populations were used for the analyses. The intent-to-treat (ITT) population included all randomized patients who received at least one administration of study drug. The modified ITT (mITT) population included ITT patients who had proven or probable IFD as determined by the DRC. Patients with appropriate host factor and clinical features could be considered to have probable IFD based on the GM criteria per the protocol (i.e., 2 consecutive serum GM values ≥ 0.5 or at least 1 serum GM value ≥ 0.7). The mITT-FDA population included ITT patients who had proven or probable IFD however patients with appropriate host factor and clinical features could be considered to have probable IFD based on the GM criteria per current FDA recommendations (i.e., 2 consecutive serum GM values ≥ 0.5 or at least 1 serum or BAL GM value ≥ 1.0). The mycological ITT (myITT) population included mITT patients with proven or probable invasive aspergillosis based on cytology, histology, culture, or GM per the protocol and assessed by the DRC. The per-protocol set (PPS) was a subset of the ITT who did not deviate from prespecified classification criteria. A subject could be excluded from the

PPS if they met any of the following: specified inclusion/exclusion criteria, received less than 7 days of study medication, withdrew consent or lost to follow up AND last evaluation day prior to Day 42, took a different study medication during the treatment period, took at least 3 consecutive days of prohibited concomitant medications including mold active systemic anti-fungal therapy after first dose of study drug through the last dose of study medication, unblinded patients, or was assessed as no IFD by the DRC. The Safety Analysis Set (SAF) included all randomized patients who received at least one dose of study drug. For the SAF population, data were analyzed according to the study drug that patients received as the first dose even if it was different from what they were randomized to. For all other analysis populations, the data were analyzed by the treatment group that patients were randomized to even though they might not be compliant with the assigned treatment.

The sample size of the trial was based on the primary efficacy endpoint variable, all-cause mortality through day 42. Approximately 255 patients per treatment group or approximately 510 patients in total were to be enrolled to ensure at least 80% power to demonstrate that the upper bound of the 95% confidence interval for the treatment difference of isavuconazole – voriconazole was no larger than 10%. This was based on a one-sided test with a 2.5% significance level and the assumption that the mortality rate would be 20% for both treatment groups.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

Overall 527 patients were randomized into the trial: 263 to the isavuconazole group and 264 to the voriconazole group. Eleven patients were randomized but did not receive any dose of study medication. Therefore, the ITT population consisted of 516 patients (258 in each treatment group). Patients were considered to have completed treatment if they received a maximum of 84 days of treatment or had a successful overall outcome and received a minimum of 7 days of therapy. Approximately 46% of the patients in the ITT population completed treatment. The most common reasons for discontinuation of treatment were AE/intercurrent illness, lack of efficacy, and death while on treatment. There are imbalances between treatment groups in the percentage of subjects who discontinued treatment due to an adverse event/undercurrent illness which favors isavuconazole and for insufficient therapeutic response which favors voriconazole. When these two categories are combined, however, the percentages are similar between treatment groups. Voriconazole is known to have some unfavorable adverse event concerns and one could assume that a patient might be discontinued from treatment due to an adverse event earlier than the decision to discontinue a patient because of an unfavorable response would be made. The latter is supported in part that the minimum time to discontinuation due to an adverse event was 1 day compared to 5 days for lack insufficient therapeutic response. Patients were considered to complete the study if they completed a follow-up visit after the EOT visit. Approximately 63% of the patients in the ITT population completed the study follow-up. The most common reasons for discontinuation during the study were death, administrative/other, and failure to return/lost to follow-up. Reasons for discontinuation during treatment and follow-up are reported in Table 2.

Table 2
9766-CL-0104
Primary Reasons for Discontinuation During Treatment and Follow-up (ITT)

	Isavuconazole (n=258)	**Voriconazole** (n=258)
Treatment Discontinuation		
Completed	118 (45.7)	120 (46.5)
Discontinued	140 (54.3)	138 (53.5)
Adverse Event/Intercurrent Illness	31 (12.0)	53 (20.5)
Death	17 (6.6)	21 (8.1)
Insufficient Therapeutic Response	39 (15.1)	23 (8.9)
Failure to Return/ Lost to Follow-up	2 (0.8)	1 (0.4)
Violation of Selection at Entry	17 (6.6)	10 (3.9)
Other Protocol Violation	10 (3.9)	6 (2.3)
Did not Cooperate	12 (4.7)	9 (3.5)
Refused Treatment	7 (2.7)	5 (1.9)
Withdrew Consent	5 (1.9)	4 (1.6)
Administrative/Other	12 (4.7)	15 (5.8)
Discontinuation During Follow-up		
Completed	170 (65.9)	155 (60.1)
Discontinued	88 (34.1)	103 (39.9)
Adverse Event/Intercurrent Illness	2 (0.8)	5 (1.9)
Death	56 (21.7)	67 (26.0)
Failure to Return/ Lost to Follow-up	8 (3.1)	9 (3.5)
Administrative/Other	15 (5.8)	15 (5.8)
Withdrew Consent	7 (2.7)	7 (2.7)

The Safety population is comprised of 516 patients. It should be noted that 1 patient was randomized to the isavuconazole group but received treatment with voriconazole for the first 7 days and was then switched to isavuconazole oral study drug. This patient is included in the voriconazole treatment group for the Safety population but included in the isavuconazole group for the ITT and ITT-related populations. Out of the 516 patients in the ITT population, 244 subjects were excluded from the mITT population because the DRC assessed the patient as having either possible or no IFD at baseline. While there is only a net difference of 3 patients between the mITT and mITT-FDA populations, the mITT-FDA population includes 20 patients who were considered probable based on a BAL GM $\geq$ 1.0 but excludes 17 patients who were considered probable in the mITT population based on a single serum GM between 0.7 and 1.0. The myITT population consists of 123 isavuconazole patients and 108 isavuconazole patients who had proven or probable invasive aspergillosis. Out of the 516 patients in the ITT population, 169 patients (32.8%) were excluded from the PPS-ITT (86 isavuconazole and 83 voriconazole). The most common reasons for exclusion from the PPS-ITT were received less than 7 days of study drug (11.4%), took prohibited concomitant medications for at least 3 consecutive days (9.9%), and DRC assessed as having no IFD (9.3%).

Table 3
9766-CL-0104
Analysis Populations

	Isavuconazole	Voriconazole
Randomized	263	264
Safety*	257	259
ITT**	258	258
mITT**	143	129
mITT-FDA**	147	128
myITT**	123	108
PPS-ITT**	172	175

*Patients analyzed according to actual treatment received as first dose
**Patients analyzed according to randomized treatment

The following table provides further characterization of the analysis populations based on the categorization of the IFD. Most of the cases were considered as probable IFD and the majority of those were probable on the basis of a positive serum GM. Approximately 85% of the population with proven or probable IFD had aspergillosis.

Table 4
9766-CL-0104
Further Characterization of Analysis Populations

	Isavuconazole	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 mold species	3 (2.1)	1 (0.8)
Non-Aspergillus 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)
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)

*Probable based on GM with the exception of 1 isavuconazole subject who was based on a culture from a non-sterile site and had adequate host factors and clinical and radiological factors

Reviewer's Comment: *The efficacy analyses presented in this review will focus on the ITT and ITT-related populations.*

Table 5 summarizes the demographic and baseline characteristics of the ITT population. There were no significant differences across treatment groups. Overall, 60% of the study population was male and 78% was white. The mean age of the patients was 51 years. The majority of the patients had hematologic malignancy as their underlying condition. The overall distribution of geographic region was: 11% US/Canada, 41% Western Europe/Australia/New Zealand, and 48%

all other regions (Argentina, Brazil, Chile, China, Egypt, Hungary, India, Israel, Malaysia, Mexico, Poland, Russia, South Korea, Thailand, and Turkey). 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, 17% of patients had corticosteroid use and 43% of patients had T-cell immunosuppressant use at baseline.

Table 5
9766-CL-0104
Demographic and Baseline Characteristics (ITT)

	Isavuconazole	**Voriconazole**
# Patients	258	258
Gender		
Male	145 (56.2)	163 (63.2)
Female	118 (43.8)	95 (36.8)
Age mean (SD)	51.1 (16.2)	51.1 (15.8)
Min, max	17, 82	18, 87
Race		
White	211 (81.8)	191 (74.3)
Black	1 (0.4)	1 (0.4)
Asian	45 (17.4)	64 (24.9)
Other	1 (0.4)	1 (0.4)
Missing	-	1 (0.4)
Geographic Region		
US/Canada	30 (11.6)	28 (10.9)
Western Europe/Australia/New Zealand	105 (40.7)	107 (41.5)
Other Region	123 (47.7)	123 (47.4)
Hematologic Malignancy	211 (81.8%)	222 (86.0%)
Prior Allogeneic BMT	54 (20.9)	51 (19.8)
Uncontrolled Malignancy at Baseline	173 (67.1)	187 (72.5)
Neutropenic	163 (63.2)	175 (67.8)
Use of Corticosteroids	48 (18.6)	39 (15.1)
Use of T-cell Immunosuppresant	111 (43.0)	109 (42.2)

Duration of study drug is summarized in Table 6. The total duration of study drug (IV and oral) was similar between the isavuconazole and voriconazole treatment groups and was a median duration 45 days overall. The median duration of IV dosing was 5 days. A total of 400 patients (77.5%) switched from IV to oral dosing. The median duration of oral dosing was 60 days for isavuconazole and 53 days for voriconazole.

Table 6
9766-CL-0104
Duration of Study Drug (Safety)

	Isavuconazole	Voriconazole
Total Duration (days)	N=257	N=259
Mean (sd)	46.9 (32.3)	46.5 (32.1)
Median	45	47
Min, Max	1, 102	1, 88
Duration of IV dosing (days)	N=257	N=259
Mean (sd)	8.1 (8.5)	8.9 (9.6)
Median	5	5
Min, Max	1, 84	1, 63
Duration of Oral dosing (days)	N=194	N=206
Mean (sd)	51.5 (28.0)	47.3 (328.9)
Median	60	53
Min, Max	0.5, 99.5	1, 85.5

3.2.1.4 Results and Conclusions

All-cause mortality rates through Day 42 are presented in Table 7 for the various ITT-related populations. The ITT population was the protocol defined primary analysis population for all-cause mortality through Day 42. In the ITT population, the all-cause mortality rate through Day 42 was 18.6% for isavuconazole and 20.2% for voriconazole. The adjusted difference between treatment groups was -1.0% with a corresponding 95% confidence interval of (-8.0, 5.9). Since the upper bound of the 95% confidence interval is less than 10%, non-inferiority of isavuconazole compared to voriconazole was demonstrated with respect to all-cause mortality through Day 42. Day 42 survival status was known for all but 3 isavuconazole and 2 voriconazole ITT patients who are imputed as deaths in these analyses. The results are robust across the various populations and are similar regardless of whether the protocol-defined or FDA-defined galactomannan criteria are used for defining the mITT population. The adjusted treatment difference for the various populations with proven or probable IFD/aspergillosis ranged from -2.7% to -2.1%. The upper bounds of the 95% confidence interval around the adjusted treatment difference across these populations ranged from 7.3% to 8.2% and are all lower than the 10% non-inferiority margin.

Table 7
9766-CL-0104
All-cause Mortality through Day 42

	Isavuconazole	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**)

*adjusted difference (Isa- Vori) and CI calculated using stratified CMH method with the strata of geographic region, allogeneic BMT status, and uncontrolled malignancy status
**survival status unknown for only 3 isavuconazole and 2 voriconazole ITT subjects

Reviewer's Comment: *The confidence intervals presented in this review are slightly different from those presented in the Applicant's study report due to method of calculation. The conclusions drawn are the same.*

All-cause mortality rates through Day 84 are presented in Table 8. In the ITT population, the all-cause mortality rate through Day 84 was 29.1% for isavuconazole and 31.0% for voriconazole. The adjusted treatment difference across the various analysis populations ranged from -5.7% to -1.4% demonstrating lower mortality rates for isavuconazole as compared to voriconazole. Day 84 survival status was known for all but 3 isavuconazole and 5 voriconazole ITT patients who are imputed as deaths in these analyses.

Table 8
9766-CL-0104
All-cause Mortality through Day 84

	Isavuconazole	**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)

*adjusted difference (Isa-Vori) and CI calculated using stratified CMH method with the strata of geographic region, allogeneic BMT status, and uncontrolled malignancy status
**survival status unknown for only 3 isavuconazole and 5 voriconazole ITT subjects

DRC-assessed overall response at EOT was the key secondary endpoint. For the mITT population, the DRC-assessed overall response rates at EOT were similar between treatment groups (35.0% for isavuconazole and 36.4% for voriconazole). The lower bound of the 95% confidence interval about the adjusted treatment difference is -12.8%. Complete response was seen in 11.9% isavuconazole patients and 10.1% voriconazole patients. Partial response was seen in 23.1% isavuconazole patients and 27.8% voriconazole patients. The results for the mITT-FDA population are similar to that of the mITT population. The results for the myITT population are also similar with a slightly higher DRC-assessed overall response at EOT for voriconazole patients as compared to isavuconazole patients. The DRC was able to provide an assessment of overall response at EOT for all subjects with an IFD.

Table 9
9766-CL-0104
DRC- assessed Overall Response at EOT

	Isavuconazole	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)	12 (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)	

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

Reviewer's Comment: *All differences presented in this review are based on isavuconazole – voriconazole. For the endpoints of DRC-assessed responses, the Applicant presents differences as voriconazole-isavuconazole in the study report.*

The DRC assessed responses only for subjects with an IFD. Therefore, results for the DRC-assessed response endpoints are not presented for the ITT population which included patients assessed by the DRC as no IFD.

Table 10 summarizes the DRC-assessed clinical, mycological, and radiological response at EOT. In the mITT population, DRC-assessed clinical response rates at EOT were 59.4% for isavuconazole patients and 56.6% for voriconazole patients. Mycological response was seen in 37.8% isavuconazole patients and 41.1% voriconazole patients and primarily due to presumed eradication. Radiological response was seen in 28.7% isavuconazole patients and 32.6% voriconazole patients. These rates are low in both treatment groups due to the number of patients without any post-baseline radiological assessments which was approximately 22%. Similar results are seen for the myITT population.

Table 10
9766-CL-0104
DRC- assessed Clinical, Mycological, and Radiological Response at EOT

Population	Response	Isavuconazole	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 Eradication	52 (36.4)	53 (41.1)	
	Persistence	12 (8.4)	13 (10.1)	
	Presumed Persistence	77 (53.9)	63 (48.8)	
	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)	
myITT	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 Eradication	45 (36.6)	48 (44.4)	
	Persistence	9 (7.3)	6 (5.6)	
	Presumed Persistence	67 (54.5)	54 (50.0)	
	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.

Reviewer's Comment: *The rates presented in Table 10 are slightly different than those presented in Applicant's study report since non-evaluable/missing was included in the denominator and treated as a unsuccessful response above but were excluded from those presented in the study report.*

Table 11 summarizes the DRC-assessed overall, clinical, mycological, and radiological response at Day 42 and Day 84. DRC-assessed overall and mycological responses at Day 42 are similar between treatment groups. DRC-assessed clinical response at Day 42 is numerically higher for isavuconazole whereas radiologic response is numerically higher for voriconazole. At Day 84, the DRC-assessed responses were numerically lower in the isavuconazole group compared to voriconazole with the exception of clinical response rates at Day 84 which were slightly higher for isavuconazole.

Table 11
9766-CL-0104
DRC- assessed Overall, Clinical, Mycological, and Radiological Response at Day 42 and Day 84

Population	Response	Isavuconazole	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. Non-evaluable/missing was included in the denominator and treated as unsuccessful response.

3.2.2 Study 9766-CL-0103 (WSA –CS-003)

3.2.2.1 Study Design and Endpoints

9766-CL-0103 was a Phase 3, open-label, multicenter trial of isavuconazole in the treatment of invasive aspergillosis in patients with renal impairment or in patients with IFD caused by rare mold, yeasts, or dimorphic fungi. The trial was conducted at 34 centers in the United States, Belgium, Germany, Brazil, India, Israel, South Korea, Lebanon, Mexico, Russia, and Thailand. Eligible patients were male or female aged ≥ 18 years in one of the following subgroups:

- Patients with proven, probable, or possible invasive aspergillosis who had renal impairment (including dialysis), defined as calculated creatinine clearance (CLCr) < 50 mL/min at enrollment who required primary therapy.
- 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 renally impaired or not who required primary therapy, were refractory to current treatment, or were intolerant to current treatment for their IFD at the time of enrollment.
- Patients who had proven or probable zygomycosis, whether renally impaired or not who required primary therapy.

Enrolled patients received isavuconazole as a loading dose of 200 mg tid IV or oral the first 2 days of treatment followed by a maintenance dose of 200 mg qd IV or oral from Day 3 to end of treatment (EOT). Patients were to receive treatment for a minimum of 7 days after resolution of all clinical symptoms and physical findings of infection. The maximum duration of treatment was initially 84 days, following a protocol amendment the maximum duration was extended to 180 days, and country-specific amendments (US, Israel, and Belgium) allowed patients who were deriving clinical benefit to continue treatment beyond 180 days.

Reviewer's Comment: *Due to the solubilizing agent used in the IV formulation of voriconazole, subjects with renal impairment should not receive IV voriconazole. Therefore, patients with renal impairment were excluded from the randomized, comparative Study 9766-CL-0104. Patients with renal impairment were enrolled in this trial in order to get an assessment of isavuconazole in this patient population.*

On treatment study visits were to occur on Day 1, Day 2, Day 3, Day 7 (+1 day), Day 14 (± 3 days), Day 28 (± 7 days), Day 42 (± 7 days), Day 84 (± 7 days), every 4 weeks until EOT (± 7 days), and Day 180 (± 3 days). A post treatment follow-up visit was conducted 4 weeks after EOT and for patients with abnormalities noted, a second post-treatment follow-up visit 8 weeks after EOT. Survival status was recorded at EOT, Day 42, Day 84, and at the post-treatment follow-up visit 1. An assessment of clinical symptoms and physical findings of IFD were performed at screening and at all subsequent visits from Day 3 onward. An assessment of clinical response was evaluated at EOT, Day 42, and Day 84. The baseline mycological assessment (screening through day 7) of the patient's IFD status was performed according to best local practice based on samples for fungal culture and isolation and/or biopsy/biological fluid samples from the infected site for histology/cytology. An assessment of mycological response was also performed at EOT, Day 42, and Day 84. Additional mycological assessments could be performed as clinically indicated and/or in line with standard clinical management. Baseline radiological assessments of IFD were performed during the screening period but assessments performed up to 7 days after the first administration of study drug may have been used to confirm the diagnosis of IFD. Radiological assessments of IFD were to be performed at EOT and on study days 42 and 84 and additional study visit days if clinically indicated. Patients were assessed for the occurrence of AEs on an ongoing basis during the course of the study and up to the follow-up visit 1 (28 days after the last administration of study drug) and follow-up visit 2 if an event was ongoing at follow-up visit 1.

An independent DRC was established to adjudicate the categorization of each patient's IFD at enrollment (including data up to day 7 as relevant) and to evaluate clinical, mycological, radiological, and overall response at EOT, Day 42 and Day 84, as well as to assess attributable mortality. The DRC consisted of experts in infectious diseases. The patient profile data reviewed by the DRC did not include the Investigator's assessments of baseline mycological criteria or response. Independent radiology experts were responsible for providing a qualitative assessment of radiology images as well as an assessment of radiological response. This information was provided to the DRC.

The DRC categorized each patient's IFD at enrollment as proven, probable, possible, or no IFD/no invasive mold infection based on the presence of adequate host factors, the presence of

adequate radiologic and clinical features, and mycological evidence from histopathology, culture and/or GM. Per the protocol, the DRC could assess a probable case of aspergillosis using GM if there were 2 consecutive serum GM values ≥ 0.05 or a single serum GM value ≥ 0.7, or a single BAL GM ≥ 1.0. The DRC categorized the pathogen causing the IFD using the following categories: Mucorales only, *Aspergillus* only, other filamentous fungi only (not *Aspergillus* or Mucorales), mold species not otherwise specified (NOS), dimorphic fungi only, non-*Candida* yeast only, mixed infection, or no pathogen identified. The DRC's assessment of overall response, clinical response, mycological response, and radiological response were as defined for Study 9766-CL-0104.

The primary objective of the trial was to describe the efficacy of isavuconazole in the treatment of invasive aspergillosis in patients with renal impairment or in patients with IFD caused by rare molds, yeasts or dimorphic fungi. The protocol specified primary efficacy endpoint was DRC-assessed overall response at Day 42, Day 84, and EOT. Secondary endpoints included each component: clinical response, mycological response, and radiological response assessed by the DRC at Day 42, Day 84, and EOT as well as survival rate at Day 42 and Day 84.

3.2.2.2 Statistical Methodologies

As this was an open-label trial without a comparator group, all analyses were descriptive. Analyses are presented by pathogen and no formal inferential analyses were performed. Crude success rates and exact 95% confidence intervals were presented.

The sample size of 150 patients was not based on statistical considerations but rather an expected number of patients to be available for the trial. Enrollment of patients with certain infections was limited in order to enroll approximately 30 renally impaired patients with IFD as well as an adequate number of patients with proven or probable mucormycosis.

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 and was further classified according to the type of pathogen causing the IFD. The mITT-Mucorales population includes patients who the DRC classified as Mucorales only. The mITT-Aspergillus population includes patients who the DRC classified as *Aspergillus* only and patients who the DRC classified as no pathogen identified but met serum GM and/or BAL GM criteria. The safety analysis set is identical to the ITT population.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

Overall 149 patients were enrolled in the trial, 146 patients took at least 1 dose of study drug and were included in the ITT population. Fifteen patients were approved to receive treatment beyond 180 days. Five of these 15 patients were still receiving study drug as of September 30, 2013 the cutoff date for inclusion of data in the study report. These subjects therefore do not have an EOT assessment by the DRC. Approximately 47% of the patients in the ITT population discontinued treatment. The most common reasons for discontinuation of treatment were death while on treatment, AE/intercurrent illness, and lack of efficacy. Patients were considered to complete the

study if they completed a follow-up visit after the EOT visit. Overall, 40% of the patients in the ITT population did not complete the study follow-up period. The most common reason for discontinuation during the study was death. Reasons for discontinuation during treatment and follow-up are reported in Table 12.

Table 12
9766-CL-0103
Primary Reasons for Discontinuation During Treatment and Follow-up (ITT)

	Renally Impaired (n=59)	**Not Renally Impaired** (n=87)	**Total** (n=146)
Treatment Discontinuation			
Completed	23 (39.0)	49 (56.3)	72 (49.3)
Ongoing	2 (3.4)	3 (3.4)	5 (3.4)
Discontinued	34 (57.6)	35 (40.2)	69 (47.3)
Death	13 (22.0)	9 (10.3)	22 (15.1)
Adverse Event/Intercurrent Illness	10 (16.9)	8 (9.2)	18 (12.3)
Insufficient Therapeutic Response	3 (5.1)	7 (8.0)	10 (6.8)
Did not Cooperate	0	5 (5.7)	5 (3.4)
Violation of Selection at Entry	1 (1.7)	3 (3.4)	4 (2.7)
Other Protocol Violation	3 (5.1)	1 (1.1)	4 (2.7)
Administrative/Other	2 (3.4)	2 (2.3)	4 (2.7)
Failure to Return/ Lost to Follow-up	2 (3.4)	0	2 (1.4)
Discontinuation During Follow-up			
Completed	30 (50.8)	52 (59.8)	82 (56.2)
Ongoing	2 (3.4)	3 (3.4)	5 (3.4)
Discontinued	27 (45.8)	32 (36.8)	59 (40.4)
Death	23 (39.0)	22 (25.3)	45 (30.8)
Failure to Return/ Lost to Follow-up	2 (3.4)	5 (5.7)	7 (4.8)
Administrative/Other	2.(3.4)	2 (2.3)	4 (2.7)
Withdrew Consent	0	3 (3.4)	3 (2.1)

Out of the 146 patients in the ITT population, 6 patients were excluded from the mITT population because the DRC assessed the patient as having either possible (3 patients) or no IFD (3 patients) at baseline. The number of patients classified in each of the mITT populations is presented in Table 13.

Table 13
9766-CL-0103
Analysis Populations

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

Table 14 summarizes the demographic and baseline characteristics of the ITT population. Overall, 68.5% of the study population was male and 74% was white. The mean age of the patients was 50 years. The overall distribution of geographic region was: 38.4% US, 11.6% Western Europe, and 50% all other regions (Russia, Mexico, Brazil, Thailand, South Korea, India, Lebanon, and Israel). The majority of the patients were enrolled to receive primary therapy. Overall, 43.2% of patients had hematologic malignancy, 17.8% of patients had a prior allogeneic BMT/HSCT, and 31.5% of patients had an uncontrolled malignancy at baseline. Approximately 36.5% of patients were neutropenic at baseline, 24% of patients had corticosteroid use, and 56% of patients had T-cell immunosuppressant use at baseline.

Table 14
9766-CL-0103
Demographic and Baseline Characteristics (ITT)

	Renally Impaired (n=59)	**Not Renally Impaired** (n=87)	**Total** (n=146)
Gender			
Male	38 (64.4)	62 (71.3)	100 (68.5)
Female	21 (35.6)	25 (28.7)	46 (31.5)
Age mean (SD)	52.9 (18.1)	47.8 (15.6)	49.9 (16.8)
Min, max	19, 92	18, 79	18, 92
Race			
White	48 (81.4)	60 (60.9)	108 (74.0)
Black	3 (5.1)	7 (8.0)	10 (6.8)
Asian	8 (13.6)	16 (18.4)	24 (16.4)
Other	0	4 (4.6)	4 (2.7)
Geographic Region			
US	30 (50.8)	26 (29.9)	56 (38.4)
Western Europe	7 (11.9)	10 (11.5)	17 (11.6)
Other Region	22 (37.3)	51 (58.6)	73 (50.0)
Therapy Status			
Primary	33 (57.9)	60 (69.8)	93 (65.0)
Refractory	17 (29.8)	21 (24.4)	38 (26.6)
Intolerant	7 (12.3)	5 (5.8)	12 (8.4)
Missing	2	1	3
Hematologic Malignancy	31 (52.5)	32 (36.8)	63 (43.2)
Allogeneic BMT/HSCT	16 (27.1)	10 (11.5)	26 (17.8)
Uncontrolled Malignancy at Baseline	18 (30.5)	28 (32.2)	46 (31.5)
Neutropenic	14 (26.9)	24 (46.2)	38 (36.5)
Use of Corticosteroids	20 (33.9)	15 (17.2)	35 (24.0)
Use of T-cell Immunosuppresant	32 (60.4)	29 (51.8)	61 (56.0)

Duration of study drug is summarized in Table 15. The median total duration of study drug (IV and/or oral) was 94 days overall. For those who received IV isavuconazole, the median duration of IV dosing was 9.5 days. For those who received oral isavuconazole, the median duration of oral dosing was 136.8 days. As previously mentioned, 5 patients were continuing to receive study treatment as of September 30, 2013.

Table 15
9766-CL-0103
Duration of Study Drug (ITT/Safety)

	Renally Impaired	Not Renally Impaired	Total
Total Duration (days)	N=59	N=87	N=146
Mean (sd)	106.8 (134.8)	141. (126.4)	127.3 (130.5)
Median	73	178	94
Min, Max	1, 735	2, 882	1, 882
Duration of IV dosing (days)	N=47	N=53	N=100
Mean (sd)	15.3 (15.9)	13.8 (13.0)	14.5 (14.4)
Median	10	9	9.5
Min, Max	0.5, 77	1.5, 77	0.5, 77
Duration of Oral dosing (days)	N=51	N=75	N=126
Mean (sd)	109.4 (130.7)	154.2 (124.8)	136 (128.6)
Median	75	175	136.8
Min, Max	1.5, 690	4, 882	1.5, 882

3.2.2.4 Results and Conclusions

Due to the non-comparative nature of the study, efficacy results will be descriptively summarized only for the key endpoints of all-cause mortality through Day 42 and Day 84 and DRC-assessed overall response at EOT, Day 42, and Day 84 for the mITT-Mucorales population, the mITT-*Aspergillosis* population, and all other mITT populations. For the mITT-Mucorales population, results will be summarized by therapy status: primary therapy, refractory, intolerant, and overall. For the mITT-Aspergillosis population, the results will be summarized by renally impaired, not renally impaired, and overall. All other mITT populations will be summarized overall.

All-cause mortality through Day 42 in the mITT-Mucorales population was 37.8% with an exact 95% confidence interval (22.5, 55.2). For those receiving primary therapy, all-cause mortality through Day 42 was 33.3% with an exact 95% confidence interval (14.6, 57.0). Through Day 84, all-cause mortality was 43.2% for the overall mITT-Mucorales population and 42.9% for those receiving primary therapy. Only one patient (a refractory patient) was lost to follow-up (prior to Day 42) and was counted as a death in the analyses of all-cause mortality. Two patients receiving primary therapy were continuing study treatment and therefore did not have an assessment of overall response by the DRC at EOT. The DRC-assessed overall response rate at EOT in the mITT-Mucorales population was 31.4% with an exact 95% confidence interval (16.9, 49.3). Complete response was assessed in 5 patients and partial response was assessed in 6 patients. For patients receiving primary therapy, 31.6% with an exact 95% confidence interval (12.6, 56.6) were assessed to have successful DRC-assessed overall response at EOT (3 complete and 3 partial). For a detailed review of the Mucorales population, please refer to the Clinical Reviewer's review.

Table 16
9766-CL-0103
Efficacy Results mITT-Mucorales Population

	Primary Therapy (n=21)	Refractory (n=11)	Intolerant (n=5)	Total (n=37)
All-cause Mortality Through Day 42	7 (33.3)	5 (45.5)	2 (40.0)	14 (37.8)
All-cause Mortality Through Day 84	9 (42.9)	5 (45.5)	2 (40.0)	16 (43.2)
DRC-assessed Overall Response at EOT	6/19* (31.6)	4 (36.4)	1 (20.0)	11/35 (31.4)
DRC-assessed Overall Response at Day 42	3 (14.3)	1 (9.1)	0	4 (10.8)
DRC-assessed Overall Response at Day 84	2 (9.5)	4 (36.4)	1 (20.0)	7 (18.9)

*Two patients who were still receiving study treatment are not included in the EOT assessment.

A total of 24 patients were assessed by the DRC as having only an *Aspergillus* infection. Twenty of these were considered to be renally impaired. In addition to these 24 patients, 11 patients had an *Aspergillus* infection in combination with an additional fungal pathogen. These patients are included in the mITT-mixed infection population and summarized with the all other mITT populations. All-cause mortality through Day 42 in the mITT-*Aspergillus* population was 12.5% with an exact 95% confidence interval (2.7, 32.4). For renally impaired patients, all-cause mortality through Day 42 was 15% with an exact 95% confidence interval (3.2, 37.9). All-cause mortality though Day 84 was 25% for the overall mITT-*Aspergillosis* population and 25% for renally impaired patients. All patients had known survival status (i.e. no lost to follow-up). One patient who was not renally impaired was continuing study treatment and therefore did not have an assessment of overall response by the DRC at EOT. The DRC-assessed overall response rate at EOT in the mITT-*Aspergillus* population was 34.8% with a 95% confidence interval (16.4, 57.3). Complete and partial response was assessed in 4 patients each. For renally impaired patients, 30% with a 95% confidence interval (11.9, 54.3) were assessed to have successful DRC-assessed overall response at EOT (3 complete and 3 partial).

Table 17
9766-CL-0103
Efficacy Results mITT-*Aspergillus* Population

	Renally Impaired (n=20)	Not Renally Impaired (n=4)	Total (n=24)
All-cause Mortality Through Day 42	3 (15.0)	0	3 (12.5)
All-cause Mortality Through Day 84	5 (25.0)	1 (25.0)	6 (25.0)
DRC-assessed Overall Response at EOT	6 (30.0)	2/3* (66.7)	8/23 (34.8)
DRC-assessed Overall Response at Day 42	5 (25.0)	2 (50.0)	7 (29.2)
DRC-assessed Overall Response at Day 84	6 (30.0)	1 (25.0)	7 (29.2)

*One patient who was still receiving study treatment is not included in the EOT assessment.

The results for all other mITT populations are summarized in Table 18. A total of 17 patients had IFD caused by other filamentous fungi. Two patients, both with *Fusarium,* died by Day 42. One additional death occurred by Day 84 in a patient with *Cladosporium*. At EOT, 11 (64.7%) other filamentous fungi patients were assessed by the DRC as an overall response. A total of 7

patients had IFD caused by mold species NOS. No mold species NOS patients died through Day 42 and only 1 died through Day 84. Two mold species NOS patients were considered an overall response at EOT by the DRC. A total of 29 patients had IFD caused by dimorphic fungi. All-cause mortality through Day 42 and 84 was 6.9% and DRC-assessed overall response at EOT was 64.3% in patients with an IFD caused by dimorphic fungi. A total of 11 patients had IFD caused by non-*Candida* yeast. All-cause mortality through Day 42 and 84 was 9.1% and DRC-assessed overall response at EOT was 72.7% in patients with an IFD caused by non-*Candida* yeast. A total of 15 patients had IFD cause by mixed infections. Three patients with mixed infections died by Day 42 and 2 additional patients died through Day 84. Two mixed infection patients were assessed by the DRC as a successful overall response at EOT. Eight of the patients had a mixed infection that included a Mucorales infection. Two of these patients died by Day 42 and 3 died by Day 84. Eleven of the patients had a mixed infection that included an *Aspergillus* infection. One patient died and one patient had unknown survival status through Day 42. One additional patient died and one additional patient had unknown survival status through Day 84.

Table 18
9766-CL-0103
Efficacy Results All Other mITT Populations

	Other Filamentous Fungi (n=17)	**Mold Species NOS** (n=7)	**Dimorphic fungi** (n=29)	**Non-*Candida* Yeast** (n=11)	**Mixed infection** (n=15)
All-cause Mortality Through Day 42	2 (11.8)	0	2 (6.9)	1 (9.1)	3 (20.0)
All-cause Mortality Through Day 84	3 (17.6)	1 (14.3)	2 (6.9)	1 (9.1)	5 (33.3)
DRC-assessed Overall Response at EOT	11 (64.7)	2 (28.6)	18 (64.3)	8 (72.7)	2 (14.3)

3.3 Evaluation of Safety

The safety data for Study 9766-CL-0104 are presented for the safety population which consisted of 257 isavuconazole patients and 259 voriconazole patients. Treatment emergent adverse events (TEAEs) were defined as an AE starting after the first dose of study drug administration until 28 days after the last dose of study drug. One or more TEAEs were reported by 96.1% of isavuconazole treated patients and 98.5% of voriconazole treated patients. The 5 most common TEAEs in the isavuconazole or voriconazole treatment groups were nausea (27.6% vs. 23.2%), vomiting (24.9% vs. 28.2%), diarrhea (23.7% vs. 23.2%), pyrexia (22.2% vs. 30.1%), and hypokalemia (17.5% vs 21.6%). A significantly lower incidence of events in isavuconazole treated patients compared to voriconazole treated patients were observed for Hepatobiliary Disorders (8.9% vs. 16.2%), Eye Disorders (15.2% vs 26.6%), and Subcutaneous Tissues Disorders (33.5% vs 42.5%). Overall, more than half of the patients experienced at least 1 serious TEAE. The number of patients who experienced a serious TEAE was 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% versus 0.4%) which were more often experienced by isavuconazole treated patients, and hallucination and visual hallucination, which were experienced by 3 voriconazole and no isavuconazole treated patients. There were fewer isavuconazole than voriconazole treated patients (14.4% vs. 22.8%) who had a TEAE leading to permanent discontinuation of study drug. The most common TEAE leading to discontinuation of

study drug was due to infections and infestations (4.3% vs 5.8%). The proportion of deaths through 28 days after the last dose of study drug and during the study was similar between treatment groups.

Table 19
9766-CL-0104
Overall Adverse Events
Safety Population

	Isavuconazole	**Voriconazole**
# Patients	257	259
Any Treatment Emergent Adverse Event (TEAE)	247 (96.1)	255 (98.5)
Serious TEAE	134 (52.1)	149 (57.5)
TEAE leading to discontinuation of Study Drug	37 (14.4)	59 (22.8)
Deaths through 28 days after the last dose of study drug	62 (24.1)	70 (27.0)
Deaths	81 (31.5)	87 (33.6)

Adapted from Table 54 of 9766-CL-0104 Study Report

The safety data for Study 9766-CL-0103 are presented for the safety population which consisted of 146 isavuconazole patients. One or more TEAEs were reported by 95.2% of patients. The most common TEAEs were vomiting (24.7%), nausea (23.3%), and diarrhea (18.5%). Overall, 61% of the patients experienced at least 1 serious TEAE. The most common serious TEAE were reported in the infections and infestations system organ class with 37.7%. The most common serious TEAE were renal failure acute (5.5%), pneumonia (4.8%), septic shock (4.1%), respiratory failure (3.4%), and abdominal pain (3.4%). Overall, 13.0% of patients had a TEAE that lead to permanent discontinuation of study drug. No TEAE leading to discontinuation of study drug was experienced by more than 2 patients. The proportion of deaths through 28 days after the last dose of study drug was 28.8% and 32.2% during the study.

Table 20
9766-CL-0103
Overall Adverse Events
Safety Population

	Isavuconazole
# Patients	146
Any Treatment Emergent Adverse Event (TEAE)	139 (95.2)
Serious TEAE	89 (61.0)
TEAE leading to discontinuation of Study Drug	19 (13.0)
Deaths through 28 days after the last dose of study drug	42 (28.8)
Deaths	47 (32.2)

Adapted from Table 59 of 9766-CL-0103 Study Report

For a detailed review of the safety data, please see the Clinical Reviewer's review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Findings in special/subgroup populations will only be presented for the randomized, comparative Study 9766-CL-0104.

4.1 Gender, Race, Age, and Geographic Region

Analyses by gender, race, age, and geographic region were conducted for all-cause mortality at Day 42 (ITT) and DRC-assessed overall response at EOT (mITT) for Study 9766-CL-0104. These results are presented in Tables 21 and 22.

Table 21
9766-CL-0104
All-cause Mortality through Day 42 by Gender, Race, Age, and Geographic Region (ITT)

	Isavuconazole	Voriconazole	Difference and 95% CI*
Gender			
Male	27/145 (18.6)	36/163 (22.1)	-3.5 (-13.1, 6.1)
Female	21/113 (18.6)	16/95 (16.8)	1.8 (-9.6, 13.2)
Race			
White	34/211 (16.1)	36/191 (18.8)	-2.7 (-10.6, 5.2)
Black	0/1	0/1	-
Asian	14/45 (31.1)	14/64 (21.9)	9.2 (-9.6, 28.0)
Other	0/1	1/1	-
Age			
≤ 45	16/94 (17.0)	17/101 (16.8)	0.2 (-11.4, 11.8)
45 to ≤ 65	21/108 (19.4)	22/99 (22.2)	-2.8 (-14.8, 9.2)
> 65	11/56 (19.6)	13/58 (22.4)	-2.8 (-19.5, 13.9)
Geographic Region			
US/Canada	5/30 (16.7)	5/28 (17.9)	-1.2 (-24.1, 21.7)
Western Europe/Australia/New Zealand	13/105 (12.4)	25/107 (23.4)	-11.0 (-22.1, 0.1)
Other regions	30/123 (24.4)	22/123 (17.9)	6.5 (4.5, 17.5)

*raw difference (Isa-Vori) and CI calculated based on normal approximation to the binomial.

Table 22
9766-CL-0104
DRC-assessed Overall Response by Gender, Race, Age, and Geographic Region (mITT)

	Isavuconazole	Voriconazole	Difference and 95% CI*
Gender			
Male	26/81 (32.1)	30/84 (35.7)	-3.6 (-19.2, 12.0)
Female	24/62 (38.7)	17/45 (37.8)	0.9 (-19.7, 21.5)
Race			
White	42/115 (36.5)	30/92 (32.6)	3.9 (-10.1, 17.9)
Black	-	0/1	-
Asian	7/27 (25.9)	17/35 (48.6)	-22.7 (-49.4, 4.0)
Other	1/1	-	-
Age			
≤ 45	22/54 (40.7)	17/44 (38.6)	2.1 (-19.4, 23.6)
45 to ≤ 65	19/55 (34.5)	22/63 (34.9)	-0.4 (-19.3, 18.5)
> 65	9/34 (26.5)	8/22 (36.4)	-9.9 (-38.6, 18.8)
Geographic Region			
US/Canada	5/19 (26.3)	9/23 (39.1)	-12.8 (-45.7. 20.1)
Western Europe/Australia/New Zealand	19/50 (38.0)	9/42 (21.4)	16.6 (-3.9, 37.1)
Other regions	26/74 (35.1)	29/64 (45.3)	-10.2 (-28.0, 7.6)

*raw difference (Isa-Vori) and CI calculated based on normal approximation to the binomial.

For gender and age, the results were similar to those seen for the overall population. There were very few subjects of Black or Other Race. However, a possible significant treatment by race interaction is suggested for the analyses of White and Asian patients. Asian patients who were treated with isavuconazole have the lowest efficacy (highest all-cause mortality through Day 42 and lowest DRC-assessed overall response at EOT) and the treatment difference for Asian patients tends to favor voriconazole. Whereas for White patients, the rates are similar between treatment groups. There are no apparent imbalances by race between treatment groups in baseline risk factors (such as uncontrolled malignancy, hematologic malignancy, neutropenia, steroid use, and t-cell immunosuppressant use) that may have an impact on outcome to explain the observed difference. Fewer Asian patients completed treatment with isavuconazole (33% compared to 55% of Asians treated with voriconazole and 48% of Whites treated with isavuconazole and 45% of Whites treated with voriconazole) and as a result they had the shortest treatment duration (median of 35 days compared to 47.5 days for Asians treated with voriconazole, 49 days for Whites treated with isavuconazole, and 46 days for Whites treated with voriconazole).

Further investigation of the Asian population suggests that the difference observed may be driven by the sites from South Korea. The South Korean sites contributed 20 patients to the ITT population and a single site made up 12 of the 20 patients. The all-cause mortality rate through Day 42 for the Korean sites was 62.5% (5/8) for isavuconazole and 8.3% (1/12) for voriconazole. Within the Korean sites, there do not appear to be any treatment imbalances in the risk factors that might have an impact on outcome to explain this difference. Only 1 isavuconazole 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 median

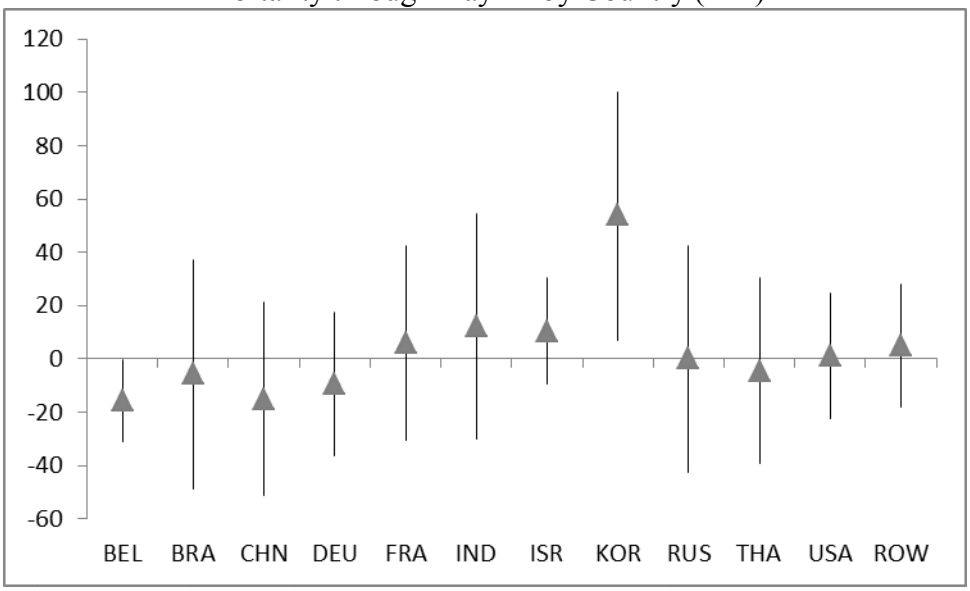
duration of treatment was 15 days for isavuconazole compared to 81.5 days for voriconazole. When a sensitivity analysis is conducted by removing the South Korean sites from the analysis, the all-cause mortality rate through Day 42 for Asian patients is 24.3% (9/37) for isavuconazole and 35.0 (13/52) for voriconazole and the DRC-assessed overall response at EOT for Asian patients is 26.3% (5/19) for isavuconazole and 38.5% (10/26) for voriconazole.

All-cause mortality through Day 42 for isavuconazole patients was numerically lower for the Western Europe/Australia/New Zealand geographic region and numerically higher in the Other regions compared to voriconazole. Similar results were seen with DRC-assessed overall response at EOT where the success rate was higher for isavuconazole in the Western Europe/Australia/New Zealand geographic region and numerically lower in the Other regions compared to voriconazole. The differences observed in the Other regions can be explained the differences observed for Asian patients since the majority of the Asian patients were from Other regions. The differences observed for the Western Europe/Australia/New Zealand geographic region can be partially explained by the results seen for the Belgium sites. Belgium sites were among the highest enrolling sites with 116 patients in the ITT population. For the Belgium sites, the all-cause mortality rate through Day 42 is 9.84% (56/61) for isavuconazole and 25.5% (14/55) for voriconazole and the DRC-assessed overall response at EOT is 34.3% (12/35) for isavuconazole and 13.6% (3/22) for voriconazole.

Reviewer's Comment: *The request for clinical inspections included two sites from Belgium on the basis of being high enrollers. The results of the site inspections are not known at the time of the writing of this review.*

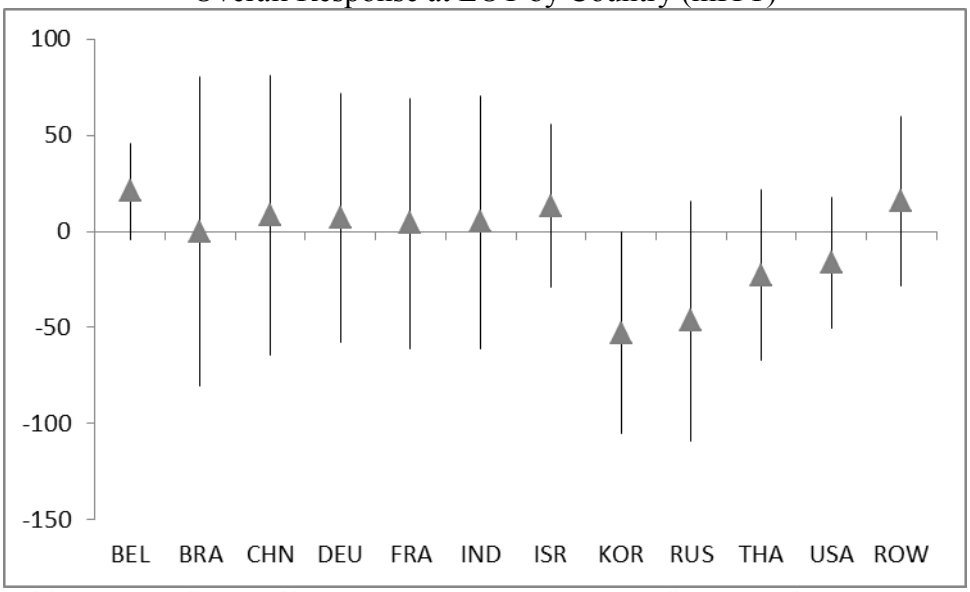
The assessments above are further described by Figures 1 and 2. These are plots of the 95% confidence intervals about the difference (isavuconazole -voriconazole) in all-cause mortality through Day 42 and DRC-assessed overall response at EOT, respectively by country. The countries presented had at least 5 patients in each treatment arm and ROW (rest of world) includes all the remaining countries combined. The confidence intervals are wide because of the relatively small sample sizes within each country.

Figure 1
9766-CL-0104
95% Confidence Interval about the Difference (Isavuconazole- Voriconazole) in All-Cause Mortality through Day 42 by Country (ITT)



BEL: Belgium, BRA: Brazil, CHN: China, DEU: Germany, FRA: France, IND: India, KOR: South Korea, RUS: Russia, THA: Thailand, USA: United States, ROW: Rest of World

Figure 2
9766-CL-0104
95% Confidence Interval about the Difference (Isavuconazole- Voriconazole) in DRC-assessed Overall Response at EOT by Country (mITT)



BEL: Belgium, BRA: Brazil, CHN: China, DEU: Germany, FRA: France, IND: India, KOR: South Korea, RUS: Russia, THA: Thailand, USA: United States, ROW: Rest of World

4.2 Other Special/Subgroup Populations

Other subgroups of interest for Study 9766-CL-0104 include the stratification factors: geographic region, allogeneic BMT status, and uncontrolled malignancy status. Geographic region was discussed in Section 4.1. The results for allogeneic BMT status and uncontrolled malignancy status of all-cause mortality through Day 42 and DRC-assessed overall response at EOT are presented in Tables 23 and 24, respectively. In general, the results were similar between treatment groups for the allogeneic BMT status subgroups for both all-cause mortality through Day 42 and DRC-assessed overall response at EOT and the uncontrolled malignancy status subgroups for all-cause mortality through Day 42. For patients who did not have an uncontrolled malignancy at baseline, the DRC-assessed overall response at EOT was numerically lower in isavuconazole than in voriconazole treated patients.

Table 23
9766-CL-0104
All-cause Mortality through Day 42 by Strata (ITT)

	Isavuconazole	Voriconazole	Difference and 95% CI*
Allogeneic BMT status			
Yes	12/54 (22.2)	9/51 (17.6)	4.6 (-12.5, 21.7)
No	36/204 (17.6)	43/207 (20.8)	-3.2 (-11.3, 4.9)
Uncontrolled Malignancy Status			
Yes	37/173 (21.4)	41/187 (21.9)	-0.5 (-9.6, 8.6)
No	11/85 (12.9)	11/71 (15.5)	-2.6 (-14.9, 9.7)

*raw difference (Isa-Vori) and CI calculated based on normal approximation to the binomial.

Table 24
9766-CL-0104
DRC-assessed overall response at EOT by Strata (mITT)

	Isavuconazole	Voriconazole	Difference and 95% CI*
Allogeneic BMT status			
Yes	8/33 (24.2)	7/27 (25.9)	-1.7 (-27.1, 23.7)
No	42/110 (38.2)	40/102 (39.2)	-1.0 (-15.1, 13.1)
Uncontrolled Malignancy Status			
Yes	32/89 (36.0)	30/89 (33.7)	2.3 (-12.8, 17.4)
No	18/54 (33.3)	17/40 (42.5)	-9.2 (-31.2, 12.8)

*raw difference (Isa-Vori) and CI calculated based on normal approximation to the binomial.

Table 25 presents all-cause mortality through Day 42 by the DRC's categorization of IFD (ITT) and the DRC assessment of the pathogen causing the IFD (mITT) at baseline for Study 9766-CL-0104.

Table 25
9766-CL-0104
All-cause Mortality through Day 42 by Categorization and Pathogen causing IFD

	Isavuconazole	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 mold species	3/3	0/1
Non-Aspergillus species only	3/5	0/6
Mold species NOS	2/14 (14.3)	6/15 (40.0)
No pathogen identified	15/72 (20.8)	16/68 (23.5)

Study 9766-CL-0104 was conducted from March 2007 to March 2013. However, between January 2009 and March 2011 no patients were enrolled. Enrollment was originally suspended pending the completion of *in vivo* genotoxicity studies and was not restarted until after the change in sponsorship from Basilea to Astellas. Therefore, analyses were conducted by enrollment period to determine if there were any temporal differences. Table 26 summarizes the results for all-cause mortality through Day 42 by enrollment period. Voriconazole all-cause mortality rates are fairly consistent regardless of the timing of enrollment. However, isavuconazole mortality rates are higher after the restart of the trial than before the restart. Before the restart of the trial, treatment differences are numerically in favor of isavuconazole. After the restart of the study, the treatment differences are numerically in favor of voriconazole. Overall, the treatment difference is non-inferior when adjusting for enrollment period.

Table 26
9766-CL-0104
All-cause Mortality through Day 42 by enrollment period

	Isavuconazole	Voriconazole	Difference and 95% CI
ITT			-1.5 (-8.3, **5.4**)*
Before restart	24/154 (15.6)	30/150 (20.0)	-4.4 (-13.7, 4.9)**
After restart	24/104 (23.1)	22/108 (20.4)	2.7 (-9.4, 14.8)**
mITT			-3.9 (-13.6, **5.8**)
Before restart	10/78 (12.8)	18/75 (24.0)	-11.2 (-24.7, 2.3)
After restart	18/65 (27.7)	12/54 (22.2)	5.5 (-11.7, 22.7)
mITT-FDA			-3.0 (-12.6, **6.5**)
Before restart	10/78 (12.8)	16/72 (22.2)	-9.4 (-22.9, 4.1)
After restart	18/69 (26.1)	12/56 (21.4)	4.7 (-11.8, 21.2)
myITT			-4.1 (-14.5, **6.3**)
Before restart	7/65 (10.8)	13/63 (20.6)	-9.8 (-23.9, 4.3)
After restart	16/58 (27.6)	11/45 (24.4)	3.2 (-15.8, 22.2)

*adjusted difference (Isa-Vori) and CI calculated using stratified CMH method with the stratum of enrollment period
**raw difference (Isa-Vori) and CI calculated based on normal approximation to the binomial.

Table 27 summarizes the results for DRC- assessed Overall Response EOT by enrollment period. The treatment differences are similar regardless of the time of enrollment. There are lower rates for both treatment groups after the restart of the trial as compared to before the restart.

Table 27
9766-CL-0104
DRC- assessed Overall Response EOT by enrollment period

	Isavuconazole	Voriconazole	Difference and 95% CI
mITT			-1.1 (**-12.5**, 10.3)*
Before restart	31/78 (39.7)	30/75 (40.0)	-0.3 (-17.1, 16.5)**
After restart	19/65 (29.2)	17/54 (31.5)	-2.3 (-20.6, 16.0)**
myITT			-3.3 (**-15.7**, 9.1)
Before restart	26/65 (40.0)	28/63 (44.4)	-4.4 (-23.1, 14.3)
After restart	17/58 (29.3)	14/45 (31.1)	-1.8 (-21.7, 18.1)

*adjusted difference (Isa-Vori) and CI calculated using stratified CMH method with the stratum of enrollment period
**raw difference (Isa-Vori) and CI calculated based on normal approximation to the binomial.

Characteristics of the patients enrolled before and after the restart were investigated to determine any impact on the results observed above by enrollment period for the ITT population. Following the restart, there was an increase in the proportion of patients enrolled from outside the US/ Canada and Western Europe/Australia/New Zealand. This is also reflected by the increase in the proportion of Asians enrolled following the restart (15% before restart compared to 30% after restart). There was also an increase in the proportion of patients with an uncontrolled malignancy at baseline enrolled after the restart compared to prior to the restart (66% before restart compared to 75% after restart). Additionally, there was an increase in the proportion of isavuconazole patients who were neutropenic (61% before restart compared to 66% after restart) and a decline in the proportion of voriconazole subjects with T-cell immunosuppressant use (45% before restart compared to 39% after restart). Based on these factors, the apparent enrollment period effect would be an increased morbidity burden from the increased uncontrolled malignancy at baseline in the period after the restart of enrollment compared to before the restart. This difference could also be accentuated in the isavuconazole group compared to the voriconazole group due to the additional increase in the proportion of neutropenic patients.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The assessment of efficacy of isavuconazole for the treatment of invasive aspergillosis is one based on showing non-inferiority of isavuconazole compared to voriconazole with respect to all-cause mortality at Day 42. The justification of non-inferiority margin of 10% is based on multiple sources of data. The estimate of the response for voriconazole is based on the original registration trial 307/602 for voriconazole in which voriconazole was shown to be superior to amphotericin B for the treatment of aspergillosis and is supplemented by additional data from a recent trial in which voriconazole was compared to voriconazole plus anidulafungin. The study

design of these two trials was similar to the current Study 9766-CL-0104 including patient population. In addition, a literature search was conducted to derive an estimate of the effect of placebo (no treatment) as well as an historical estimate of the effect of amphotericin B.

Table 28
All-cause mortality at Day 42 for Voriconazole

	Voriconazole	**Amphotericin B**	**Difference (95% CI)**
Study 307/602	27/144 (18.8) (12.7, **26.1**)	46/133 (34.6)	-15.8 (-26.1, **-5.5**)
Voriconazole + Anidulafungin Study	39/142 (27.5) (20.3, **35.6**)	NA	NA
Pooled (raw)	66/286 (23.1) (18.3, **28.4**))	NA	NA
Pooled (meta-analysis)	22.9 (14.4, **31.4**)	NA	NA

Table 29
All-cause mortality at Day 42 for Placebo and Amphotericin B from Literature Search

	Mortality Day 42
Placebo	21/21 (**83.9**, 100)
Amphotericin B	82/137 (59.9) (51.1, **68.1**)
Effect of Amphotericin B over placebo	68.1-83.9= -15.8

The estimate of the effect of voriconazole over placebo was determined based on a direct comparison of the voriconazole estimates to the placebo estimates as well as an indirect comparison of the the effect of voriconazole compared to amphotericin B plus the effect of amphotericin B over placebo. These results are presented in Table 30.

Table 30
Estimate of the Effect of Voriconazole Over Placebo for All-cause Mortality at Day 42

	Mortality Day 42
Direct (vori - placebo)	26.1-83.9=-57.8
Direct (vori - placebo) pooled vori data	31.4-83.9= -52.5
Indirect [(vori - amphotericin B) +(amphotericin B - placebo)]	-5.5 + ½(-15.8)=-13.4

Based on the direct estimates of voriconazole over placebo, the M1 can be estimated to be approximately 52% to 58%. A highly conservative estimate of M1 comes from the indirect method which is based on the effect of voriconazole over amphotericin B seen from Study 307/602 and a discounted effect of amphotericin B over placebo derived from the literature. This estimate is approximately 13%. Therefore, a non-inferiority margin of 10% based on clinical judgment for M2 is acceptable for assessing all-cause mortality through Day 42.

The key secondary endpoint in Study 9766-CL-0104 was DRC-assessed overall response at EOT. Based on historical data available, an estimate for M1 for overall response at EOT cannot be derived. However, data is available to provide an estimate for M1 for global (overall) response at Week 6. This data suggests that M1 is at least 20%. Therefore, a non-inferiority margin of 15% for an endpoint of global response at Week 6 has been accepted for an ongoing clinical trial of another investigational drug. Since the median total duration of treatment in Study 9766-CL-0104 was 45 days, which is approximately 6 weeks, the clinical interpretive criterion of 15% that was specified by the Applicant for assessing DRC-assessed overall response at EOT is acceptable.

The basis of approval for the treatment of invasive mucormycosis indication is the subgroup of patients with invasive mucormycosis enrolled in the open-label, non-comparative trial of isavuconazole, Study 9766-CL-0103. The Applicant conducted a review of the published literature to review the natural history of invasive mucormycosis and to provide historical antifungal comparator data to facilitate the interpretation of the efficacy data from Study 9766-CL-0103. While it is acknowledged that invasive mucormycosis is associated with a high mortality in the setting of no antifungal treatment, there is minimal data available to provide an actual estimate of mortality in the setting of no antifungal treatment. Two articles referenced by the Applicant provided information on patients who did not receive antifungal treatment. The paper by Roden et al (2005) indicated an overall mortality rate of 97% for cases that were not treated. Most of these cases, however, were identified post-mortem. Of the 241 patients who received no treatment, 8 survived, 18 were diagnosed pre-mortem, and 215 were diagnosed post-mortem. So of those who had a diagnosis pre-mortem, the mortality rate was 69.2% (18/26) with a 95% confidence interval of (49.6%, 88.9%). However, details regarding the underlying condition of these specific patients are not discernable from the available information. Thus, making the use of this information limited since it is unknown if the patient population is comparable to that in Study 9766-CL-0103. In the article by Skiada et al (2011), a total of 24 patients received no treatment: 10 were diagnosed post-mortem and 14 were diagnosed during the last 24 hours prior to death. This study therefore offers limited support. There was a third article (Chamilos, 2008) that looked at the effect of delaying antifungal therapy in a population with hematologic malignancy. Based on this article, a delay of at least 6 days in treatment resulted in a 12 week mortality of 82.9% for the 35 patients [95% confidence interval (68.9, 96.8)]. The use of this information is also limited in that it represents a delay of treatment of at least 6 days and not the absence of treatment although it might be considered a conservative estimate of no treatment. One additional concern is the reason for the delay in treatment. While all patients were treated with an antifungal for at least a presumed fungal infection, it is not known if those patients who died were not definitively diagnosed with mucormycosis until post-mortem. Therefore, in the absence of an estimate of mortality in the setting of no antifungal treatment, inferential testing of the isavuconazole data is not possible. The determination of the effectiveness of isavuconazole will be based on a clinical assessment of the results.

5.2 Collective Evidence

The pivotal evidence to support the efficacy of isavuconazole for the treatment of invasive aspergillosis was based on the single Phase 3 trial, Study 9766-CL-0104. This trial showed that treatment with isavuconazole was non-inferior to voriconazole with respect to all-cause mortality

through Day 42. The all-cause mortality rate through Day 42 in the ITT population was 18.6% in the isavuconazole group and 20.2% in the voriconazole group. The upper bound of the 95% confidence interval of the adjusted difference (isavuconazole - voriconazole) was 5.9% and lower than the prespecified and justified 10% non-inferiority margin. The results are robust across the various populations based on patients with proven or probable IFD/aspergillosis. The adjusted treatment difference for the various populations with proven or probable IFD/aspergillosis ranged from -2.7% to -2.1%. The upper bound of the 95% confidence interval around the adjusted treatment difference across these populations ranged from 7.3% to 8.2% and is all lower than the 10% non-inferiority margin. The key secondary endpoint of DRC assessed overall response at EOT was similar between treatment groups (35.0% for isavuconazole and 36.4% for voriconazole, mITT population). The lower bound of the 95% confidence interval about the adjusted treatment difference is -12.8% which is greater than the clinical interpretive criterion of -15%.

Additionally, 24 patients in Study 9766-CL-0103 were assessed by the DRC as having only an *Aspergillosis* infection. Twenty of these 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 all patients with only an *Aspergillosis* infection and 30.0% for those that were renally impaired. Although the number of patients is small, the results including those of renally impaired patients are similar to those observed in Study 9766-CL-0104.

The pivotal evidence to support the efficacy of isavuconazole for the treatment of invasive mucormycosis was based on the single open-label Phase 3 trial, Study 9766-CL-0103. This study enrolled 46 patients with mucormycosis, 37 were assessed by the DRC as having proven or probable invasive mucormycosis infection only, 1 was assessed as having possible Mucorales infection and the remaining 8 patients had mixed infections. Of the 37 proven or probable invasive mucormycosis infection only patients, 21 received isavuconazole as primary therapy. The all-cause mortality rate through Day 42 was 37.8% for those with proven or probable invasive mucormycosis infection only and 33.3% in the primary therapy patients. The DRC assessed overall response at EOT was 31.4% for those with proven or probable invasive mucormycosis infection only and 31.6% in the primary therapy patients.

In order to compare the efficacy of isavuconazole in the treatment of mucormycosis with the efficacy of standard of care therapy used in clinical practice, patients who were assessed by the DRC as having proven or probable invasive mucormycosis infection only and received isavuconazole as primary therapy were matched with patients from the Fungiscope Registry Database. The Fungiscope Registry is global web-based database coordinated from the Clinical Trials Center at the University of Cologne, Germany. It contains the largest collection of information on rare fungal infections, including more than 150 cases of invasive mucormycosis diagnosed and treated between 2003 and 2013. Patients from Study 9766-CL-0103 were matched with up to 3 controls from the Fungiscope Registry Database based on the 3 most relevant factors considered to be predictive of outcome in patients with invasive mucormycosis. These factors are: severe disease defined as CNS involvement or disseminated disease, surgery intended as therapeutic intervention defined as resection/debridement at the site of infection 7 days prior to or after the start of their primary treatment, and underlying condition of

hematologic malignancy. The 21 primary therapy isavuconazole patients in Study 9766-CL-0103 were matched to 33 Fungiscope controls. All of the Fungiscope matched controls received treatment with some form of amphotericin B therapy as primary treatment and 12 controls were switched to posaconazole for continued therapy. All-cause mortality through Day 42 rates were 33.3% (7/21) with a 95% confidence interval (14.6, 57.0) for the Study 9766-CL-0103 isavuconazole cases and 39.4% (13/33) with a 95% confidence interval (22.9, 57.9) for the Fungiscope matched controls. While a direct comparison of the isavuconazole cases with the Fungiscope matched controls is not made due the inability to define a non-inferiority margin for assessing the effect of treatment with amphotericin B over no therapy, the all-cause mortality rate through Day 42 for isavuconazole appears to be consistent with that seen for the Fungiscope matched controls who primarily received some form of amphotericin B which is the only anti-fungal approved for invasive mucormycosis.

5.3 Conclusions and Recommendations

Based on the results of the Phase 3 trial Study 9766-CL-0104, all-cause mortality through Day 42 was shown to be non-inferior for isavuconazole as compared to voriconazole for the treatment of patients with proven or probable aspergillosis. Additionally, the rates of DRC-assessed overall response at the EOT were similar between isavuconazole and voriconazole treated patients. Although only a limited number of subjects with renal impairment and invasive aspergillosis were studied in Study 9766-CL-0103, the results for all-cause mortality through Day 42 and of DRC-assessed overall response at the EOT were similar to those seen in Study 9766-CL-0104 for patients treated with isavuconazole. Therefore, there is adequate evidence of efficacy to support the indication of treatment of invasive aspergillosis for isavuconazole.

The results of the subgroup of patients with invasive mucormycosis from Study 9766-CL-0103 indicate an all-cause mortality rate through Day 42 of 37.8% with exact 95% confidence interval (22.5, 55.2) and a DRC-assessed overall response rate at EOT of 31.4% with exact 95% confidence interval (16.9, 49.3) from treatment with isavuconazole. While inferential testing to define the benefit of isavuconazole treatment relative to no treatment or even to another active anti-fungal is not possible, these results do indicate some evidence of efficacy for isavuconazole in the treatment of invasive mucormycosis. In conjunction with the successful outcome of the larger randomized, comparative Study 9766-CL-0104 in invasive aspergillosis, another difficult to treat fungal infection, it is recommended that the results of Study 9766-CL-0103 be considered adequate evidence of efficacy to support the indication of treatment of invasive mucormycosis for isavuconazole. The final decision, however, is left to the Medical Division.

5.4 Labeling Recommendations

The following are recommendations for Section 14.1 Treatment of Invasive Aspergillus:

- The Applicant is proposing to report for Study 9766-CL-0104 the results of all-cause mortality through Day 42 for the ITT and mITT populations and the results of DRC-assessed overall results at EOT for the mITT population. Since the actual indication requested is the treatment of invasive aspergillosis, it is recommended that the results for the myITT population, i.e. proven or probable aspergillosis also be included. The confidence intervals presented throughout this review were based on a slightly different method of calculation conducted by this reviewer. Since there are not differences in the

interpretation of the results, the confidence intervals presented in the labeling can use those calculated by the Applicant. Thus, the following is recommended for Tables 7 and 8 as described in the proposed labeling:

Table 7. All-Cause-Mortality Through Day 42

	CRESEMBA		Voriconazole		
	N	**All-cause Mortality n (%)**	**N**	**All-cause Mortality n (%)**	**Difference[a] (95% CI)%**
ITT	258	48 (18.6)	258	52 (20.2)	-1.0 (b) (4)
(b) (4)					
Proven or Probable Aspergillosis	123	23 (18.7)	108	24 (22.2)	-2.7 (b) (4)

[a]Adjusted treatment difference (CRESEMBA-voriconazole) by Cochran-Mantel-Haenszel method stratified by the randomization factors

Table 8. Overall Response Success at End of Treatment

	CRESEMBA		Voriconazole		
	N	**Success n (%)**	**N**	**Success n (%)**	**Difference[a] (95% CI) %**
(b) (4)					
Proven or Probable Aspergillosis	123	43 (35.0)	108	42 (38.9)	(b) (4)

[a]Adjusted treatment difference (voriconazole-CRESEMBA) by Cochran-Mantel-Haenszel method stratified by the randomization factors

- Although Study 9766-CL-0103 provided supportive information for the treatment of invasive aspergillosis indication, the results do not add to the information available from Study 9766-CL-0104 for understanding the efficacy of isavuconazole. (b) (4)

The information proposed by the Applicant to be included in Section 14.2 Treatment of Invasive Mucormycosis is acceptable.

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/s/

CHERYL A DIXON
12/08/2014

KAREN M HIGGINS
12/08/2014
I concur.

TSAE YUN D LIN
12/08/2014

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 207500 and 207501

Applicant: Astellas

Stamp Date: July 8, 2014

Drug Name: Cresemba (isavuconazonium sulfate) capsules and intravenous infusion

NDA/BLA Type: Priority

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____
If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant. N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. N/A

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

These NDAs are for Cresemba (isavuconazonium sulfate). NDA 207500 is for the hard capsules and NDA 207501 is for the intravenous infusion. The proposed indications for Cresemba are the treatment of invasive aspergillosis and invasive mucormycosis in patients 18 years of age and older. Isavuconazonium sulfate is designated as a Qualified Infectious Disease Product and has an Orphan drug-designation. Isavuconazole is the active moiety of isavuconazonium sulfate.

The invasive aspergillosis indication is supported by a phase 3 study (Study 9766-CL-0104). This was a randomized, double-blind, noninferiority, comparative group study, which evaluated the efficacy and safety of isavuconazole 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 indication is also supported by data from patients with renal impairment that were enrolled in the open-label phase 3 study (Study 9766-CL-0103). Study 9766-CL-0103 was an open-label, multicenter, single arm study of isavuconazole for the treatment of invasive aspergillosis in patients with renal impairment or in patients with IFD caused by rare moulds, yeasts or dimorphic fungi.

The invasive mucormycosis is supported by data from a subpopulation of patients enrolled in Study 9766-CL-0103, who were confirmed to have proven or probable invasive mucormycosis as determined by an independent Data Review Committee. The mucormycosis results from Study 9766-CL-0103 are supplemented by a literature review as well as a matched-case control analysis using the Fungiscope Registry Database.

Cheryl Dixon, Ph.D.	8/13/14
Reviewing Statistician	Date
Karen Higgins, Sc.D.	8/13/14
Supervisor/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/

CHERYL A DIXON
08/13/2014

KAREN M HIGGINS
08/13/2014