

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207500Orig1s000 / 207501Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	207500	Reviewer: Banu Sizanli Zolnik, Ph.D.	
Division:	DAIP	Team Leader (Acting): Elsbeth Chikhale, Ph.D.	
Applicant:	Astellas Pharma	Biopharmaceutics Supervisory Lead (Acting): Paul Seo, Ph.D.	
Trade Name:	Cresemba		
Generic Name:	Isavuconazonium sulfate	Date Assigned:	July 15, 2014
Indication:	For the treatment of invasive aspergillosis and invasive mucormycosis in patients 18 years of age and older	Date of Review:	December 23, 2014
Dosage Form/ strength	Capsules/186.3 mg of isavuconazonium sulfate (equivalent to 100 mg isavuconazole)	Route of Administration: Oral	
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission Dates July 8, 2014 (Original Submission) September 26, 2014 (Sequence 0006) October 8, 2014 (Sequence 0008) December 11, 2014 (Sequence 0015) December 18, 2014 (Sequence 0017)		Date of informal/ Formal Consult	PDUFA DATE
		NA	March 8, 2015
Type of Submission:	505 (b) (1)		
Key review points	Evaluation of dissolution method and acceptance criterion		

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I) SUMMARY OF BIOPHARMACEUTICS FINDINGS

Submission:

This 505 (b)(1) NDA submission contains new molecular entity isavuconazonium sulfate in a hard capsule oral formulation. Isavuconazonium sulfate is a water-soluble triazole prodrug. Isavuconazole acts by inhibiting sterol 14-alpha-demethylase, a microsomal p450 enzyme essential for ergosterol biosynthesis in fungi. Isavuconazonium is indicated for the treatment of invasive aspergillosis and invasive mucormycosis in patients 18 years of age and older

The following dissolution method and acceptance criterion for isavuconazonium sulfate capsules are agreed upon and are acceptable for batch release and stability testing.

USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
USP II (paddle)	75 rpm	900 mL	37°C	Diluted McIlvaine buffer* + 0.5% Sodium lauryl sulfate	Q = 75% at 75 minutes

* Diluted McIlvaine buffer: Mix disodium hydrogen phosphate solution 12.5 mM and Citric acid solution 6.25 mM to attain a pH 6 solution.

II) RECOMMENDATION

ONDQA-Biopharmaceutics had reviewed NDA 207500 for isavuconazonium sulfate capsules and its amendments Seq. 0006, 0008, 0015 and 0017 submitted on September 26, October 8, December 11, and December 18, 2014, respectively. From the Biopharmaceutics perspective, NDA 207500 for Cresamba (isavuconazonium sulfate) capsules is recommended for **APPROVAL**.

Banu Sizanli Zolnik, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Team Leader (Acting)
Office of New Drug Quality Assessment

**Banu S.
Zolnik -S**

Digitally signed by Banu S. Zolnik -S
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Date: 2014.12.23 14:37:15 -05'00'

**Elsbeth G.
Chikhale -S**

Digitally signed by Elsbeth G. Chikhale -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300136142, cn=Elsbeth G. Chikhale -S
Date: 2014.12.23 14:53:01 -05'00'

III) QUESTION BASED REVIEW – BIOPHARMACEUTICS EVALUATION

A) GENERAL ATTRIBUTES

- 1 What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?**

Isavuconazonium sulfate is an amorphous material. The solubility of the drug substance is greater than 1 g/mL in any of the pH conditions. The exact saturation solubility was difficult to be determined due to degradation. Isavuconazonium sulfate was designed as a water soluble prodrug with its high solubility. Physicochemical properties of the drug substance are summarized in Table 1 below.

Table 1 Summary of General Properties

Items	Results
Appearance	White powder
Melting Point (by DSC)	No melting point is observed.
pH (1%(w/v))	(b) (4)
Dissociation Constant (pKa)	2.0, 7.3
Specific Rotation (10 mg/mL in methanol)	-12°
Partition Coefficient (cLog P [†])	-1.31
Solubility Profile [‡] (At room temperature, 20±5°C)	Water > 1.0 g/mL (very soluble) (b) (4)
	(b) (4)

[†] Log P calculated by the software "ACD/Percepta 14.0.0 (Build 2203)" (Advanced Chemistry Development, Inc.)

[‡] Description according to USP and Ph. Eur. definitions of solubility

Drug Product

Isavuconazonium sulfate capsules are hard capsules which contains 186.3 mg isavuconazonium sulfate corresponding to 100 mg isavuconazole. The composition of the formulation is described in Table 2 below.

Table 2 Composition of Isavuconazonium Sulfate Capsules

Components	Reference Quality Standard	Function	Quantity (mg/capsule)
Isavuconazonium sulfate	In house	Drug substance	186.3 (corresponding to 100 isavuconazole)
Magnesium citrate	USP		(b) (4)
Microcrystalline cellulose	NF		
Talc	USP		
Colloidal silicon dioxide	NF		
Stearic acid	NF		
	(b) (4)		(b) (4)
Capsule (size #0 elongated)	-	Capsule shell	
Ink	(b) (4)	Ink	
Total capsule weight (mg)			695.9

USP: United States Pharmacopeia, NF: National Formulary

(b) (4)

- 2 **Is there any information on BCS classification? What claim did the applicant make based on BCS classification? What data are available to support this claim?**

The Applicant claimed isavuconazonium sulfate as a BSC class 1 (high solubility and high permeability) drug based on its (b) (4). The Applicant stated that the active moiety isavuconazole is highly permeable based on its mean absolute bioavailability of 98% following a single oral dose of isavuconazonium sulfate hard capsules (equivalent to 400 mg isavuconazole).

- 3 **Does the proposed product meet the extended release designation claim? What data are provided to support the Applicant's claim?**

NA

B) DISSOLUTION INFORMATION

B.1. DISSOLUTION METHOD

- 4 **What is the proposed dissolution method?**

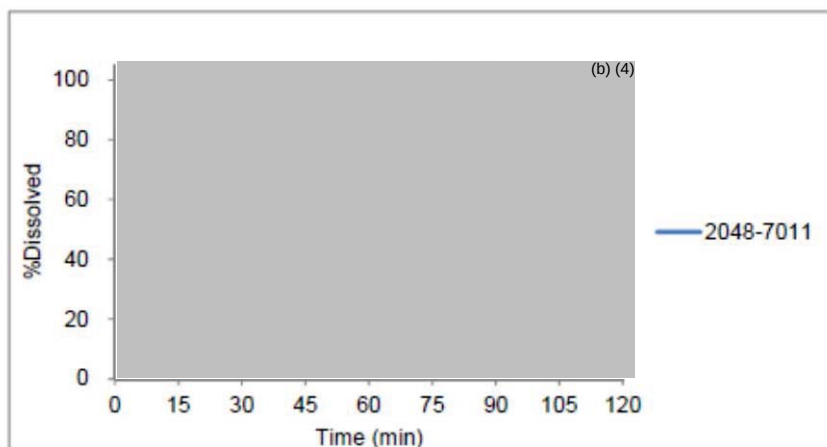
The dissolution method proposed as a quality control test for isavuconazonium sulfate is summarized below:

USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium
USP II (paddle)	75 rpm	900 mL	37°C	Diluted McIlvaine buffer* + 0.5% sodium lauryl sulfate (SLS)

* Diluted McIlvaine buffer: Mix disodium hydrogen phosphate solution 12.5 mM and Citric acid solution 6.25 mM to attain a pH 6 solution.

The Applicant provided dissolution data of 13 clinical batches and 3 registration batches (Figure 1 below). The batch 2048-7011 is the biobatch used in the absolute bioavailability study. Although this batch showed the slowest dissolution profile amongst all the batches, this batch demonstrated 98% bioavailability.

Figure 1 Dissolution of 13 Clinical Batches and 3 Registration Batches of Isovuconazonium Sulfate Hard Capsules (Apparatus 2, 75 rpm, diluted McIlvaine Buffer pH 6 with 0.5% SLS)



The blue line represents the dissolution profile of the batch 2048-7011, which is a biobatch used in the absolute bioavailability study (9766-CL-0010). The black lines represent the dissolution profiles of the other 12 clinical batches and 3 registration batches.

FDA Request (74-Day Letter dated September 16, 2014):

1. *We could not locate in your NDA submission the complete dissolution profile data for the clinical and registration batches of your drug product. Please provide the data collected at 15, 20, 30, 45, 60, 75 and 90 minutes for the clinical and registration batches (i.e., individual, mean, SD, profiles; n=12); or if submitted, indicate where these data are located.*
2. *To support the bridging between the clinical and commercial drug products, provide the dissolution profile comparison data (n=12) with the statistical testing comparing the profiles for the clinical and commercial batches using the proposed dissolution method.*

Please note, that if the percent coefficient of variation is higher than 20% for earlier time points (i.e., 10, 15 min) or higher than 10% for the other time points the f2 test cannot be used and therefore alternative methods (i.e., multivariate model independent or dependent approaches) should be used to estimate the profiles similarity. For detail information on the requirements/limitations of f2 testing, please refer to the dissolution guidance (FDA CDER Guidance for Industry-Dissolution Testing of Immediate Release Solid Oral Dosage Forms” August 1997). If an alternative method is used, include all the input and output files generated for this analysis.

B.2. ACCEPTANCE CRITERIA

10

What are the proposed dissolution acceptance criteria for this product?

Proposed Dissolution Acceptance Criteria for Isavuconazonium Capsules	
Q	(b) (4)% at 75 minutes

11 What data are available to support these criteria?

**Table 18 Dissolution Data at (b) (4) min of the Historical Batches.
(Apparatus 2, 75 rpm, diluted McIlvaine buffer pH6.0 with 0.5% SLS)**

Batch		Acceptance criteria	%Dissolution Mean (Min – Max)
Registration stability	2048-11501A	Q = (b) (4)% at 75 min	(b) (4)
Registration stability	2048-11502A		
Registration stability	2048-11503A		
Clinical	459A0010		
Clinical	459A0020		
Clinical	2048-7010		
Clinical	2048-7011		
Clinical	2048-8013		
Clinical	2048-8014		
Clinical	2048-09101		
Clinical	2048-10102A ⁽¹⁾		
Clinical	2048-10102B ⁽¹⁾		
Clinical	2018-11101		
Clinical	2048-11102		
Clinical	2048-11104		
Clinical	2048-12101		

The Applicant's proposed dissolution acceptance criterion is (b) (4). The below comment was sent to the Applicant in the IR request dated December 08, 2014.

- *We do not agree with the acceptance criterion Q = (b) (4)% at 75 minutes you proposed for the dissolution method and recommend that you set the dissolution acceptance criterion as Q (b) (4)% at 75 minutes for your proposed product. This recommendation is based on the in vitro performance of the clinical and stability batches. Please submit an updated Drug Product Specification Table and Stability Protocol as amendment to the NDA by December 11, 2014 reflecting this recommendation.*

Reviewer's Assessment for the Applicant's Response provided in the amendment dated December 11, 2014 (Seq. 0015) – NOT SATISFACTORY

The Applicant did not accept the FDA recommended acceptance criterion, and proposed Q = (b) (4)% at 75 minutes. They provided dissolution data for 3 registration batches, 1 validation batch and 14 clinical batches. The Applicant stated that 5 (4 clinical batches

and 1 process validation batch) out of the 18 batches have individual values lower than (b) (4) % at 75 minutes (b) (4). However, it is the ONDQA-Biopharmaceutics team's opinion that, based on a mean dissolution values around (b) (4) % at 75 minutes for the registration batches, and a mean dissolution values around (b) (4) % at 75 minutes for the clinical batches, the FDA proposed dissolution acceptance criterion (Q = (b) (4) % at 75 minutes) is appropriate for the proposed drug product. The below comment with a t-con request was sent to the Applicant via email on December 15, 2014.

- ***We acknowledge your amendment (Seq. 0015) dated December 11, 2014. We don't agree with your proposal for the dissolution acceptance criterion of Q = (b) (4) % at 75 minutes. It should be noted that the setting of the dissolution acceptance criteria is based on mean values and therefore, it must be recognized that some batches may require (b) (4) (b) (4) with the FDA's recommended dissolution acceptance criterion of Q = (b) (4) % at 75 minutes. Therefore, revise and submit your drug product specifications and stability protocol accordingly.***

During the t-con on 12/17/2014, the ONDQA-Biopharmaceutics review team and the Applicant discussed the acceptance criterion for the dissolution method. The FDA reiterated that the provided dissolution data do not support the Applicant's proposed dissolution acceptance criterion (Q = (b) (4) % at 75 minutes) and explained that it is acceptable that some batches (b) (4). FDA also stated that based on the provided data with mean dissolution values around (b) (4) % at 75 minutes for the registration batches, and mean dissolution values around (b) (4) % at 75 minutes for the clinical batches, the FDA proposed dissolution acceptance criterion (Q = (b) (4) % at 75 minutes) is appropriate for the proposed drug product. The Applicant expressed their concern of too many future commercial batches going to (b) (4) and proposed Q = (b) (4). FDA stated that this proposal is not acceptable and is not based on the provided data.

Reviewer's Assessment for the Applicant's Response provided in the amendment dated December 18, 2014 (Seq. 0017) – SATISFACTORY

The Applicant accepted the FDA proposed acceptance criterion of Q = (b) (4) % at 75 minutes in an amendment (Seq 0017 dated 12/18/2014).

- 12 Is the acceptance criterion acceptable? If not, what is the recommended criterion? Is the setting of the dissolution acceptance criterion based on data from clinical and registration batches? If not, is the setting based on BE or IVIVC data?**

An agreement has been reached (Seq.0017) for the dissolution acceptance criterion based on the clinical and registration batches.

FDA and the Applicant agreed Dissolution Acceptance Criterion
Q= (b) (4) % at 75 minutes

C) DRUG PRODUCT FORMULATION DEVELOPMENT AND BRIDGING ACROSS PHASES

13 What are the highlights of the drug product formulation development?

The initial formulation development i.e. Phase 1 and Phase 2 was conducted with isavuconazonium chloride as the drug substance. Due to the formation related (b) (4) the salt form of isavuconazonium was switched from chloride salt to the sulfate salt.

The proposed commercial formulation is the same as the formulation that has been used in Phase 3 clinical studies except color and imprint of the capsule shells. This change in color and imprint is not expected to impact in vivo performance of the capsules.

14 Are all the strengths evaluated in the pivotal clinical trials? What data are available to support the approval of lower strengths?

NA

15 Are there any manufacturing changes implemented (e.g. formulation changes, process changes, site change, etc.) to the clinical trial formulation? What information is available to support these changes?

Refer to the response in Question 13.

D) DISSOLUTION APPLICATIONS

D.1 BIOWAIVERS

16 Is there a request for a waiver of the submission of in vivo BE data (Biowaiver)? What is the purpose of the biowaiver request?

N/A

17 Is there any in vitro alcohol dose-dumping information submitted? What data are provided to support the Applicant's claim of lack of dose-dumping in the presence of alcohol?

N/A

18 Is there any IVIVC information submitted? What is the regulatory application of the IVIVC in the submission? What data is provided to support the acceptability of the IVIVC?

N/A

D.2 SURROGATES IN LIEU OF DISSOLUTION

- 19** Are there any manufacturing parameters (e.g. disintegration, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data is available to support this claim?

N/A

D.3 DISSOLUTION AND QBD

- 20** If the application contains QbD elements, is dissolution identified as a CQA for defining design space?

N/A

- 21** Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution? What is the risk assessment been performed to evaluate the criticality of dissolution?

The Applicant evaluated the potential impact of formulation attributes on the final product quality by employing a design of experiments (DoE) approach. Dissolution was selected as one of the quality attributes. The amount of (b) (4) in the formulation was identified as having a (b) (4) as shown Table 3.

Table 3 Potential Impact of Formulation Attributes on Product Quality: Risk Levels of Isavuconazonium Sulfate Hard Capsules, Sorted by Quality Attributes of Drug Products

Product Critical Quality Attributes	Risk Level
Dissolution	(b) (4)
Appearance of the capsule shell	
Appearance of the capsule content	
Assay	
Uniformity of dosage units	
Related Substances	
2-butenal	
Stability	

(b) (4)

Based on the design of experiments as shown in Table 4 below, various formulations were prepared (Table 5).

Reviewer's Comment:

As shown in Table 5, dissolution was not affected by the formulation attributes, at (b) (4) minutes almost (b) (4) % of drug is released and there are no trends observed upon storage of the samples.

22 What biopharmaceutics information is available to support the clinical relevance of the proposed design space?

N/A

23 Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?

N/A

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA#	207,500 and 207501
Date of Original Submission	July 04, 2014
Brand Name	Cresemba [®]
Generic Name	Isavuconazonium sulfate
Strength and Formulation	200 mg IV lyophilized powder for infusion and 100 mg capsule
Sponsor	Astellas Inc.
Indication	Treatment of invasive aspergillosis and invasive mucormycosis
Submission Type	Original NDA (NME), Priority.
Clinical Pharmacology Review Team	Dakshina M. Chilukuri, Philip Colangelo, Jeffry Florian, Yang He, Dhananjay Marathe, Islam Younis and Yongheng Zhang

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EXECUTIVE SUMMARY

Isavuconazonium sulfate is a water-soluble triazole antifungal agent that has been developed for use in adult patients for the treatment of life-threatening invasive fungal infections such as invasive aspergillosis (IA) and invasive mucormycosis (IM). Isavuconazonium sulfate is available as a sterile lyophilized powder for intravenous infusion and as hard gelatin capsules for oral administration. Isavuconazole is the active moiety of isavuconazonium sulfate.

Isavuconazole inhibits the cytochrome P450 dependent lanosterol-14 α -demethylase in yeasts and moulds. Isavuconazole has in vitro antifungal activity against *Aspergillus* spp. with MIC₉₀ ranging from 1 to 2 mg/L. In vivo, isavuconazole reduced tissue fungal burden and/or increased the survival rate in animal models of *Aspergillus* spp., *R. oryzae*, or *Candida* spp. fungal infections. Like other triazoles, the pharmacodynamic parameter AUC/MIC correlated with treatment outcome as demonstrated in in vitro studies and in vivo animal studies. In vivo and in vitro dynamic models utilizing both wild-type and isolates with elevated MICs to triazoles or well-characterized mutations in the target gene demonstrated that efficacy could be optimized by increasing the isavuconazole concentrations.

The evidence in support of approval for the indication of IA is provided by data from a single Phase 3 study, Study 9766-CL-0104. This was a randomized, double-blind, noninferiority, active-controlled study, which randomized 527 adult patients with suspected invasive fungal disease (IFD) caused by *Aspergillus* species or other filamentous fungi. Patients were to remain on therapy until they had reached a treatment endpoint or until they had received treatment for a maximum period of 84 days. Evidence for the efficacy of isavuconazole in renally impaired patients comes from Study 9766-CL-0103. This was an open-label trial that enrolled renally impaired patients with IFD caused by *Aspergillus* species or patients with IFD caused by rare molds, yeasts or dimorphic fungi.

The indication of IM is supported by data from a subpopulation of patients enrolled in Phase 3 Study 9766-CL-0103 who were confirmed to have proven or probable IM as determined by an independent Data Review Committee (DRC). Patients in this study received isavuconazole for primary therapy or for salvage therapy, in case of refractory infection or intolerance of prior antifungal therapy. The efficacy of isavuconazole for the primary treatment of IM from Study 9766-CL-0103 was also assessed in the context of published literature on the treatment of mucormycosis and case-matching from a global registry database.

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

Isavuconazole is extensively distributed with a steady state volume of distribution (V_{ss}) of approximately 450 L after IV administration. Isavuconazole is highly protein bound (> 99%), predominantly to albumin. Isavuconazole is a sensitive CYP3A substrate, an inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 and an inducer of CYP3A4/5, CYP2B6, CYP2C8, and CYP2C9. The population mean half-life of isavuconazole was approximately 130

hours for both routes of administration across a range of isavuconazonium doses, suggesting that the elimination process of isavuconazole is not dependent on dose or route of administration. The absolute oral BA of isavuconazole administered as capsules was 98%.

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

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

(b) (4)

1.1. Recommendation

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

Decision	Acceptable to OCP?	Comment
Overall	☒ Yes ☐ No ☐ NA	Pending labeling agreements with the sponsor.
Proposed dose regimen	☒ Yes ☐ No ☐ NA	Loading dose of 200 mg every 8 hours, for 48 hours (6 total doses), via

		oral or IV administration and a maintenance dose of 200 mg once per day via oral or IV administration, starting 12 to 24 hours after the last loading dose
Pivotal BE	☐ Yes ☐ No ☒ NA	No pivotal BE study required
Labeling	☒ Yes ☐ No ☐ NA	Pending satisfactory agreement with the sponsor.

1.2. Phase 4 Commitments

There are no Phase 4 commitments.

1.3. Summary of Important Clinical Pharmacology Findings

Table 1. Important PK properties of isavuconazole

PK Property	PK Parameter	
Dose-proportionality	PK dose-proportional for doses 100 – 600 mg	
Absorption	T _{max} (median)	~2-3 hr.
	Food Effect	No effect of food
Distribution	Protein Binding	> 99%
Elimination	T _{1/2 term} ~ 5 days	
Metabolism	Pathways	Substrate of CYP3A4 and 3A5.
Excretion	Equally excreted in feces and urine	

- After single or multiple oral administration of Cresemba in healthy volunteers, isavuconazole reached maximum plasma concentrations (C_{max}) in 2 to 3 hours. The absolute bioavailability of isavuconazole was 98%. No significant concentrations of the prodrug or inactive cleavage product were detected in plasma after oral administration.
- Following IV administration of Cresemba, concentrations of the prodrug and inactive cleavage product were detectable during infusion and declined rapidly following the end of administration. The prodrug was below the level of detection by 1.25 hours after the start of a 1 hour infusion. The total exposure of the prodrug based on AUC was less than 1% that of isavuconazole. The inactive cleavage product was quantifiable in some subjects up to 8 hours after the start of infusion. The total exposure of inactive cleavage product based on AUC was approximately 1.3% that of isavuconazole.
- Studies in healthy subjects demonstrated that the PK of isavuconazole is dose proportional up to 600 mg per day. Based on a population PK analysis of healthy subjects and patients, the mean half-life was 130 hours and the mean volume of distribution (V_{ss}) was approximately 450 L. Isavuconazole is highly protein bound (>99%), predominantly to albumin.
- Coadministration of Cresemba equivalent to isavuconazole 400 mg oral dose with a high-fat meal reduced isavuconazole C_{max} by 9% and increased AUC by 9%. Cresemba can be taken with or without food.

- Isavuconazonium sulfate is rapidly hydrolyzed in blood to isavuconazole by esterases, predominately by butyrylcholinesterase. Isavuconazole is a substrate of CYP3A4 and 3A5.
- Following single doses of [cyano ^{14}C] isavuconazonium and [pyridinylmethyl ^{14}C] isavuconazonium in humans, in addition to the active moiety (isavuconazole) and the inactive cleavage product, a number of minor metabolites were identified. Except for the active moiety isavuconazole, no individual metabolite was observed with an AUC > 10 % of drug related material. *In vivo* studies indicate that CYP3A4, CYP3A5 and subsequently uridine diphosphate-glucuronosyltransferases (UGT) are involved in the metabolism of isavuconazole.
- Following oral administration of radio-labeled isavuconazonium sulfate to healthy volunteers, a mean of 46.1% of the radioactive dose was recovered in the feces and 45.5% was recovered in the urine. Renal excretion of isavuconazole itself was less than 1% of the dose administered. The inactive cleavage product is primarily eliminated by metabolism and subsequent renal excretion of the metabolites. Renal elimination of intact cleavage product was less than 1% of the total dose administered. Following IV administration of radio-labeled cleavage product, 95% of the total radioactive dose was excreted in the urine.
- Isavuconazole is a substrate of CYP3A4 and CYP3A5. *In vitro*, isavuconazole is an inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. Isavuconazole is an inhibitor of P-gp, BCRP and OCT2-mediated drug transporters. *In vitro*, isavuconazole is also an inducer of CYP3A4/5, CYP2B6, CYP2C8, and CYP2C9.
- Upon coadministration, ketoconazole increased the isavuconazole $C_{\max}$ by 9% and isavuconazole AUC by 422% after multiple dose administration of ketoconazole (200 mg twice daily) for 24 days and a single dose of isavuconazonium equivalent to 200 mg of isavuconazole. Isavuconazole is a sensitive CYP3A4 substrate and use with strong CYP3A4 inhibitors is not recommended. Lopinavir/ritonavir (400 mg/100 mg twice daily) increased the $C_{\max}$ and AUC of isavuconazole (clinical dose) 74% and 96%, respectively, with concurrent decreases in the mean AUCs of lopinavir and ritonavir by 27% and 31%, respectively.
- Multiple doses of Cresemba increased the $C_{\max}$ and AUC of midazolam by 72% and 103%, respectively. Multiple oral doses of Cresemba increased the $C_{\max}$ and AUC of sirolimus by 65% and 84%, respectively. Multiple doses of Cresemba increased the $C_{\max}$ and AUC of tacrolimus by 42% and 125%, respectively. Caution is advised if Cresemba is co-administered with CYP3A4 substrates with narrow therapeutic indexes such as immunosuppressants (tacrolimus, sirolimus, and cyclosporine). Concentration-monitoring of tacrolimus, cyclosporine and sirolimus should enable concomitant administration with Cresemba.
- The AUC of isavuconazole following a single oral dose of 200 mg in elderly subjects (≥ 65 years) was similar to that in younger volunteers (18 to 45 years). The AUC was similar between younger female and male subjects and between elderly and younger males. Elderly female AUC values were 38% and 47% greater than AUC obtained in males and younger females, respectively. The PK differences in elderly females receiving isavuconazole are not considered to be clinically significant. Therefore, no dose adjustment is required based on age and gender.

- A 2-compartment population pharmacokinetic model was developed to assess the pharmacokinetics of isavuconazole between healthy Western and Chinese subjects. Chinese subjects were found to have on average a 40% lower clearance compared to Western subjects (1.6 L/hr for Chinese subjects as compared to 2.57 L/hr for Western subjects) and therefore approximately 50% higher AUC than Western subjects. Body mass index (BMI) did not play a role in the observed differences. No dose adjustment is recommended for Chinese patients.
- Isavuconazole AUC and C_{max} were not affected to a clinically meaningful extent in subjects with mild, moderate and severe renal impairment relative to healthy controls. No dose adjustment is necessary in patients with renal impairment. Isavuconazole is not readily dialyzable. A dose adjustment is not warranted in patients with ESRD.
- After a single 100 mg (Oral and IV) dose of isavuconazole was administered to 32 patients with mild (Child-Pugh Class A) hepatic insufficiency and 32 patients with moderate (Child-Pugh Class B) hepatic insufficiency, the total isavuconazole exposure (AUC_{last}) increased 27% to 42% Child-Pugh Class A group and 11% to 69% in Child-Pugh Class B group, respectively, relative to 32 age and weight-matched healthy subjects with normal hepatic function. No dosage adjustment of Cresemba is being recommended in patients with mild to moderate hepatic disease. Cresemba has not been studied in patients with severe hepatic disease (Child-Pugh Class C) and therefore administration is not recommended.
- In the pivotal comparator-controlled phase 3 study, there was no exposure-response (E-R) relationship for any of the adverse events of interest explored (anxiety, nausea, headache, pruritus, fatigue) or liver function tests (i.e., ALT elevation) with isavuconazole exposure (C_{trough} at Day 7). There was an apparent E-R trend in efficacy endpoint of imputed mortality before day 42 (primary endpoint) or mortality by the end of treatment (day 84) with isavuconazole exposures, with higher mortality in highest exposure quartile (Q4) compared to lower quartiles. But this observation was confounded by Asian subjects (either subjects with Asian race or subjects enrolled in Asian countries), since there were ~47% Asians in highest exposure quartile compared to just 2-10% in lower quartiles and Asians also had apparently higher mortality rates compared to the non-Asian population. The evaluation of E-R relationship within subgroups of Asian and non-Asian subjects suggested that there was no E-R relationship for efficacy (mortality) in non-Asians and Asians and the relationship was flat. No such differences in mortality across these subgroups (Asians vs. non-Asians) were seen in the comparator voriconazole arm. None of the other potential risk factors (age, uncontrolled malignancy status, neutropenia, hematological malignancy or serum galactomannan [(GM) +ve status] could explain the selectively higher mortality rates in this subgroup of Asian patients in isavuconazole arm. But, this apparent higher mortality in the Asian population was highly influenced by the results in enrolled population in South Korea (KOR) and removal of this country during sensitivity analysis resulted in resolution of the discrepancy in mortality between Asians vs. non-Asians for isavuconazole treatment. Thus, the mortality differences are not attributable to race or region specific differences in disease/drug/background standard-of-care effects and therefore no action is recommended for isavuconazole treatment for the subgroup of Asian population.
- The Thorough QT (TQT) studies conducted by the sponsor were reviewed by QT-IRT. The conclusions of the review were that isavuconazole is not a QT prolonger. There is a

concentration dependent decrease in the QT interval. The package insert for Cresemba will include statements regarding caution when it is administered with other QT shortening drugs.

2.2. General Clinical Pharmacology

2.2.1. *What are the design features of the clinical studies used to support dosing or claims?*

The substantial evidence in support of the indication of IA is provided by data from a single adequate and well-controlled, multiregional Phase 3 study, Study 9766-CL-0104. This was a randomized, double-blind, noninferiority, active-controlled study, which randomized 527 adult patients with suspected invasive fungal disease (IFD) caused by *Aspergillus* species or other filamentous fungi. Patients were to remain on therapy until they had reached a treatment endpoint or until they had received treatment for a maximum period of 84 days. Evidence for the efficacy of isavuconazole in renally impaired patients comes from Study 9766-CL-0103. This was an open-label trial that enrolled renally impaired patients with IFD caused by *Aspergillus* species or patients with IFD caused by rare molds, yeasts or dimorphic fungi. A posthoc pooled analysis was conducted in order to examine the effectiveness of isavuconazole in renally impaired patients with invasive aspergillosis in comparison to nonrenally impaired patients from Studies 9766-CL-0103 and 9766-CL-0104.

The indication of IM is supported by data from a subpopulation of patients enrolled in Phase 3 Study 9766-CL-0103 who were confirmed to have proven or probable IM as determined by an independent Data Review Committee (DRC). Patients in this study received isavuconazole for primary therapy as well as for salvage therapy, in case of refractory infection or intolerance of prior anti-fungal therapy. The efficacy of an isavuconazole for the primary treatment of IM from Study 9766-CL-0103 was also assessed in the context of published literature on the treatment of mucormycosis and case-matching from a global registry database.

A third Phase 3 study, 9766-CL-0105 (WSA-CS-008), is a double-blind, randomized trial evaluating the safety and efficacy of isavuconazole versus caspofungin followed by a voriconazole regimen in the treatment of candidemia and other invasive *Candida* infections. This study is still ongoing and was not reviewed in this current NDA submission.

Population PK analyses were performed by the sponsor based on data obtained from healthy subjects in Phase 1 studies and from patients with invasive aspergillosis in Phase 3 study 9766-CL-0104.

2.2.2. *What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?*

The primary endpoint was all-cause mortality through day 42. All-cause mortality through day 42 was evaluated with a non-inferiority margin of 10% in the intent to treat (ITT) population. A blinded, independent DRC reviewed clinical, mycological and radiographic data to classify patients as proven, probable, and possible or no evidence of IFD and to assess response. Overall response at end of treatment (EOT) was a key secondary endpoint and was based on clinical, mycological and radiological responses. For the overall response, patients with a complete or partial response were considered a success and patients that remained stable, progressed, died or with missing responses were considered a failure.

The pharmacodynamic index associated with efficacy is defined as AUC/MIC, similar to the other triazoles. The PD target values were determined from experimental studies performed with isavuconazole and *Aspergillus fumigatus* species. In each of the 3 infection models, successful outcomes were demonstrated in *Aspergillus* isolates with isavuconazole MIC values of up to 2 and 4 mg/L for CLSI and EUCAST methodologies, respectively, which are within the MIC₉₀ for most *Aspergillus* species. Under CLSI conditions, the PD targets (total drug AUC/MIC) ranged from 11.2 to 503.

2.2.3. Are the active moieties in the biological fluid appropriately identified and measured to assess pharmacokinetic parameters?

The active moiety, isavuconazole, was appropriately identified and measured in plasma by a validated LC-MS/MS assay. Please see Section 2.6 for details regarding the bioanalytical methods.

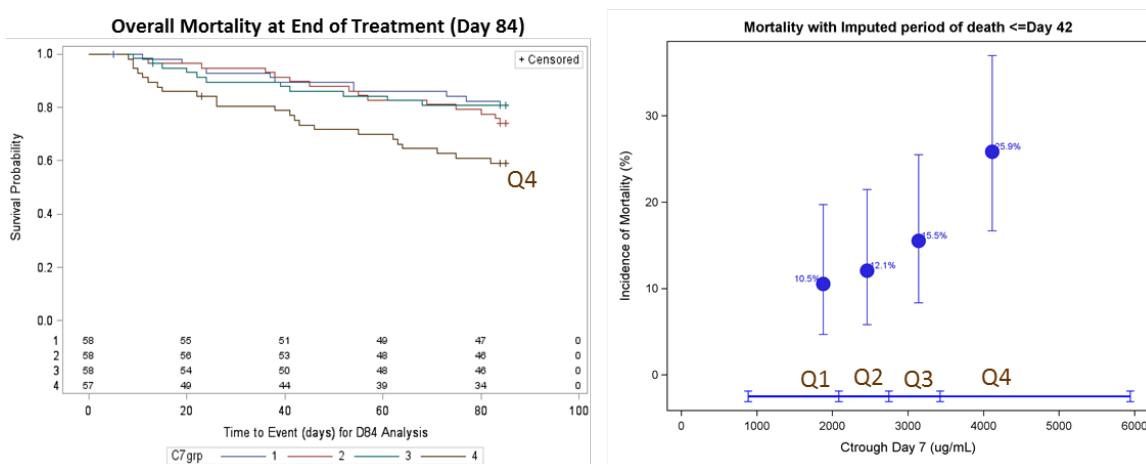
2.2.4. Exposure-Response

2.2.4.1. What are the characteristics for exposure-response (E-R) relationships (dose-response, concentration-response) for efficacy?

In the pivotal comparator-controlled Phase 3 study, there was no E-R relationship for efficacy endpoint of imputed mortality before day 42 (primary endpoint) or mortality by the end of treatment (day 84) with isavuconazole exposures.

The initial investigation with the overall population did show an apparent E-R trend in these efficacy endpoints with isavuconazole exposures, with higher mortality in highest exposure quartile (Q4) compared to lower quartiles (Figure 2).

Figure 2. Exposure-response analysis for efficacy endpoints of mortality in voriconazole-controlled pivotal phase 3 trial for Cresemba. Panel A shows Kaplan-Meier plot for overall mortality at end of treatment (Day 84) while panel B shows incidence of mortality with imputed period of death ≤ Day 42 (primary efficacy endpoint) across isavuconazole exposure quartiles. Isavuconazole population-PK predicted C_{trough} at Day 7 was used for exposure quartiles. (Source: Reviewer's analysis)



But this observation was confounded by Asian subjects (either subjects with Asian race or subjects enrolled in Asian countries), since there were ~47% Asians in highest exposure quartile compared to just 2-10% in lower quartiles and Asians also had apparently higher mortality rates compared to the non-Asian population (Table 1). No such differences in mortality across these subgroups (Asians vs. non-Asians) were seen in the comparator arm of voriconazole in this pivotal Phase 3 study (Table 1). None of the other potential mortality related risk factors (age, uncontrolled malignancy status, neutropenia, hematological malignancy or serum galactomanan (GM) +ve status) could explain the selectively higher mortality rates in the subgroup of Asian subjects in isavuconazole arm (Table 2). The evaluation of E-R relationship within subgroups of Asian and non-Asian subjects suggested that there was no E-R relationship for efficacy (mortality) in non-Asians and Asians and the relationship was relatively flat (Figure 3). Figure 4 shows that Asian Q_{low} quantile (patients with C_{trough} values less than the median in Asians) has similar C_{trough} exposure as non-Asian Q_{high} subgroup (patients with C_{trough} values greater than the median in non-Asians), but a higher mortality, which reflects that the mortality is not driven by exposure.

Table 1. Comparison of incidences of all cause mortality (ACM) in Asian vs. Non-Asian population (based on race or countries) for isavuconazole vis-à-vis voriconazole treatment arms in pivotal phase 3 study. (Source: Reviewer's analysis)

Mortality with Imputed period of death <= Day 42						
	CRESEMBA		Voriconazole		CRESEMBA (E-R dataset)	
	N	ACM n (%)	N	ACM n (%)	N	ACM n (%)
Non-Asian	213	34 (16.0%)	194	38 (19.6%)	192	25 (13.0%)
Asian	44	14 (31.8%)	65	14 (21.5%)	39	12 (30.8%)

	CRESEMBA		Voriconazole		CRESEMBA (E-R dataset)	
	N	ACM n (%)	N	ACM n (%)	N	ACM n (%)
Non-Asian Countries	213	34 (16.0%)	194	38 (19.6%)	192	25 (13.0%)
Asian Countries (CHN, IND, KOR, MYS, THA)	44	14 (31.8%)	65	14 (21.5%)	39	12 (30.8%)

Overall Mortality at End of Treatment (Day 84)

	CRESEMBA		Voriconazole		CRESEMBA (E-R dataset)	
	N	ACM n (%)	N	ACM n (%)	N	ACM n (%)
Non-Asian	213	55 (25.8%)	194	59 (30.4%)	192	45 (23.4%)
Asian	44	17 (38.6%)	65	16 (24.6%)	39	15 (38.5%)

	CRESEMBA		Voriconazole		CRESEMBA (E-R dataset)	
	N	ACM n (%)	N	ACM n (%)	N	ACM n (%)
Non-Asian Countries	213	54 (25.4%)	194	59 (30.4%)	192	44 (22.9%)
Asian Countries (CHN, IND, KOR, MYS, THA)	44	18 (40.9%)	65	16 (24.6%)	39	16 (41.0%)

Table 2. Comparison of possible risk factors for mortality across subgroup of Asian vs. Non-Asian population (based on Asian countries) for isavuconazole treatment arm in pivotal phase 3 study. (Source: Reviewer's analysis)

	Neutropenia	Serum GM +ve	Uncontrolled Malignancy	Hemat. Malignancy	Age >65yr
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Non-Asian Countries	130/192 (67.7%)	41/172 (23.8%)	135/192 (70.3%)	165/192 (85.9%)	46/192 (24.0%)
Asian Countries (CHN, IND, KOR, MYS, THA)	20/39 (51.3%)	12/28 (42.9%)	21/39 (53.9%)	25/39 (64.1%)	5/39 (12.8%)

Figure 3. Exposure-response analysis for efficacy endpoints of mortality in voriconazole-controlled pivotal phase 3 trial for Cresemba. Figure shows Kaplan-Meier plot for overall mortality at end of treatment (Day 84) across exposure quartiles for Non-Asians (panel A) and for Asians (panel B). Isavuconazole population-PK predicted C_{trough} at Day 7 was used for exposure quartiles. (Source: Reviewer's analysis)

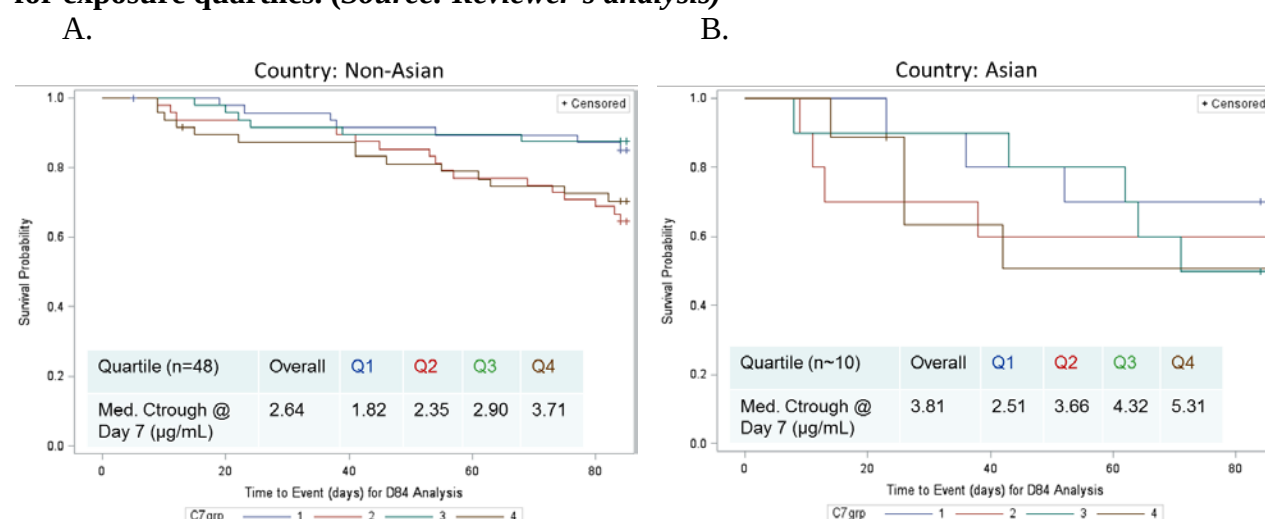
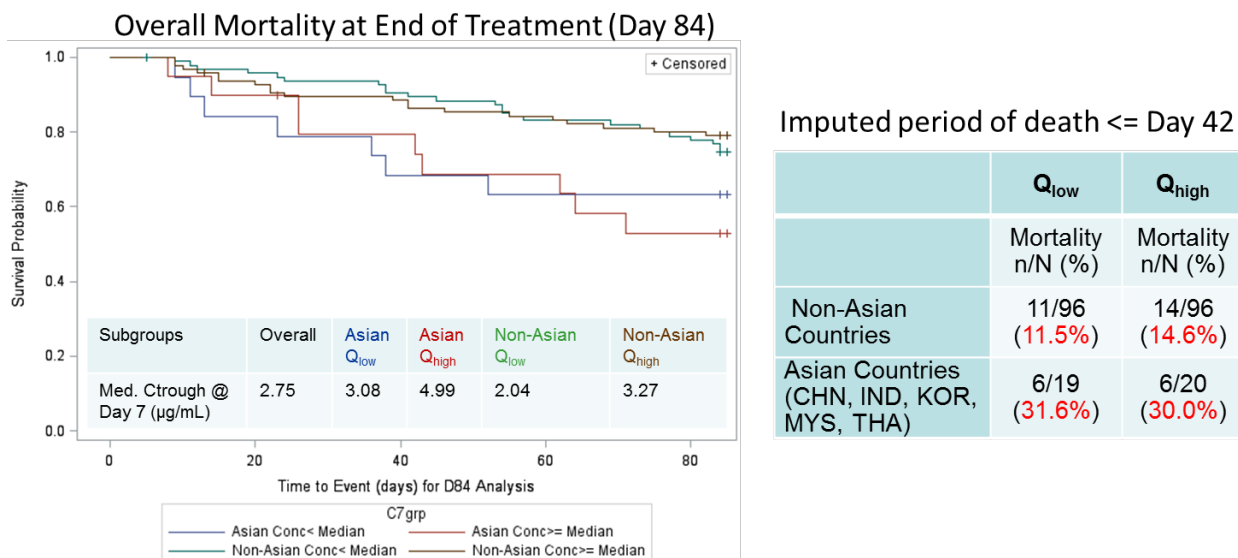


Figure 4. Q_{low} subgroup (quantile with conc. below median) of Asians have similar Ctrough exposure but higher mortality compared to Q_{high} subgroup (quantile with conc. above median) for non-Asians, suggesting that the higher mortality is not attributable to exposure levels alone. (Source: Reviewer's analysis)



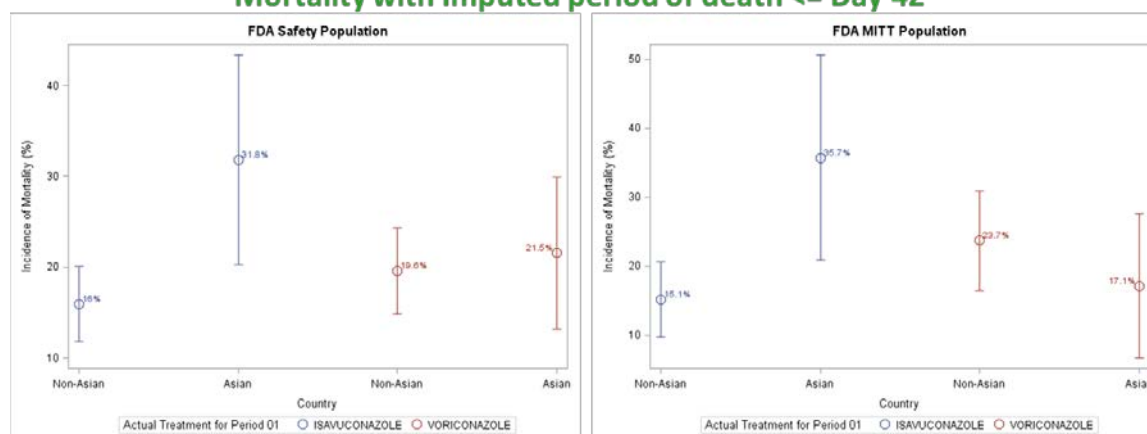
Further sensitivity analysis was carried out to verify the subgroup mortality findings in isavuconazole arm. For this, FDA-MITT population was considered since this population contained only the patients with probable or proven invasive mould infection as against the overall safety population which had also patients categorized as possible or no invasive fungal disease/invasive mould infection (Table 3). The sensitivity analysis using FDA-MITT population also showed relatively unfavorable outcome for Cresemba in Asians compared to non-Asians (Figure 5)

Table 3. Distribution of patients by categories for detection of fungal infection in the isavuconazole treatment arm in pivotal phase 3 study. (Source: Reviewer's analysis)

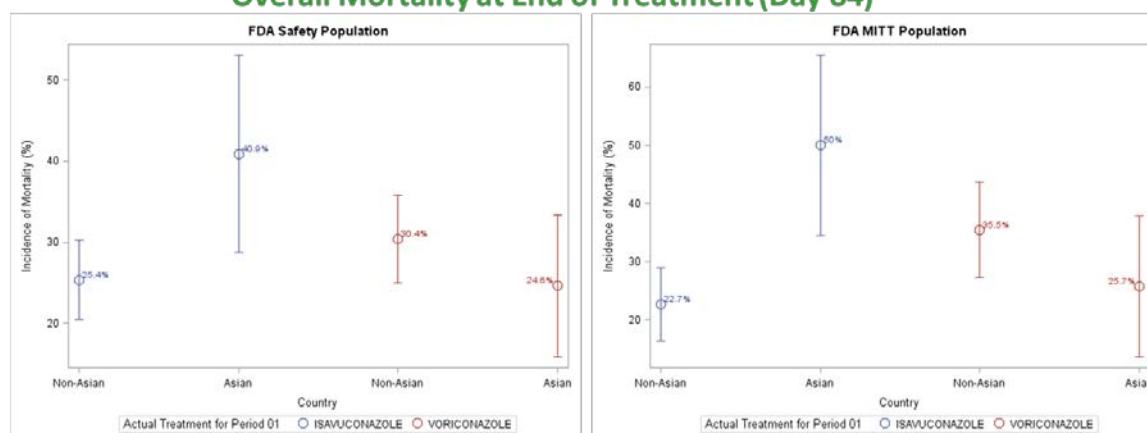
FDA-MITT pop.	No IFD/ No invasive mould infection	Possible	Probable	Proven	Total (N=516)
No	48 (9.3%)	193 (37.4%)	0	0	241 (46.7%)
Yes	0	0	210 (40.7%)	65 (12.6%)	275 (53.3%)

Figure 5 Sensitivity analysis using FDA-MITT population also showed relatively unfavorable outcome for Cresemba in Asians compared to non-Asians. Note: The Asians/non-Asians are categorized here by country/region where patients are enrolled/treated, though similar relationship was seen when categorized by race. (Source: Reviewer's analysis)

Mortality with Imputed period of death <= Day 42



Overall Mortality at End of Treatment (Day 84)



Further analysis of relative risk of mortality between Cresemba and voriconazole arm across countries of enrollment showed that patients in South Korea (KOR) had relatively much higher mortality compared to the average population in Cresemba arm and much lower mortality compared to average population in voriconazole arm which resulted in very high relative risk for Cresemba arm (Figure 6). Therefore, further sensitivity analysis for mortality was carried out by removing the patients enrolled in KOR. Indeed, after removing these patients from the overall population, the mortality in Asians in the Cresemba arm got scaled down to levels seen in voriconazole arm (Figure 7). Thus, the apparent higher mortality in the Asian population was highly influenced by the results in enrolled population in KOR and removal of this country during sensitivity analysis resulted in resolution of the discrepancy in mortality between Asians vs. non-Asians for isavuconazole treatment. Thus, the mortality differences are not attributable to race or region specific differences in disease/drug/background standard-of-care effects and therefore no action is recommended for isavuconazole treatment for the subgroup of Asian population.

Figure 6 Relative risk for mortality between Cresemba treatment vs. Voriconazole treatment across countries. (Source: Reviewer's analysis)

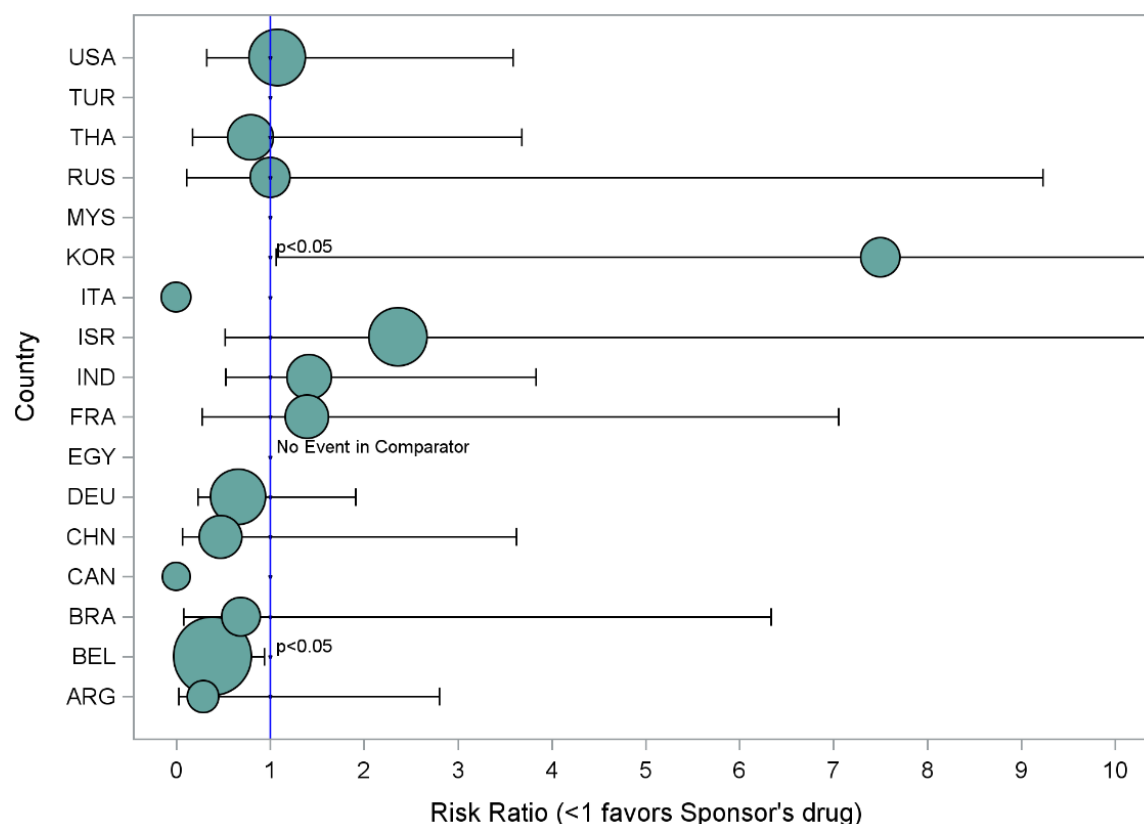
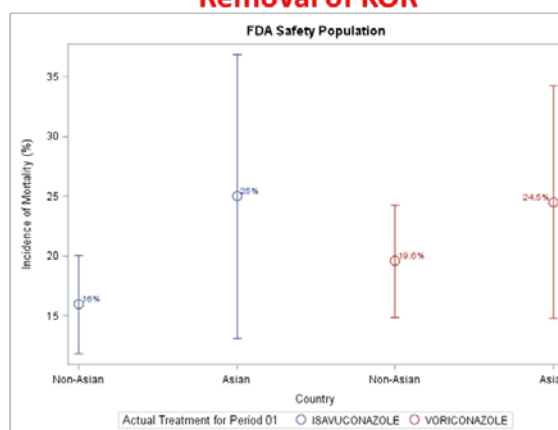


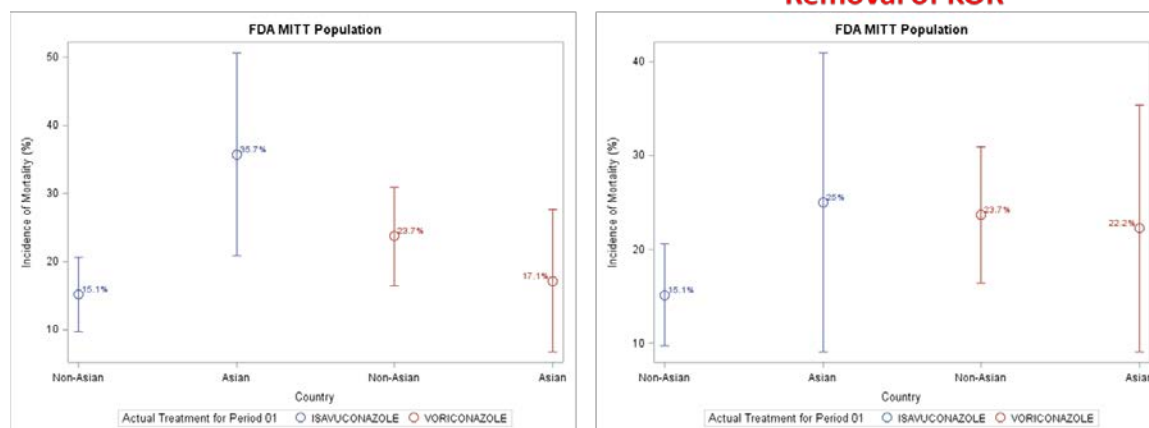
Figure 7 Sensitivity analysis for mortality in overall safety population (top panels) and FDA-MITT population (bottom panels) using exclusion of patients enrolled in South Korea (KOR). While the results for Day 42 mortality are shown here, similar results are seen with Day 84 mortality (data not shown). Note: The Asians/non-Asians are categorized here by country/region where patients are enrolled/treated, though similar relationship was seen when categorized by race. (Source: Reviewer's analysis)

Mortality with Imputed period of death <= Day 42



Removal of KOR

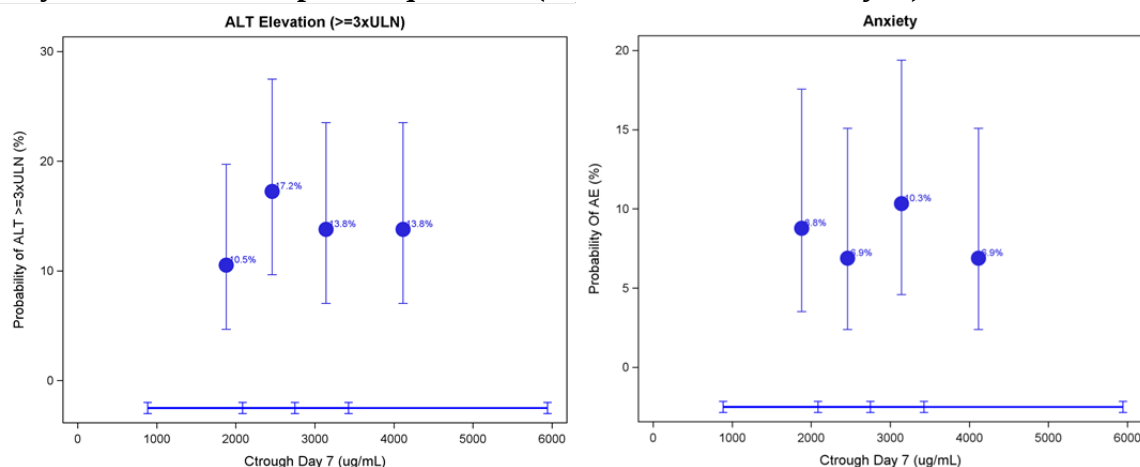


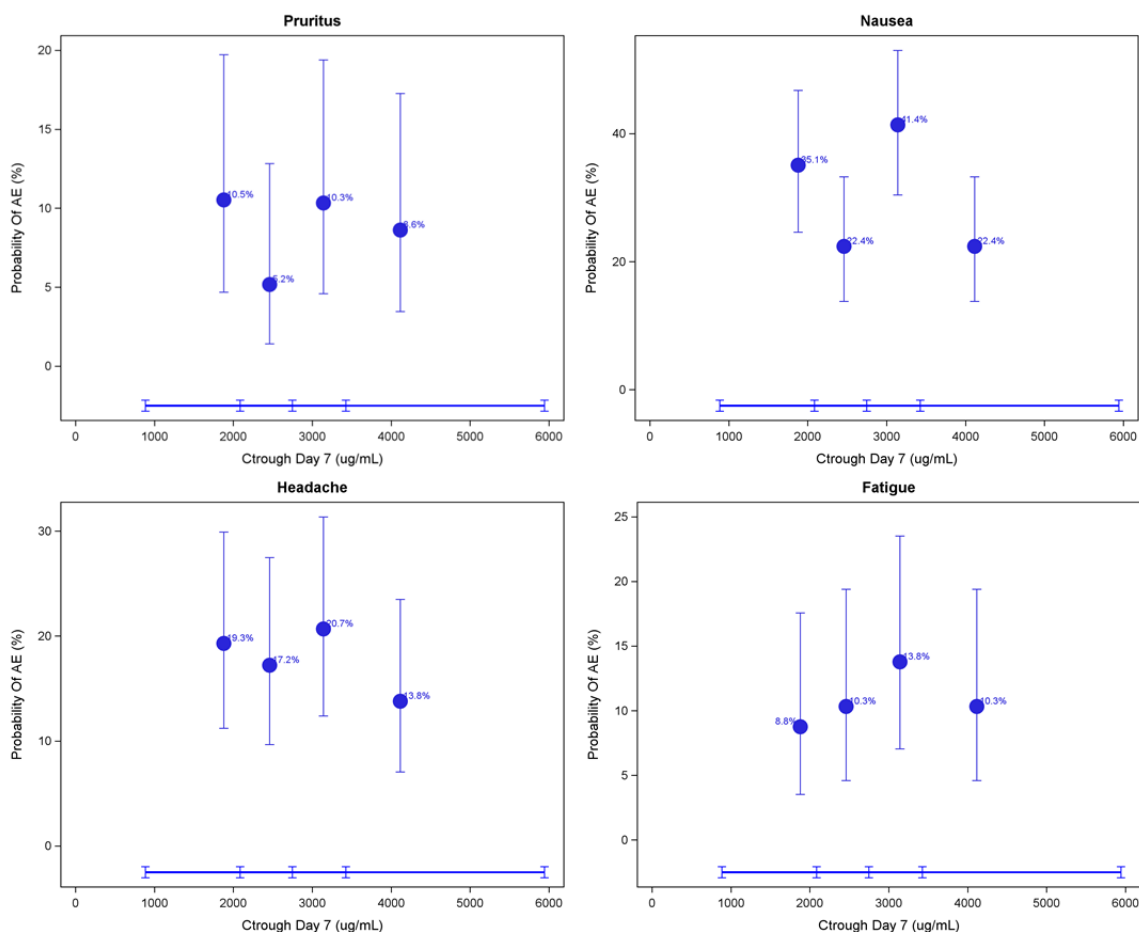


2.2.4.2. What are the characteristics for exposure-response relationships (dose-response, concentration-response) for safety?

In the pivotal comparator-controlled Phase 3 study, there was no E-R relationship for any of the adverse events of interest explored (anxiety, nausea, headache, pruritus, fatigue) or liver function test (i.e., ALT elevation) with isavuconazole exposure (C_{trough} at Day 7) as seen in Figure 8.

Figure 8. Exposure-response analysis for ALT elevation and other safety events of interest across exposure quartiles. Isavuconazole population-PK predicted C_{trough} at Day 7 was used for exposure quartiles. (Source: Reviewer's analysis)





Thorough QT Trial:

The QT-IRT concluded the following based on a review of the TQT trial conducted by the sponsor:

- At an oral isavuconazonium capsule dose 3 times the recommended therapeutic maintenance dose, isavuconazole did not prolong the QT interval to any clinically relevant extent. In fact, a dose-and-concentration-related shortening of the QTc interval was observed with isavuconazole, probably correctly attributed by the sponsor to slight block of the calcium channel
- There is also a small effect (about 10 ms at the highest tested exposure) of reducing the PR interval. This is not believed to be clinically relevant.

2.2.4.3. Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issues?

The dose for Phase 3 studies was selected to ensure rapid achievement of trough exposures above the epidemiologic cut-off values for *Aspergillus spp.* (i.e., 1 to 2 mg/L). From the multiple ascending dose concentration time profile, it was determined that a loading dose regimen would be required to ensure rapid attainment of trough target concentrations. A loading dose regimen of 200 mg isavuconazole q8 hours for 6 doses and then 200 mg q24 hours administered intravenously or orally to patients with IA was utilized in Phase 3 studies.

For IM, in vivo pharmacodynamics models are not available to guide target exposures and dose selection. Furthermore, MIC values have not been found to be helpful in guiding therapy. Thus, the same dose regimen selected for IA was utilized for treatment of IM in Study 9766-CL-0103.

Population PK/PD modeling found no association between exposure and response, which might be expected if exposures exceed the AUC/MIC target. Lack of association between exposure and response would be expected if exposures exceed AUC/MIC target for organisms within the wild type population. While the number of isolates from Studies 9766-CL-0104 and 9766-CL-0103 is very limited, no clear MIC threshold was identified for response and responses were seen up to MICs of 8 mg/L. For IA, isavuconazole was non-inferior to the standard of care, voriconazole. Day 42 mortality in the ITT and mITT populations as well as other populations and subgroups was similar between treatment groups. In Study 9766-CL-0103, IM patients treated with isavuconazole had outcomes similar to that reported in the literature and matched controls treated with amphotericin B. The safety profile of the intended dose regimen has been well-characterized in healthy volunteers and patients with IFD. Overall, the intended dose regimen was well tolerated, with fewer isavuconazole than voriconazole patients experiencing AEs associated with liver, skin, visual disturbances, and hallucinations.

Overall, the data appear to support the Cresemba dose regimen for treatment of IA and IM: 200 mg isavuconazole loading dose q8 hours for 48 hours (6 total doses), via oral or intravenous administration, followed by 200 mg isavuconazole maintenance dose once per day via oral or IV administration starting 12 to 24 hours after the last loading dose.

2.2.5. What are the PK characteristics of Isavuconazonium?

The prodrug, isavuconazonium, was not detected in plasma or urine after oral administration in healthy subjects. After IV administration of isavuconazonium, exposure to intact isavuconazonium in plasma was consistently low at all dose levels examined. Isavuconazonium $t_{\max}$ was reached within 0.75 hours and isavuconazonium concentrations were below the LLOQ within 1.25 hours (40 mg dose) after the start of a 1-hour infusion. Mean isavuconazonium AUC_{last} was < 1% and mean $C_{\max}$ was < 15% of the corresponding isavuconazole exposures (Table 4).

Table 4. Mean Pharmacokinetic Parameters of Isavuconazonium and Isavuconazole Following Single and Multiple Intravenous Doses of Isavuconazonium (Source: Sponsor's report)

Study	Dose (mg eq.) [†]	n	Isavuconazonium			Isavuconazole		
			C _{max} (ng/mL)	AUC _{last} (ng·h/mL)	t _{max} (h)	C _{max} (ng/mL)	AUC _‡ (ng·h/mL)	t _{max} (h)
Single Dose								
9766-CL-0002	40	6	30.58 (21.9%)	15.56 (34.8%)	0.500	445.8 (17.1%)	11510 (41.9%)	0.750
	80	6	121.2 (88.4%)	78.42 (89.8%)	0.375	1030 (17.9%)	26194 (24.3%)	1.000
	160	6	351.3 (50.9%)	254.7 (53.2%)	0.750	2472 (15.1%)	72134 (17.8%)	1.000
Multiple Dose								
9766-CL-0003	40	5	103.5 (51.4%)	60.31 (35.9%)	0.250	1172 (20.2%)	14229 (37.5%)	1.000
	80	6	249.1 (35.5%)	162.3 (52.2%)	0.500	2552 (34.6%)	33473 (28.4%)	1.000

Values of pharmacokinetics parameters are mean (%CV). Median for t_{max}.

eq.: equivalent

† Isavuconazonium dosage is expressed in terms of the quantity of the active moiety isavuconazole (in mg eq.).

‡ AUC = AUC_{inf} for single dose results, AUC_{tau} for multiple dose results.

Source: Clinical Study Reports 9766-CL-0002, Tables 20.1 and 20.2; 9766-CL-0003, Tables 17.1.3 and 17.2.3.

Further details on the PK of isavuconazole are discussed below.

2.2.5.1. What are the single dose and multiple dose PK parameters?

Single Dose Pharmacokinetics of isavuconazole

The pharmacokinetics of isavuconazole following single dose **oral** administration are summarized in Table 5.

Table 5: Pharmacokinetics of isavuconazole in Plasma After Administration as Single Oral Dose (Source: Sponsor's report)

Dose	Statistic	C _{max} (ng/mL)	t _{max} (h)	AUC _{last} (h·ng/mL)	AUC _{inf} (h·ng/mL)	t _{1/2} (h)	CL/F (mL/h)	Vz/F (L)
100 mg	n	6	6	6	6	6	6	6
	Mean (SD)	1446.7 (176.651)	1.881 (0.1854)	36276.6 (6695.90)	36738.8 (6744.32)	62.301 (20.8087)	2805.2 (548.88)	246.72 (78.336)
	Median	1516.0	1.975	37335.1	37683.0	62.472	2675.6	217.40
	Min, Max	1191, 1629	1.58, 2.03	26694, 43744	27303, 44448	39.23, 96.81	2250, 3663	165.1, 369.6
200 mg	n	6	6	6	6	6	6	6
	Mean (SD)	2587.8 (449.024)	1.925 (0.5506)	77202.5 (10855.03)	77891.7 (10683.72)	73.515 (12.3180)	2609.2 (365.10)	280.87 (82.842)
	Median	2680.0	1.800	78664.1	79105.0	72.478	2531.2	264.60
	Min, Max	1853, 3097	1.50, 2.95	62935, 91588	64207, 92466	54.39, 92.57	2163, 3115	185.0, 416.0
400 mg	n	3	3	3	3	3	3	3
	Mean (SD)	5566.3 (211.342)	2.700 (0.5487)	209377.9 (41559.70)	210586.0 (41631.19)	56.206 (2.4770)	1956.6 (433.73)	159.44 (41.515)
	Median	5507.0	3.000	228027.8	229140.7	56.470	1745.7	135.94
	Min, Max	5391, 5801	2.07, 3.03	161760, 238346	162904, 239714	53.61, 58.54	1669, 2455	135.0, 207.4

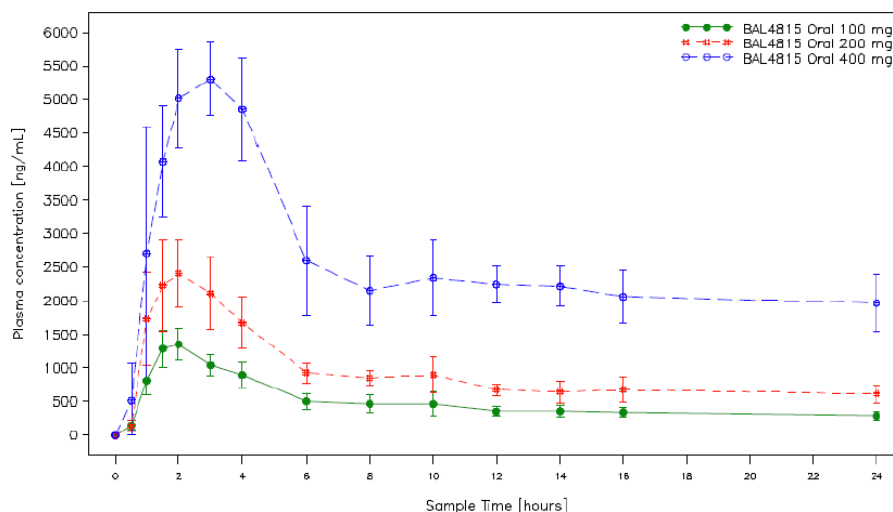
All volunteers from the Safety Population for whom sufficient plasma concentration data were available to derive at least 1 pharmacokinetic parameter (Pharmacokinetic Analysis Set)

Max: maximum; Min: minimum

Source: Section 12.4.2, Table 20

The plasma concentration-time profiles following administration of single doses of oral isavuconazonium are given below:

Figure 9. Mean (+/- std) Plasma Concentrations–Time Profile of Isavuconazole (Source: Sponsor’s report)



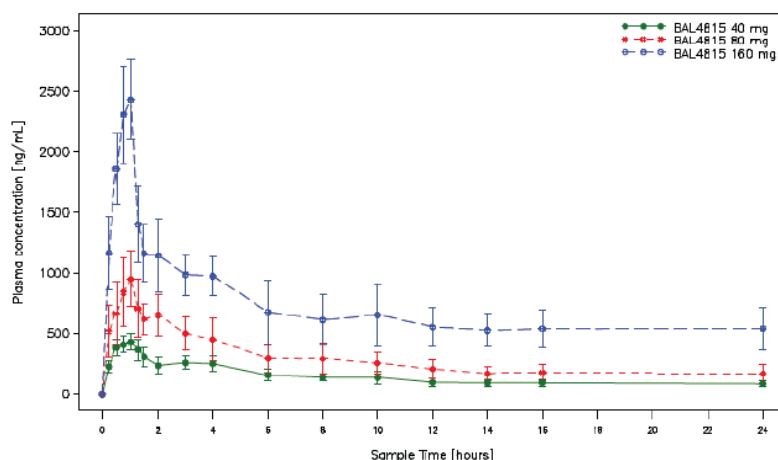
The pharmacokinetics of isavuconazole following single dose **IV** administration are summarized in Table 6.

Table 6. Mean (SD) Plasma Concentration-time profile of Isavuconazole following Single IV administration (Source: Sponsor’s report)

Dose	Statistic	C _{max} (ng/mL)	t _{max} (h)	AUC _{last} (h*ng/mL)	AUC _{inf} (h*ng/mL)	t _{1/2} (h)	CL _{tot} (mL/h)	V _z (L)
40 mg (n = 6)	Mean (SD)	445.8 (76.072)	0.750 (0.2236)	10341.8 (3990.89)	11509.5 (4822.51)	81.557 (53.8145)	4044.6 (1695.70)	490.21 (210.452)
	Median	463.5	0.750	10081.1	10848.1	70.984	3714.1	500.68
	Min, Max	345, 527	0.50, 1.00	6008, 15788	6472, 18371	31.85, 165.80	2177, 6180	239.2, 807.5
80 mg (n = 6)	Mean (SD)	1030 (184.12)	0.917 (0.1291)	24700.9 (5975.85)	26194.3 (6359.50)	92.703 (46.0201)	3224.9 (867.82)	405.45 (191.995)
	Median	1029	1.000	24736.4	25683.1	99.233	3137.1	366.96
	Min, Max	782, 1260	0.75, 1.00	16465, 32558	16880, 34789	36.89, 149.85	2300, 4739	181.0, 746.2
160 mg (n = 6)	Mean (SD)	2472 (374.19)	0.958 (0.1021)	71122.2 (12628.54)	72134.3 (12868.15)	83.735 (41.6774)	2283.5 (442.50)	265.20 (106.446)
	Median	2440	1.000	74328.0	75503.3	71.098	2124.9	248.80
	Min, Max	2000, 2900	0.75, 1.00	53988, 83011	54443, 84534	49.82, 158.50	1893, 2939	160.7, 432.8

The plasma concentration-time profiles following administration of single doses of IV isavuconazonium are given below:

Figure 10. Mean (SD) Plasma Concentration-time profile of Isavuconazole following IV administration (Source: Sponsor’s report)



Multiple Dose Pharmacokinetics of isavuconazole

The pharmacokinetics of isavuconazole upon repeat oral and IV administration is given below:

Table 7. Pharmacokinetics of isavuconazole in Plasma After Administration as Multiple Doses (Source: Sponsor's report). Oral low dose of 100 mg on day 1 and maintenance dose of 50 mg QD from day 2 to day 21. Oral high dose of 200 mg on day 1 and maintenance dose of 100 mg QD day 2 to day 21. IV low dose of 80 mg on day 1 and maintenance dose of 40 mg QD from day 2 to day 14. IV high dose of 160 mg on day 1 and maintenance dose of 80 mg QD day 2 to day 14)

Day Parameter Statistic	Isavuconazole			
	Oral		Intravenous	
	Low (n = 6)	High (n = 6)	Low (n = 6)	High (n = 6)
Day 1				
C_{max} (ng/mL)				
Mean (SD)	1101.7 (173.45)	1849.5 (326.32)	1276.8 (122.21)	2318.2 (445.13)
%CV	15.7	17.6	9.6	19.2
Median	1052.0	1836.0	1262.5	2264.5
Min, Max	902.4, 1402	1407, 2287	1137, 1458	1718, 3022
Geometric mean	1091.0	1825.1	1272.0	2282.9
t_{max} (h)				
Median	2.000	2.000	0.750	1.000
Min, Max	2.00, 3.00	1.25, 3.07	0.50, 1.00	0.75, 1.00
AUC₂₄ (h•ng/mL)				
Mean (SD)	8680.6 (1255.51)	18048.0 (3313.20)	7260.4 (1086.49)	12780.4 (1937.87)
%CV	14.5	18.4	15.0	15.2
Median	8441.4	16774.1	7443.2	13036.4
Min, Max	7264, 10503	14891, 22556	5438, 8545	10133, 15574
Geometric mean	8606.4	17806.6	7187.3	12656.3
Day 8				
C_{max} (ng/mL)				
Mean (SD)	1202.3 (214.91)	2326.0 (472.11)	986.58 (180.454)	2519.5 (1052.40)
%CV	17.9	20.3	18.3	41.8
Median	1098.5	2300.0	985.6	2008.5
Min, Max	1032, 1485	1641, 2916	702.3, 1196	1922, 4593
Geometric mean	1187.2	2284.5	971.89	2381.8
t_{max} (h)				
Median	2.000	3.000	1.000	0.750
Min, Max	1.50, 3.00	2.00, 12.00	0.50, 1.50	0.50, 1.00
AUC₂₄ (h•ng/mL)				
Mean (SD)	18023.8 (4440.76)	33881.4 (5656.67)	12315 (3747.9)	24401.2 (5847.44)
%CV	24.6	16.7	30.4	24.0
Median	15889.9	34848.4	12716	23448.8
Min, Max	14772, 25754	26069, 40158	6486, 18073	18185, 31981
Geometric mean	17618.5	33470.0	11788	23825.1
Day 14				
C_{max} (ng/mL)				
n	6	6	5	6
Mean (SD)	1401.5 (177.77)	2608.2 (365.40)	1172.3 (237.30)	2552.0 (883.20)
%CV	12.7	14.0	20.2	34.6
Median	1353.5	2632.0	1141.0	2334.0
Min, Max	1205, 1674	2033, 3151	813.3, 1436	1817, 4149
Geometric mean	1392.4	2586.2	1151.2	2441.9

Table continued on next page

Day Parameter Statistic	Isavuconazole			
	Oral		Intravenous	
	Low (n = 6)	High (n = 6)	Low (n = 6)	High (n = 6)
t_{max} (h)				
Median	3.000	2.250	1.000	1.000
Min, Max	1.25, 4.00	1.50, 4.00	0.75, 1.00	0.75, 1.50
AUC₀₋₂₄ (h•ng/mL)				
n	6	6		
Mean (SD)	21996.6 (4911.36)	41434.3 (5982.59)		
%CV	22.3	14.4		
Median	20530.3	40704.9		
Min, Max	16825, 30063	33727, 48842		
Geometric mean	21569.9	41074.4		
Day 21				
C_{max} (ng/mL)				
Mean (SD)	1366.7 (229.56)	2562.0 (434.04)		
%CV	16.8	16.9		
Median	1297.5	2354.5		
Min, Max	1105, 1704	2213, 3154		
Geometric mean	1351.1	2532.9		
t_{max} (h)				
Median	2.250	3.500		
Min, Max	1.50, 3.00	2.00, 4.00		

2.2.5.2. How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The predicted AUC values derived from individual CL values based on the population PK analysis in patients are compared against the mean PK parameters observed in healthy volunteers in Table 8.

Table 8. A comparison of the AUC between healthy volunteers and patients (Source: Sponsor's report) following repeat doses of 200 mg loading doses followed by 100 mg single doses

AUC (ug•hr/mL)	Healthy Subjects	Patient Population
Mean (SD)	92.25 (32.79)	97.85 (57.16)
Median	88.04	86.68
Min	32.73	26.29
Max	257.48	684.88
CV%	35.54	58.41

As seen above, the mean AUC in healthy volunteers appear to be comparable to those seen in patients.

2.2.5.3. What are the characteristics of drug absorption?

In Vitro Absorption Studies

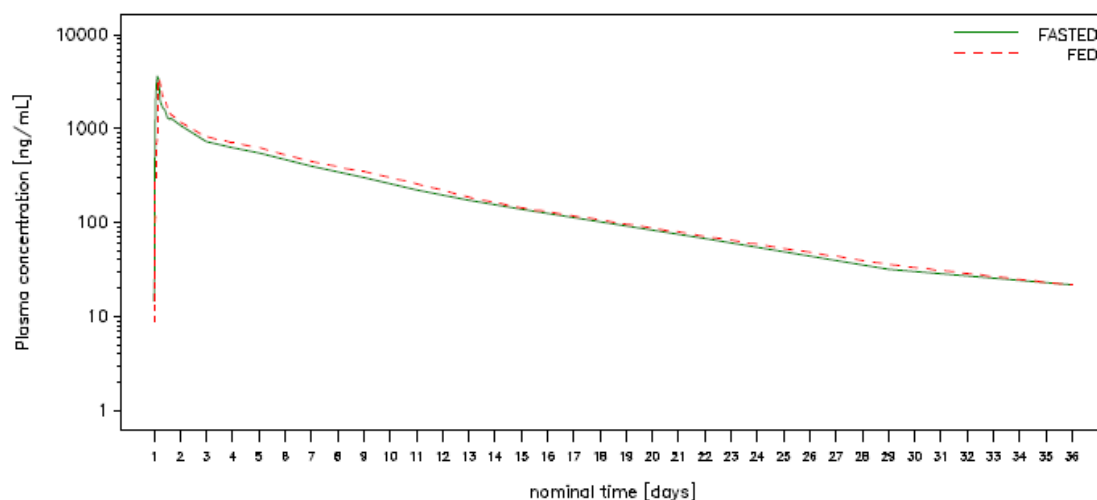
The prodrug isavuconazonium was rapidly hydrolyzed by esterases (predominately butylcholinesterase) to the active moiety (isavuconazole) in human blood, plasma, liver and intestinal microsomes and liver and intestinal homogenates. Isavuconazonium is a charged species with a high molecular weight, and showed very low apical-to-basolateral transport across Caco-2 cell monolayers with P_{app} of 0.03 x 10⁻⁶ cm/s, which suggests that the prodrug will be

poorly absorbed in vivo. In contrast to the prodrug, isavuconazole showed high trans-epithelial transport across Caco-2 cell monolayers with Papp of 9.18 to 13.45×10^{-6} cm/s, which was comparable to the high permeability reference compound in the in vitro study. The result suggested that no active uptake or efflux process was involved in isavuconazole absorption.

Clinical Trials Evaluating Effect of Food on Isavuconazole Absorption

Concurrent administration of isavuconazonium sulfate capsules with a high-fat breakfast had no clinically relevant effect on the pharmacokinetics of isavuconazole. The 90% CIs for isavuconazole $C_{\max}$ and AUC_{inf} ratios with and without food were contained entirely within the default no effect boundaries of 80% to 125%. The 2-hour delay in $t_{\max}$ with food is not considered clinically relevant. Pivotal clinical efficacy and safety trials were conducted without food restrictions. The proposed dosing recommendation for oral isavuconazonium in relation to food is that isavuconazonium can be taken with or without food.

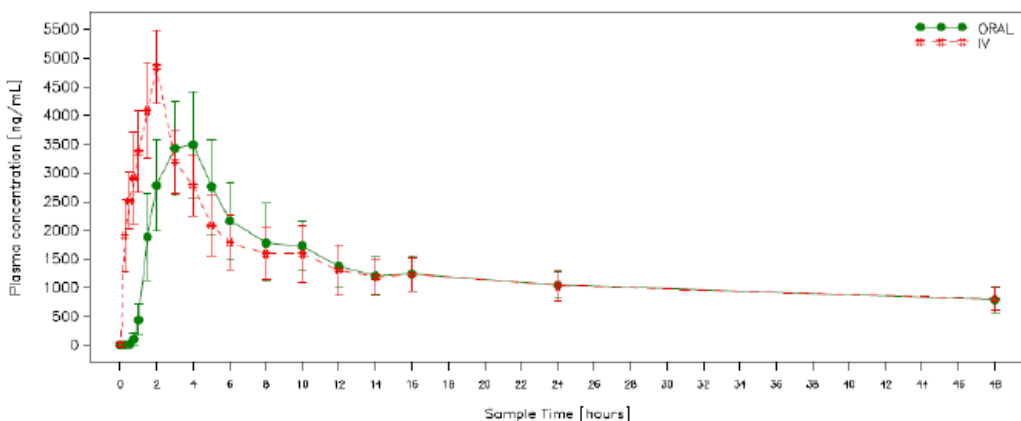
Figure 11. Effect of food on the systemic profile of isavuconazole (Source: Sponsor's report)



Absolute Bioavailability of Oral formulation

The absolute bioavailability of the oral formulation was approximately 98%. The 90% CIs of the ratios of oral to IV for AUC_{inf} and AUC_{last} were within 80% to 125%. The oral-to-IV $C_{\max}$ ratio was 78.12%, with the 90% CI of that ratio falling outside of the 80% to 125% range.

Figure 12. Mean Isavuconazole concentration time profiles of oral and IV formulations (Source: Sponsor's report)



All subjects who provided an adequate number of blood samples, as determined by the pharmacokineticist, to calculate at least one of the primary plasma pharmacokinetic parameters AUC_{last} , AUC_{inf} and C_{max} (Pharmacokinetic Analysis Set)

Isavuconazole and BAL4815 denote the same compound.

Source: Section 12.4, Figure 2.1.4

2.2.5.4. What are the characteristics of drug distribution?

Isavuconazole is extensively distributed with a mean volume of distribution at steady-state of approximately 450 L. Isavuconazole is extensively bound (> 99%) to plasma proteins in vitro. The binding of ^{14}C -isavuconazole to human plasma proteins was highest for HSA at 98.9%, followed by HDL at 94.2%, LDL at 91.0%, α_1 -AGP at 56.2% and γ -globulin at 38.8%. Binding was independent of concentration.

Following a single oral solution dose of [cyano- ^{14}C]-labeled isavuconazonium, mean blood-to-plasma concentration ratios of radioactivity ranged from 0.482 to 0.665 through 264 hours postdose, indicating minimal sequestration of radioactivity within red blood cells. Similar blood-to-plasma concentration ratios were obtained following a single IV dose of [pyridinylmethyl- ^{14}C]-labeled isavuconazonium sulfate.

2.2.5.5. Does the mass balance trial suggest renal or hepatic as the major route of elimination?

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

Isavuconazole accounted for the majority of the radioactivity in feces (33% up to 144 hours postdose). Evidence of enterohepatic recycling in various Phase 1 studies and nonclinical results in bile-duct cannulated rats suggests that isavuconazole does undergo significant biliary excretion.

The majority of the [cyano- ^{14}C]-radioactivity recovered in urine was excreted as metabolites of isavuconazole. Renal excretion of isavuconazole itself was less than 1% of

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

The cleavage product obtained upon hydrolysis of isavuconazonium to isavuconazole is primarily eliminated by metabolism and renal excretion of the metabolites.

2.2.5.6. What are the characteristics of drug metabolism?

In plasma, isavuconazonium was rapidly and quantitatively converted to isavuconazole by esterases, mainly BChE, with a $t_{1/2}$ of < 2 min in vitro.

The *in vitro* metabolism of isavuconazole was investigated in human hepatocytes and liver microsomes. Isavuconazole is metabolized to a small extent to oxidative and further conjugated metabolites. Incubations in recombinant human CYP isoenzymes showed metabolism of isavuconazole in CYP3A4 and CYP3A5 samples, suggesting that these are the primary responsible enzymes for in vitro oxidative metabolism of isavuconazole.

2.2.5.7. What are the characteristics of drug excretion?

Following IV administration of [pyridinylmethyl- ^{14}C] isavuconazonium sulfate, 95% of the total radioactive dose was excreted in the urine; the major form of urine radioactivity was the oxidative carbamate cleavage metabolite M4 (56% of total dose) Renal elimination of intact cleavage product was less than 1% of the total dose administered.

2.2.5.8. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The dose proportionality of isavuconazole exposure after oral and intravenous administration of isavuconazonium was explored in three studies in healthy subjects. As shown in Figures 13 and 14, dose proportional increases in AUC and C_{max} were observed following both the IV and oral dose administration:

Figure 13. Dose proportionality following single ascending doses of oral isavuconazonium (Source: Reviewer's analysis)

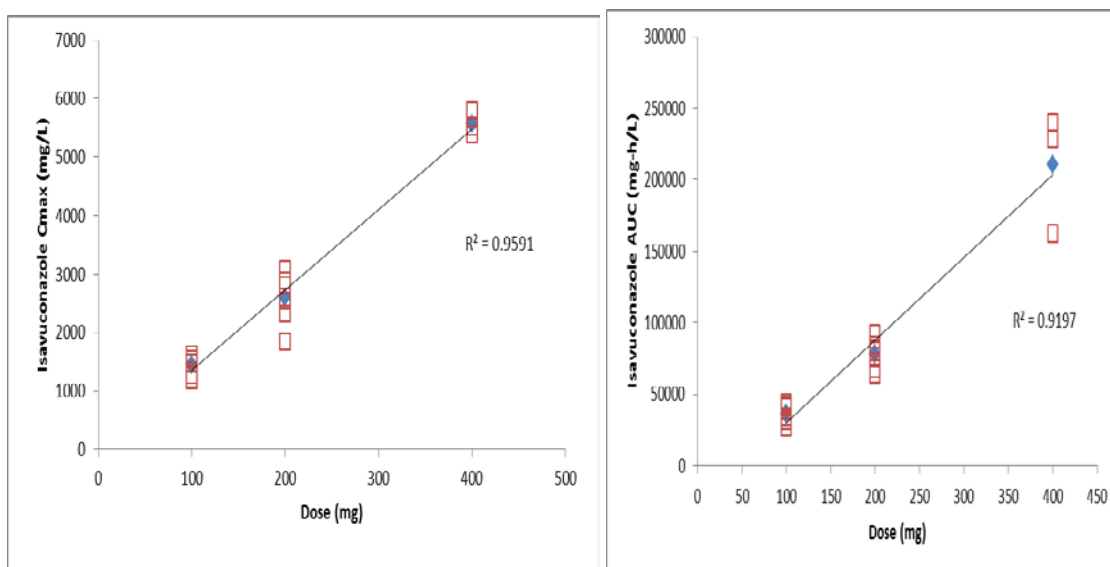
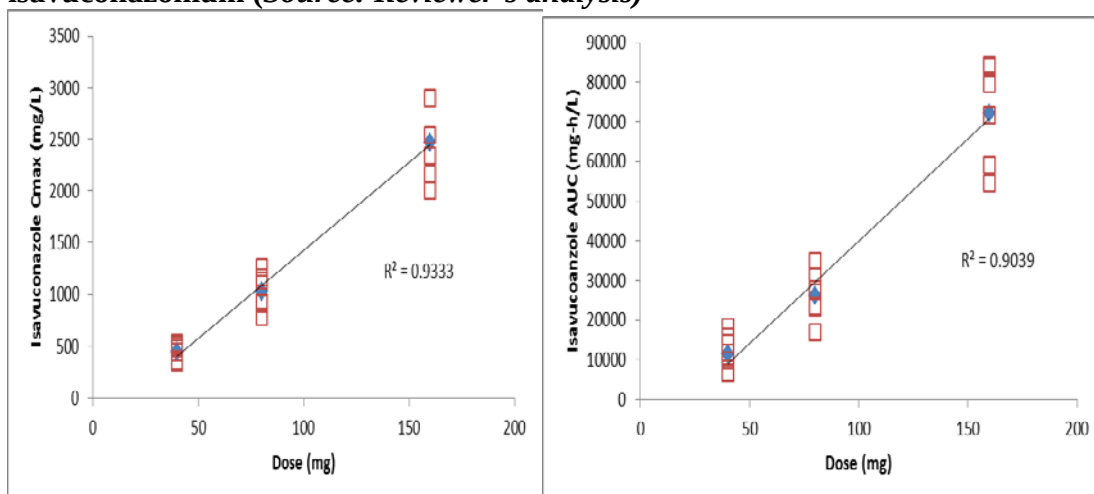


Figure 14. Dose proportionality following single ascending doses of IV isavuconazonium (Source: Reviewer's analysis)



Linearity in the PK was demonstrated by comparing the clearance across dose groups (i.e., both CLss/F and CLss following administration of oral and IV dosage forms, respectively). Median clearance was found to be constant (approximately 2500 mL/h) as a function of dose indicating linearity in PK.

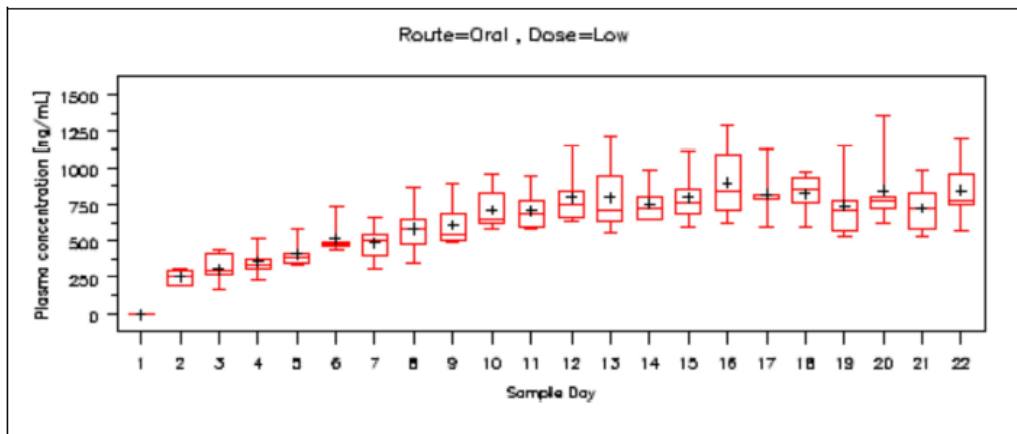
2.2.5.9. How do the PK parameters change with time following chronic dosing?

Multiple dose Study 9766-CL-0003 indicated that isavuconazonium does not accumulate over the dose range 40 to 80 mg isavuconazole IV or 50 to 100 mg isavuconazole orally. Assessment of isavuconazole predose trough concentrations (Figure 15) indicated that near steady-state conditions were achieved within 14 days of once daily oral and IV dosing. This is consistent with an apparent terminal half-life of approximately 130 hours. Mean isavuconazole AUC increased approximately 4- to 5-fold after once daily administration relative to single-dose data after maintenance doses of 50 and 100 mg.

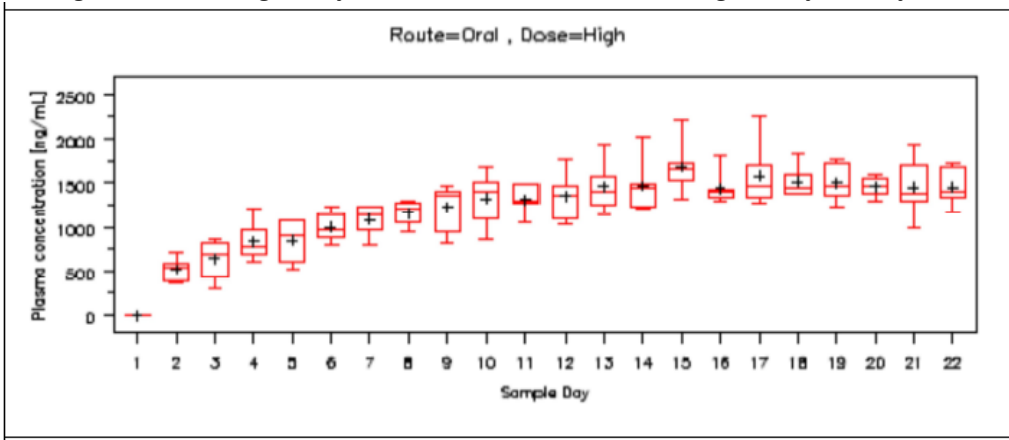
This estimation is based on a comparison of mean dose-normalized AUC₂₄ on day 1 and day 14 (IV)/21 (PO) and assumes approximately dose-proportional pharmacokinetics. Isavuconazole C_{max} was approximately 2- to 3-fold higher at steady state compared to a single dose. The prodrug and the cleavage product did not accumulate after once daily intravenous doses of isavuconazonium.

Figure 15 Mean Isavuconazole Trough Plasma Concentrations Following Oral and Intravenous Administration of Isavuconazonium Chloride (Source: Sponsor's report)

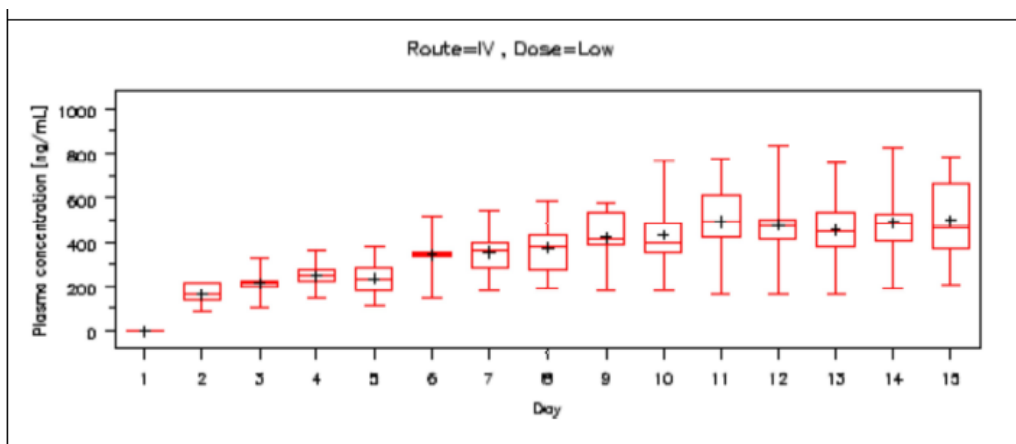
Oral low dose of 100 mg on day 1 and maintenance dose of 50 mg QD from day 2 to day 21



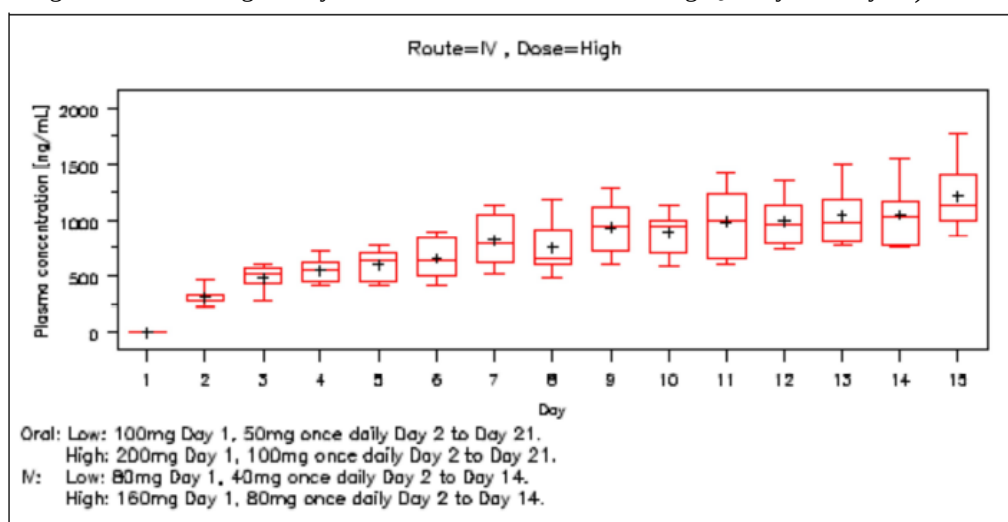
Oral high dose of 200 mg on day 1 and maintenance dose of 100 mg QD day 2 to day 21



IV low dose of 80 mg on day 1 and maintenance dose of 40 mg QD from day 2 to day 14



IV high dose of 160 mg on day 1 and maintenance dose of 80 mg QD day 2 to day 14)



2.2.5.10. What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

After oral and IV administration of a single dose of isavuconazonium sulfate, corresponding to isavuconazole 400 mg orally or as a 2 hour infusion in healthy volunteers, intersubject variability in isavuconazole C_{max} was low after both oral (21%) and IV dosing (13%). Intersubject variability in isavuconazole AUC_{inf} was moderate (%CV of 37%) and similar for both routes of administration, suggesting that variability in isavuconazole PK is mainly due to differences in disposition. Based on population PK, intersubject variability for AUC was (%CV) 58% and intra subject variability was (%CV) 45%.

2.3. Intrinsic Factors

2.3.1. What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Based on population PK analysis, race (Asian/non-asian) was a significant covariate on clearance and BMI was a significant covariate on volume of distribution of isavuconazole. None of the

covariates of age, gender, weight or race require dose adjustment based on exposure since the overall E-R relationship for efficacy and safety was flat within the concentration range achieved in the pivotal phase 3 study 9766-CL-0104.

2.3.2. *Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.*

2.3.2.1. Weight

Population PK analysis of the cumulative study data from 9 phase 1 studies and 1 phase 3 study (n=190 healthy subjects and 232 patients) did not identify weight as a significant covariate after accounting for significant effect of race on clearance and BMI on volume of distribution. Thus, weight may have been indirectly accounted for by these two covariates. Overall, as expected from these covariate relationships, there was a trend of decreasing AUC and Ctrough at Day 7 with increasing body weight (Figure 16 A & B). But this decrease in exposure parameters with increasing body weight did not translate to increase in mortality (Figure 17). Thus, no dose adjustment is needed based on body weight.

Figure 16 Relationship between exposure (AUC in panel A and Ctrough at Day 7 in panel B) and body weight for the non-weight based dosing regimen of isavuconazole in Phase 3 study 9766-CL-0104 (E-R dataset). (Source: Reviewer's analysis)

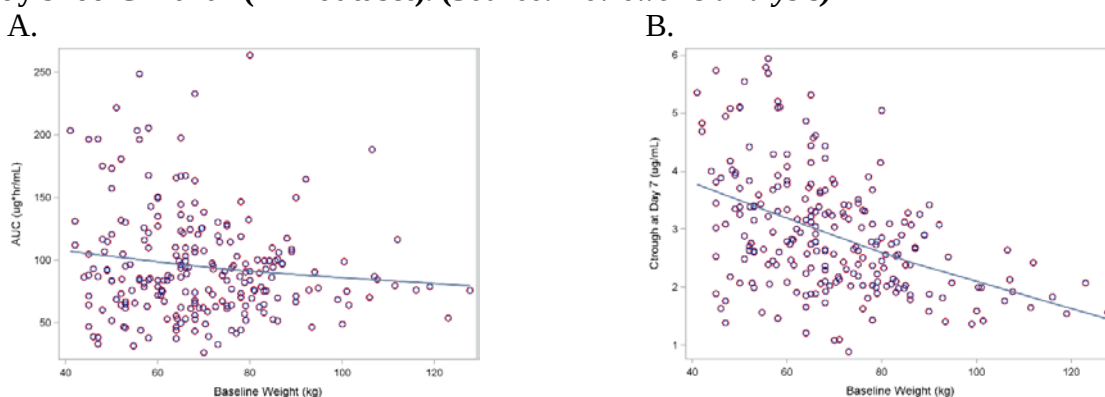
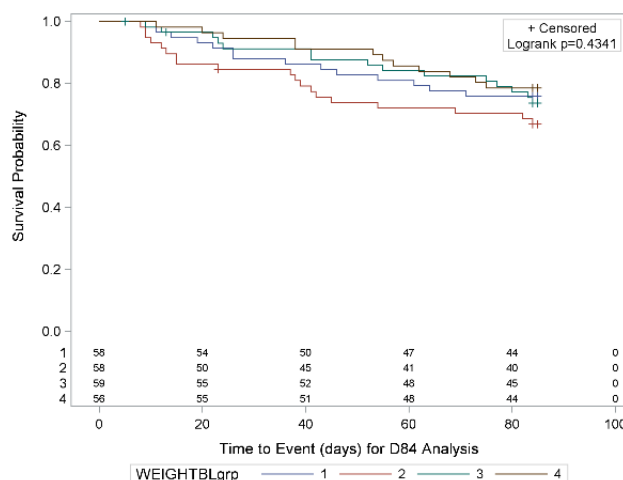


Figure 17 Kaplan-Mier analyses of mortality vs. body weight in isavuconazole treatment arm in Phase 3 study 9766-CL-0104 (E-R dataset). (Source: Reviewer's analysis)



2.3.2.2. Elderly

PK in healthy male and female elderly (≥ 65 year) or non-elderly subjects (18 to 45 years) was investigated in Study 9766-CL-0041 using single oral dose of 200 mg isavuconazole. Population PK analysis of this study data showed that the AUC of isavuconazole in elderly subjects was similar to that in younger subjects. The AUC was similar between younger female and male subjects as well as between elderly and younger males. Elderly females had 38% higher AUC than elderly males and 47% higher AUC than younger females as shown in Table 9. Based on the flat exposure-response relationship for efficacy and safety within the concentrations achieved with Phase 3 dosing, these differences in PK in elderly females are not clinically significant. Analysis of mortality data also did not show any gender specific trends in Phase 3 study 9766-CL-0104 (Figure 18). There was a slight trend of increase in incidence of mortality (Day 84) with higher age in this study, which is logical, and is unrelated to differences in isavuconazole exposure. This trend was not evident based on primary efficacy endpoint of imputed mortality by Day 42 (Figure 19). Based on these cumulative evidences, no dose adjustment is required based on age (elderly/non-elderly) and gender.

Table 9. Comparison of AUC across age (elderly/non-elderly) and gender based on population pk based analysis (Source: Sponsor's report)

Parameter	Comparison	Ratio (%)	90% CI of Ratio
AUC (ug*hr/mL)	Elderly Female Vs Male	137.86	(118, 160.95)
	Elderly Female Vs Non Elderly Female	147.42	(123.27, 176.29)
	Non Elderly Female Vs Male	93.52	(80.10, 109.18)

Results based on ANOVA of natural log transformed AUC. Exponential values of the least square means based on natural log-transformed data

Figure 18 Kaplan-Meier analyses of mortality vs. gender in isavuconazole treatment arm in Phase 3 study 9766-CL-0104 (E-R dataset). (Source: Reviewer's analysis)

Overall Mortality at End of Treatment (Day 84)

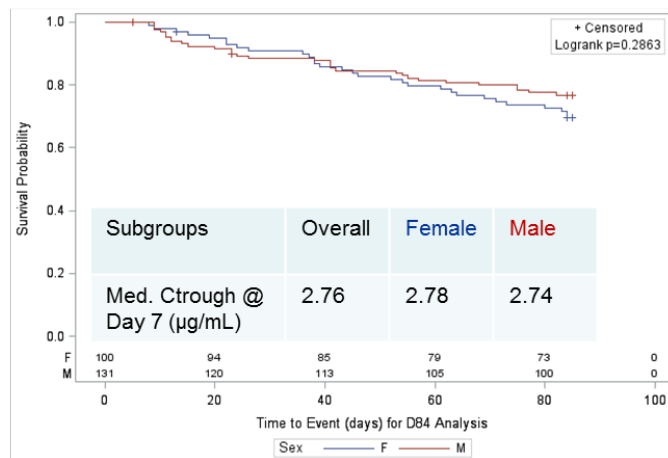
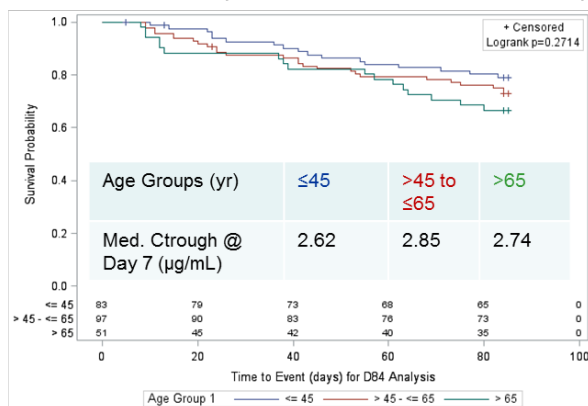


Figure 19 Slight age related (statistically non-significant) trends in mortality incidences in isavuconazole treatment arm in Phase 3 study 9766-CL-0104 (E-R dataset) at day 84; no such trend in Day 42 mortality analysis. (Source: Reviewer's analysis)

Overall Mortality at End of Treatment (Day 84)



Imputed period of death ≤ Day 42

Age Groups	≤45	>45 to ≤65	>65
	Mortality n/N (%)	Mortality n/N (%)	Mortality n/N (%)
All subjects	11/83 (13.3%)	17/97 (17.5%)	9/51 (17.7%)

2.3.2.3. Pediatric patients

No information was collected in pediatric patients

2.3.2.4. Gender

See section 2.3.2.2 above.

2.3.2.5. Race

PK in healthy Chinese and Western (predominantly Caucasian) subjects were compared by cross trial comparison of single and multiple dose trials following single and multiple oral and intravenous doses of isavuconazole (200 mg equivalent isavuconazole) as shown in Table 10.

Table 10. Comparison of isavuconazole exposure in healthy Chinese and Western subjects after single- and multiple-dose administration of isavuconazonium (200 mg equivalent isavuconazole). (Source: Sponsor's Clinical Pharmacology Summary)

Parameter	Single Dose		Multiple Dose	
	Chinese Subjects	Western Subjects	Chinese Subjects	Western Subjects
Study	9766-CL-0038	9766-CL-0041	9766-CL-0038	9766-CL-0017
n	12	24	12	37
C _{max} (µg/mL)	3.391 (0.500)	2.318 (0.524)	8.891 (1.651)	7.499 (1.893)
AUC (µg·h/mL) [†]	116.4 (36.3)	96.26 (27.7)	140.4 (32.8)	121.4 (35.8)

Values of pharmacokinetics parameters are mean (SD).

[†] AUC = AUC_{inf} for single dose results, AUC_{tau} for multiple dose results.

Population PK evaluation of this data concluded that Chinese subjects have on average a 40% lower clearance compared to Western subjects (1.6 L/hr for Chinese subjects as compared to 2.57 L/hr for Western subjects) which translated to ~50% higher exposure than Western subjects. In Phase 3 study 9766-CL-0104, the median AUC levels and Ctrough at Day 7 levels were 1.7-fold (145 µg·hr/mL vs. 84 µg·hr/mL) and 1.4-fold (3.81 µg/mL vs. 2.64 µg/mL) in Asians as compared to non-asians. Though there was numerically higher incidence of mortality in Asians as compared to non-Asians, this apparent higher mortality was highly influenced by the results in enrolled population in South Korea and removal of this country during sensitivity analysis resulted in resolution of the discrepancy in mortality (Refer to section 2.2.4.1 and 2.2.4.2 for details). Overall since there was flat E-R relationship for efficacy (mortality) and safety within the range of exposures achieved in pivotal Phase 3 study, from both exposure and response perspective, no dose adjustment would be needed based on race (Asian/non-Asian).

2.3.2.6. Renal impairment

Isavuconazole PK was evaluated in subjects with various degrees of renal impairment, in subjects with end stage renal disease (ESRD) on dialysis, and in matched healthy volunteers (based on age, sex, smoking status) following the administration of isavuconazonium (372.6 mg), designed to deliver 200 mg equivalent of isavuconazole, over a 1 hour infusion (Study 9766-CL-0018). The Cockcroft-Gault equation was used to estimate creatinine clearance (CLcr) to categorize the degree of renal impairment as follows: normal (CLcr > 80 mL/min), mild (CLcr = 50 – 80 mL/min), moderate (CLcr = 30 < 50 mL/min), severe (CLcr = < 30 mL/min), and ESRD (CLcr < 15 mL/min/1.73 m² and requiring hemodialysis).

Isavuconazole AUC₇₂ and C_{max} were 34% and 21% lower, respectively, for subjects with ESRD dialyzed 1 hour prior to dosing compared to subjects with normal renal function (Table 11). This can be attributed to hemodilution associated with a rapid flux of intracellular water into the vascular space post-dialysis prior to administration of the intravenous infusion of isavuconazole. Isavuconazole was not removed by hemodialysis which is expected because of isavuconazole is highly bound to plasma proteins (Table 12).

Table 11. Statistical Assessment of the Effect of ESRD on the pharmacokinetics of isavuconazole (Source: Sponsor's report)

Parameter	ESRD		Normal Renal Function		Ratio (%) ESRD/Normal [‡]	90% CI for Ratio [‡]
	n	Geometric Least Squares Mean [†]	n	Geometric Least Squares Mean [†]		
AUC ₇₂ (ng•h/mL)	8	23732	8	35773	66.34	(50.79, 86.66)
C _{max} (ng/mL)	8	3544	8	4467	79.33	(60.59, 103.88)

Table 12. Isavuconazole Percent Protein Binding in Subjects with Normal and Impaired Renal Function (Source: Reviewer's analysis)

	Part 1		Part 2			
Renal Function Group	Normal	ESRD	Normal	Mild	Moderate	Severe
Median	99.82	99.64	99.72	99.65	99.59	99.53

Renal impairment has no effect on isavuconazole exposure (Table 13) and therefore no dose adjustment is recommended in patients with any degree of renal impairment.

Table 13. Statistical Assessment of the Effect of renal impairment on the pharmacokinetics of isavuconazole (Source: Sponsor's report)

Parameter	Comparison	Renal Impairment		Normal Renal Function		Ratio (%) Impaired/ Normal [‡]	90% CI for Ratio [‡]
		n	Geometric Least Squares Mean [†]	n	Geometric Least Squares Mean [†]		
AUC _{inf} (ng•h/mL)	Severe vs Normal	5	90373	8	89610	100.85	(67.07, 151.64)
	Moderate vs Normal	8	93492	8	89610	104.33	(72.96, 149.20)
	Mild vs Normal	8	87607	8	89610	97.76	(68.36, 139.81)
AUC _{last} (ng•h/mL)	Severe vs Normal	5	71803	8	72604	98.90	(73.54, 133.00)
	Moderate vs Normal	8	71032	8	72604	97.84	(75.45, 126.87)
	Mild vs Normal	8	74185	8	72604	102.18	(78.79, 132.50)
C _{max} (ng/mL)	Severe vs Normal	5	3440	8	4020	85.57	(65.36, 112.01)
	Moderate vs Normal	8	3752	8	4020	93.32	(74.36, 117.12)
	Mild vs Normal	8	4194	8	4020	104.32	(79.92, 136.17)

2.3.2.7. Hepatic impairment

Isavuconazole pharmacokinetics were evaluated in two studies in subjects with liver cirrhosis and mild to moderate hepatic impairment and in matched healthy volunteers (based on age, sex, body weight and BMI) following the administration of isavuconazonium sulfate both orally and over a 1 hour infusion. The net isavuconazole dose was 100 mg. Child-Pugh classification was used to stage hepatic impairment. The two studies were identical in design and the only difference was the etiology of liver cirrhosis. Viral hepatitis infection (A or B or C or a combination) was the underlying cause for liver impairment in one study (Study 9766-CL-0014) while alcoholic cirrhosis was the underlying cause for liver impairment in the second study (Study 9766-CL-0008).

Study 9766-CL-0014 (viral hepatitis A or B or C): Following IV administration, the total isavuconazole exposure increases approximately 30% to 48% in subjects with mild liver impairment and approximately 69% to 106% in subjects with moderate liver impairment. Following oral administration, the total isavuconazole exposure increases approximately 27% to 41% in subjects with mild liver impairment and approximately 30% to 85% in subjects with moderate liver impairment. Liver impairment did not affect the extent of isavuconazole protein binding (Table 14). No dose adjustment is required following the administration of isavuconazole to patients with mild or moderate hepatic impairment due to hepatitis A, B, or C infection (Table 15).

Table 14. Average Percent Protein Binding for Isavuconazole by Hepatic Impairment Group and Dose Route (Source: Sponsor's report)

Statistic	Dose Route / Hepatic Impairment Group					
	Intravenous			Oral		
	Healthy (n = 8)	Mild (n = 8)	Moderate (n = 8)	Healthy (n = 8)	Mild (n = 8)	Moderate (n = 8)
% Protein Binding†						
Mean (SD)	99.87 (0.012)	99.86 (0.017)	99.82 (0.036)	99.88 (0.009)	99.88 (0.015)	99.78 (0.127)
Median	99.87	99.86	99.82	99.87	99.88	99.80
Minimum – Maximum	99.85 – 99.89	99.83 – 99.89	99.75 – 99.87	99.86 – 99.89	99.85 – 99.90	99.48 – 99.88
Geometric mean	99.87	99.86	99.82	99.88	99.88	99.78

All subjects who provided an adequate number of blood samples, as determined by the pharmacokineticist, to calculate at least one of the primary pharmacokinetic parameters (total and unbound) AUClast, AUCinf and Cmax (pharmacokinetic analysis set).

† Average of the 2 postdose samples collected on day 1 and day 10.

Table 15. Statistical Analysis of the Effect of Hepatic Impairment Due to Liver Cirrhosis Caused by Hepatitis A, B, or C on Isavuconazole Pharmacokinetics (Source: Sponsor's report)

Parameter	Number in Hepatic Impairment Group		Ratio (%) Impaired/Healthy†	90% CI of Ratio†
Intravenous Administration				
AUC _{inf} † (h•ng/mL)	Healthy	8	NA	NA
	Mild impairment	8	147.8	(108.9, 200.5)
	Moderate impairment	8	205.6	(151.5, 279.0)
AUC _{last} (h•ng/mL)	Healthy	8	NA	NA
	Mild impairment	8	130.0	(99.1, 170.5)
	Moderate impairment	8	168.9	(128.8, 221.5)
C _{max} (ng/mL)	Healthy	8	NA	NA
	Mild impairment	8	92.0	(72.8, 116.3)
	Moderate impairment	8	73.5	(58.1, 92.9)
Oral Administration				
AUC _{inf} † (h•ng/mL)	Healthy	8	NA	NA
	Mild impairment	8	140.9	(98.9, 200.6)
	Moderate impairment	8	185.1	(130.0, 263.6)
AUC _{last} (h•ng/mL)	Healthy	8	NA	NA
	Mild impairment	8	127.3	(102.5, 158.2)
	Moderate impairment	8	130.2	(104.8, 161.7)
C _{max} (ng/mL)	Healthy	8	NA	NA
	Mild impairment	8	137.3	(108.4, 173.9)
	Moderate impairment	8	79.0	(62.3, 100.0)

All subjects in the safety population whose pharmacokinetic data were adequate for the calculation of at least one of the primary pharmacokinetic parameters (pharmacokinetic analysis set). An analysis of variance with fixed effect for hepatic impairment group was performed on natural log-transformed parameters for oral and intravenous dose groups separately.

NA: not applicable.

† Ratios and confidence limits were transformed back to raw units by exponentiating and expressed as a percent.

‡ Results for AUCinf values from all available subjects.

Study 9766-CL-0008 (alcoholic cirrhosis subjects): Following IV administration, the total isavuconazole exposure increases approximately 31% to 59% in subjects with mild liver impairment and approximately 63% to 119% in subjects with moderate liver impairment. Following oral administration, the total isavuconazole exposure increases approximately 42% to 118% in subjects with mild liver impairment and approximately 11% to 41% in subjects with moderate liver impairment. Liver impairment did not affect the extent of isavuconazole protein binding (Table 16). No dose adjustment is required following the administration of isavuconazole to patients with mild or moderate hepatic impairment due to alcoholic cirrhosis (Table 17).

Table 16. Average Percent Protein Binding for Isavuconazole by Hepatic Impairment Group (Alcoholic Cirrhosis) and Dose Route (Source: Sponsor's report)

Statistic	Dose Route / Hepatic Impairment Group					
	Intravenous			Oral		
	Healthy (n = 8)	Mild (n = 8)	Moderate (n = 8)	Healthy (n = 8)	Mild (n = 8)	Moderate (n = 8)
% Protein Binding†						
Mean (SD)	99.31 (0.079)	99.17 (0.216)	99.16 (0.133)	99.34 (0.051)	99.27 (0.121)	98.94 (0.285)
Median	99.30	99.17	99.11	99.32	99.26	99.04
Minimum – Maximum	99.22 – 99.46	98.88 – 99.43	98.97 – 99.32	99.28 – 99.42	99.10 – 99.40	98.44 – 99.24
Geometric mean	99.31	99.17	99.16	99.34	99.27	98.94

All subjects who provided an adequate number of blood samples, as determined by the pharmacokineticist, to calculate at least one of the primary pharmacokinetic parameters (total and unbound) AUClast, AUCinf and Cmax (pharmacokinetic analysis set)

† Average of the 2 postdose samples collected on day 1 and day 10

Table 17. Statistical Analysis of Hepatic Impairment Due to Alcoholic Liver Cirrhosis on the Isavuconazole Pharmacokinetics (Source: Sponsor's report)

Total Isavuconazole Pharmacokinetic Parameter (unit)	Hepatic Impairment Group	n	Geometric LS Mean[†]	Ratio (%) Impaired/Healthy[‡]	90% CI of Ratio[‡]
Intravenous route					
AUC _{inf} (h·ng/mL) [§]	Healthy	8	37517.2	NA	NA
	Mild impairment	8	59628.0	158.9	(98.8, 255.5)
	Moderate impairment	7	82199.2	219.1	(134.0, 358.2)
AUC _{last} (h·ng/mL)	Healthy	8	34844.9	NA	NA
	Mild impairment	8	45725.6	131.2	(94.5, 182.2)
	Moderate impairment	8	56669.8	162.6	(117.1, 225.9)
C _{max} (ng/mL)	Healthy	8	1079.6	NA	NA
	Mild impairment	8	927.1	85.9	(69.9, 105.5)
	Moderate impairment	8	827.3	76.6	(62.4, 94.1)
Oral route					
AUC _{inf} (h·ng/mL) [§]	Healthy	8	42282.9	NA	NA
	Mild impairment	8	91977.0	217.5	(154.3, 306.6)
	Moderate impairment	8	59505.4	140.7	(99.8, 198.4)
AUC _{last} (h·ng/mL)	Healthy	8	38700.7	NA	NA
	Mild impairment	8	54974.2	142.0	(110.2, 183.1)
	Moderate impairment	8	43106.5	111.4	(86.4, 143.6)
C _{max} (ng/mL)	Healthy	8	828.4	NA	NA
	Mild impairment	8	713.0	86.1	(69.9, 106.0)
	Moderate impairment	8	456.5	55.1	(44.7, 67.9)

All subjects who provided an adequate number of blood samples, as determined by the pharmacokineticist, to calculate at least one of the primary pharmacokinetic parameters (total and unbound) AUC_{last}, AUC_{inf} and C_{max} (pharmacokinetic analysis set). An analysis of variance (ANOVA) with fixed effect for hepatic impairment group was performed on natural log-transformed parameters for oral and intravenous dose groups separately.

LS: least squares; NA: not available.

[†] The exponentiated value of the least squares mean based on natural log-transformed data.

[‡] Ratios and CIs were transformed back to raw units by exponentiating and expressed as a percentage.

[§] Results for AUC_{inf} values from all available subjects

The pharmacokinetics of isavuconazole were not evaluated in subjects with severe hepatic impairment and therefore administration of isavuconazole is not recommended in patients with severe hepatic impairment. In general, although there were increases in exposure for mild to moderate hepatic impairment and the upper bounds of the 90% CI's show increased exposure, particularly with IV administration, since there were no exposure-safety trends observed, no dose adjustment is needed for hepatic impairment.

2.3.2.8. Pregnancy/Lactation

There is no information on the effect of pregnancy and lactation on the PK of isavuconazonium.

2.4. Extrinsic Factors

2.4.1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response? Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors?

The effects of extrinsic factors such as herbal products, smoking and alcohol use have not been studied. The effect of co-administering other drugs with isavuconazonium is addressed below.

2.4.2. Drug-Drug Interactions

2.4.2.1. *Is there an in vitro basis to suspect in vivo drug-drug interactions?*

In vitro metabolism, inhibition/induction, and transporter experiments suggest the potential for in vivo drug interactions.

2.4.2.2. *Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?*

Isavuconazole is a substrate of CYP3A4 and CYP3A5. No genetic influence on the metabolism was studied.

2.4.2.3. *Is the drug an inhibitor and/or an inducer of CYP enzymes?*

Isavuconazole is an in vitro inhibitor of human CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 in human liver microsomes (HLMs), with K_i values of 2.86, 4.78, 5.40, 4.82 and 0.622-1.93 $\mu\text{mol/L}$, respectively. In an in vitro study using cultured human hepatocytes, isavuconazole caused an increase of up to 2.77-, 13.4-, 2.63- and 3.43-fold in CYP1A2, CYP2B6, CYP2C8 and CYP3A4/5 activity, respectively, and was $\leq 10\%$ (CYP1A2), 84.3% (CYP2B6), 37.4% (CYP2C8) and 42.2% (CYP3A4/5) as effective as their respective positive control at inducing CYP activity.

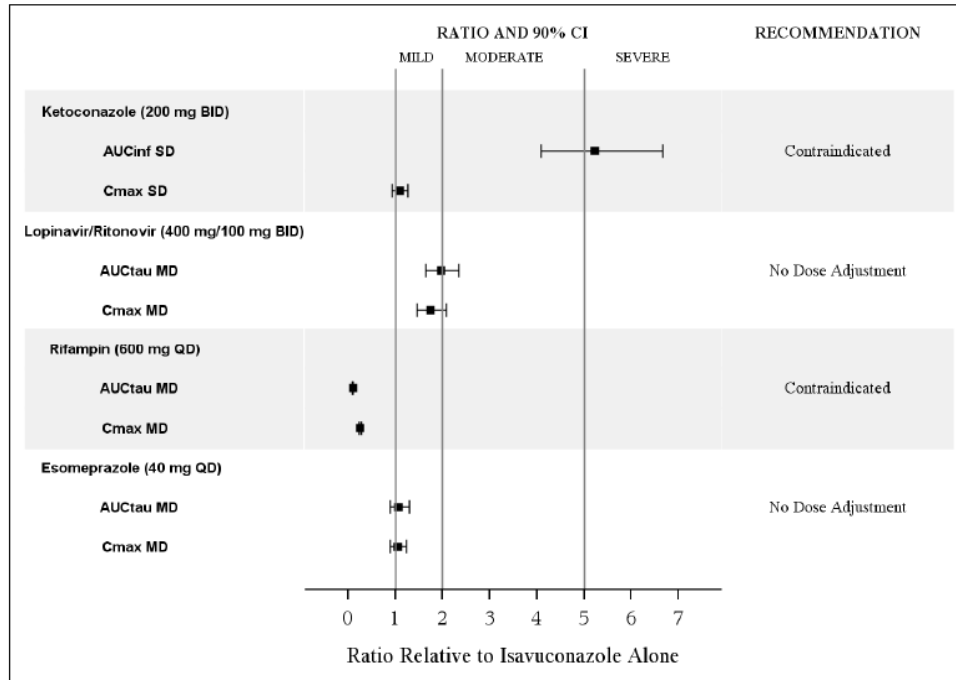
2.4.2.4. *Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?*

Isavuconazole is not an in vitro substrate of P-gp or BCRP efflux nor OATP1B1 or OATP1B3 uptake transporters. However, it is an inhibitor of P-gp (IC_{50} of 25.7 $\mu\text{mol/L}$), BCRP (IC_{50} of 92.0 $\mu\text{mol/L}$), OATP1B1 (IC_{50} of 11.2 $\mu\text{mol/L}$), OCT1 (K_i of 1.74 $\mu\text{mol/L}$), OCT2 (K_i of 0.590 $\mu\text{mol/L}$) and MATE1 (IC_{50} of 6.31 $\mu\text{mol/L}$) drug transporters.

2.4.3. *Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated? What co-medications are likely to be administered to the target patient population?*

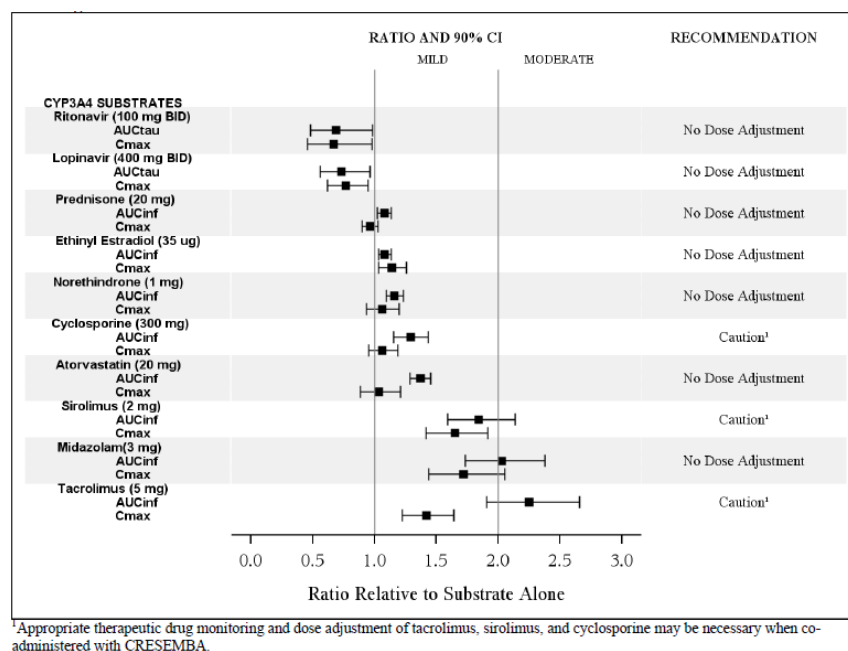
The in vivo drug interaction potential of isavuconazole has been evaluated in several in vivo interaction studies. The results of the DDI studies have been evaluated by the clinical pharmacology team and are found to be acceptable. The results of the DDI studies and the accompanied recommendations for dosage adjustments are given below:

The effect of co-administered drugs on isavuconazole exposure is given below (Source: Sponsor's Forest Plots).



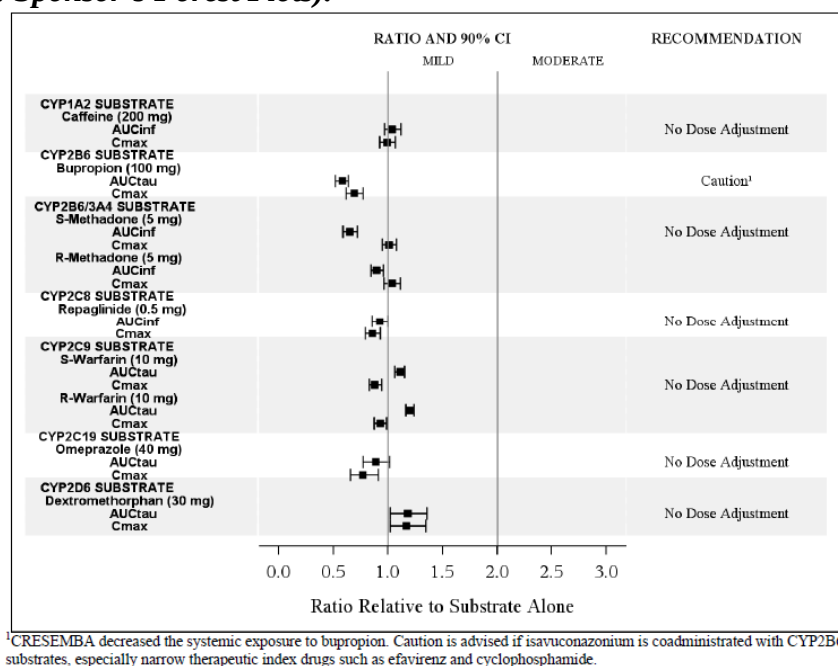
As seen above, given the large increases in exposure seen for isavuconazole, when given with ketoconazole, the coadministration of potent inhibitors of CYP3A4 is contraindicated. Similarly, given the decrease in exposure of isavuconazole when coadministered with rifampin, coadministration of potent inducers of CYP3A4 is contraindicated. Caution is recommended when Cresemba is coadministered with lopinavir/ritonavir. A 96% and 74% increase in AUCtau and Cmax were observed for isavuconazole when isavuconazole was given with lopinavir/ritonavir. However, given that no exposure-safety relationships were observed, the coadministration of these two drugs is not being contraindicated. But physicians should monitor their patients for known toxicity issues of isavuconazole when these two drugs are coadministered.

The effect of isavuconazole on co-administered CYP3A4 substrate medications is given below (Source: Sponsor's Forest Plots).



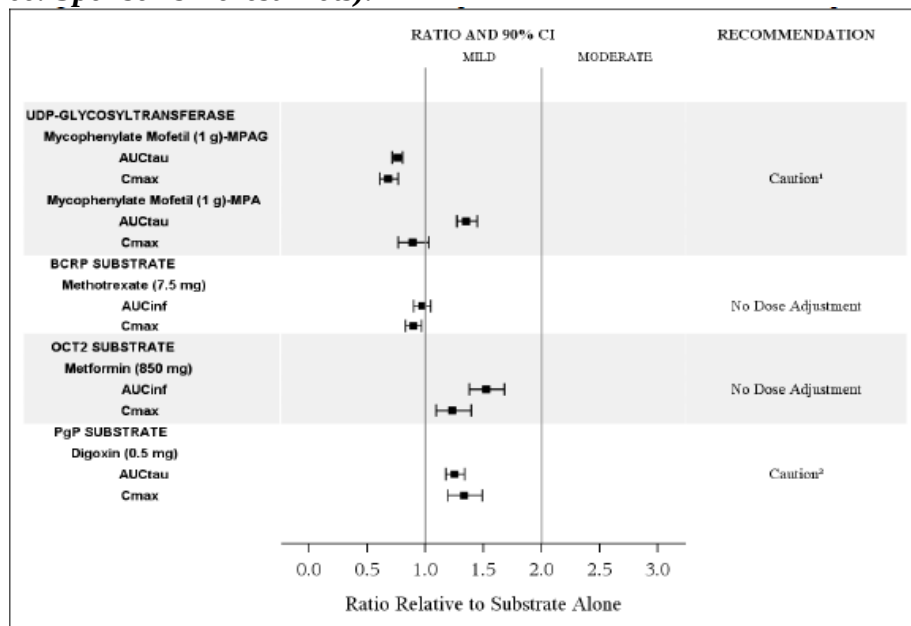
As shown in the above figure, cautionary statements should be included in the label about concomitant use of isavuconazole with ritonavir/lopinavir, cyclosporine, sirolimus and tacrolimus. In the case of cyclosporine, tacrolimus and sirolimus, therapeutic drug monitoring of those drugs should be performed more frequently when given with isavuconazole.

The effect of isavuconazole on exposure of co-administered CYP substrate drugs is given below (Source: Sponsor's Forest Plots).



As shown in the above figure, cautionary statements should be included in the label about concomitant use of isavuconazole with bupropion.

The effect of isavuconazole on exposure on the substrates of UGT and transporters is given below (Source: Sponsor's Forest Plots).



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

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

As shown in the above figure, cautionary statements should be included in the label about concomitant use of isavuconazole with MMF and digoxin.

2.4.3.1. *Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?*

There is no known mechanistic basis for pharmacodynamic drug-drug interactions.

2.4.3.1.1. *Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?*

There are no other unresolved questions related to metabolism, active metabolites and drug interactions, or protein binding.

2.4.4. *What issues related to dose, dosing regimens, or administration are unresolved and represents significant omissions?*

There are no other unresolved questions related to dosing, dosing regimens or administration.

(b) (4)

(b) (4)

(b) (4)

The studies 9766-CL-0104 and 9766-CL-0103 carried out microbiological MIC evaluations with samples from a subset of patients. The microbiology dataset contained 28 subjects with *A. fumigatus* as the single fungal infection species, 21 of whom had partial or complete clinical response (partial resolution or resolution of all attributable clinical symptoms and physical findings at day 42). Out of these 28 patients, 19 subjects were from pivotal phase 3 study 9766-CL-0104 and had predicted isavuconazole exposure values from population PK analysis. The analysis of these 19 patients by grouped MIC values versus clinical response showed that 13 out of 15 (86.7%) subjects with MIC values ≤ 1 $\mu\text{g/mL}$ had partial or complete clinical response while 1 out of 3 (33.3%) subjects with MIC values ≥ 4 $\mu\text{g/mL}$ had partial or complete clinical response with the exposures achieved with the proposed dosing regimen of isavuconazole (Table 19).

(b) (4)

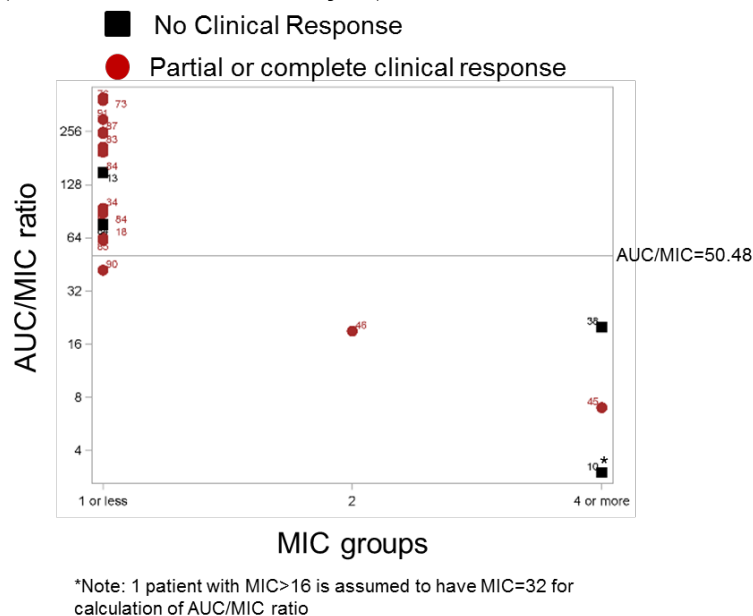
(U) (4)

Table 19. Comparison of clinical response in patients grouped by subsets of MIC values for combination of isavuconazole and *A. fumigatus* species; study 9766-CL-0104. (Source: Reviewer's analysis)

	MIC			Total
	≤ 1 $\mu\text{g/mL}$	2	≥ 4 $\mu\text{g/mL}$	
No Clinical Response	2 (13.3%)	0	2 (66.7%)	4
Partial or Complete Clinical Response	13 (86.7%)	1 (100%)	1 (33.3%)	15
Total	15	1	3	19

In general, the dosing regimen evaluated in the Phase 3 study resulted in achieving AUC/MIC ratios above target ratio of 50.48 for majority of patients with MIC values ≤ 1 $\mu\text{g/mL}$ as seen in Figure 20 for this subset of patients from Phase 3 study with available exposures and MIC values.

Figure 20 AUC/MIC ratio for subjects from phase 3 study with available exposures and MIC values, grouped by MIC thresholds and visualized by clinical response category.
(Source: Reviewer's analysis)



2.5. General Biopharmaceutics

2.5.1. *Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?*

Based on the solubility and permeability data, the prodrug (isavuconazonium) is highly soluble and the active moiety (isavuconazole) is highly permeable. The applicant has not sought BCS classification designation in this application.

2.5.2. *How is the proposed to-be-marketed formulation linked to the clinically used formulation?*

The proposed to-be-marketed (TBM) formulation is not different from the Clinical Trial Material (CTM).

2.5.3. *What is the effect of food on the bioavailability of the drug product?*

Isavuconazole bioavailability from a single oral dose of isavuconazonium sulfate was approximately 98%. The 90% CIs for the oral-to-IV geometric mean ratio (GMR) for AUC extrapolated to infinity (AUC_{inf}) of isavuconazole was contained within the limits of 80% to 125%. After oral administration, isavuconazole C_{max} was reached at approximately 3.5 hours postdose and was 22% lower compared to IV administration (90% CI for GMR: 72.2%, 84.5%). The two formulations are considered to be interchangeable.

2.6. Analytical Section

2.6.1. *What bioanalytical methods are used to determine drug concentrations? Briefly describe the methods and summarize the assay performance.*

Simultaneous quantification of isavuconazole, isavuconazonium and the cleavage product in human plasma or urine was performed by liquid chromatography tandem mass spectrometry (LCMS/MS). All plasma and urine assays were validated according to the applicable guidelines.

(b) (4)

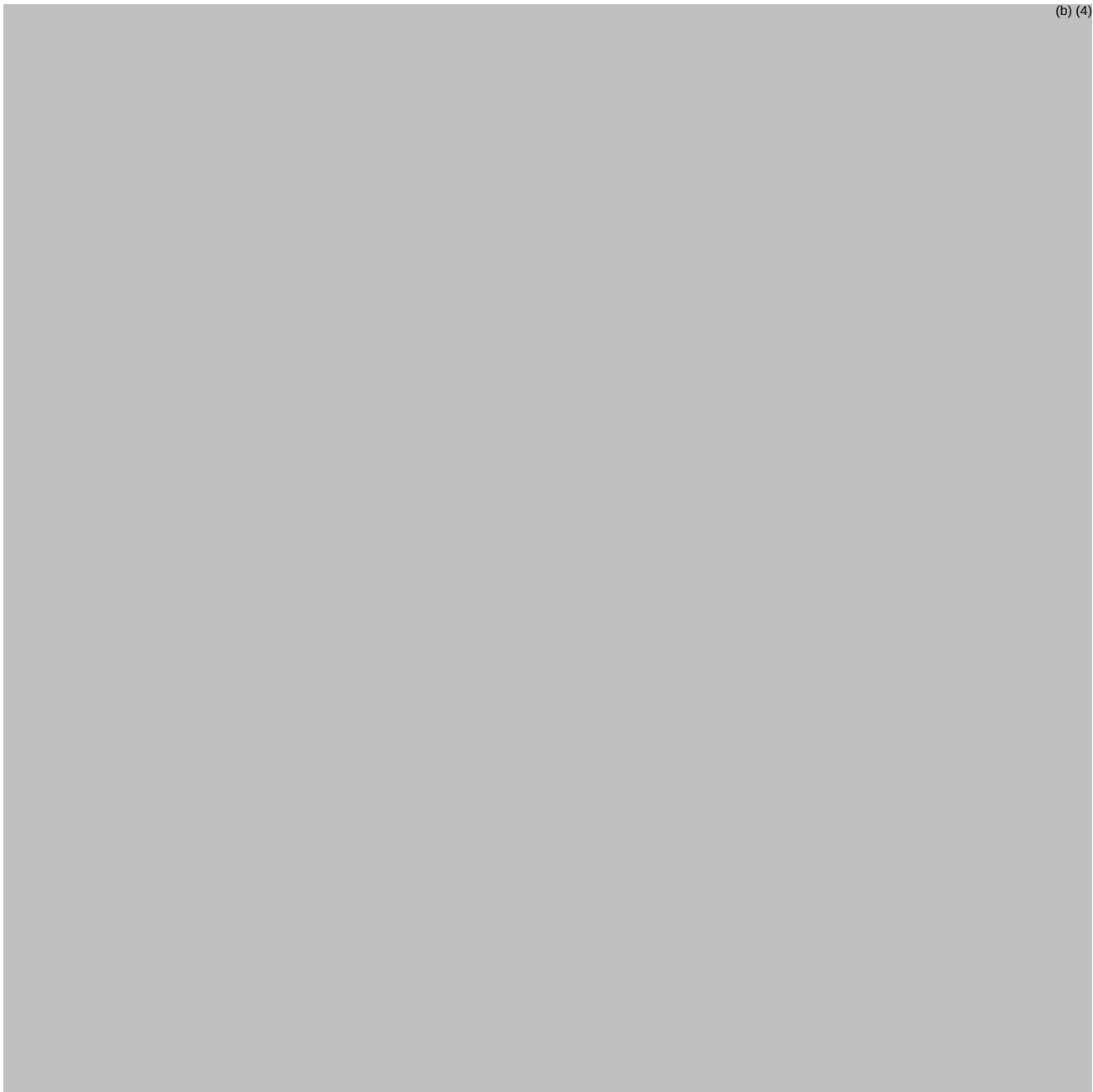


Table 20. Isavuconazole in Plasma (Source: Sponsor's report)

Study Number	9766-ME-0027 (INO-02-013)	9766-ME-0029 (MA527 Amendment 1)	9766-ME-0030 and amendment (INO-04-004)	9766-ME-0040 (PA055)
Clinical studies supported	9766-CL-0001	9766-CL-0002	9766-CL-0003 9766-CL-0004 9766-CL-0006 9766-CL-0009 9766-CL-0102	9766-CL-0005 9766-CL-0007 9766-CL-0010 9766-CL-0015
Analyte	Isavuconazole	Isavuconazole	Isavuconazole	Isavuconazole
Matrix	EDTA plasma stabilized with citric acid and paraoxon	EDTA plasma specified stabilized with citric acid and paraoxon	EDTA plasma stabilized with citric acid and paraoxon	EDTA plasma acidified with citric acid
Assay Method	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS
Sample Preparation	Protein precipitation	Protein precipitation	Protein precipitation	Protein precipitation
Internal Standard		(b) (4)	BAL4815-d ₄	BAL4815-d ₄
LLOQ (ng/mL)	5.000	5.00	5.000	5.00
Assay Volume (mcL)	50	150	50	50
QC Concentrations (ng/mL)	5,000, 15.00, 100.0, 1000	15.0, 150 and 400	5,000, 15.00, 100.0, 1000	15.0, 100, 1000
Calibration Curve Range (ng/mL)	5.000 – 1280	5.00 – 500	5.000 – 1280	5.000 – 1280
Within-Run Accuracy (%)	Not evaluated	0.1 – 6.0	0.6 – 12.4	4.2 – 6.7
Between-Run Accuracy (%)	-10.1 – (-3.5)	-2.5 – 0.4	2.9 – 8.5	3.1 – 7.5
Within-Run Precision (%CV)	1.3 – 10.2	1.8 – 3.4	2.5 – 10.5	0.9 – 3.4
Between-Run Precision (%CV)	3.1 – 10.1	3.1 – 4.6	4.1 – 9.4	2.2 – 6.9
Dilution integrity (%)	10-fold Accuracy: -5.9 Precision: 0.8	Not evaluated	12.8-fold Accuracy: -10.8 Precision: 17.1	4-fold Accuracy: -1.8 Precision: 2.3
Selectivity	No relevant interferences	No relevant interferences	No relevant interferences	No relevant interferences
Short-term stability in matrix	(b) (4)			
Long-term stability in matrix				
Table continued on next page				
Study Number	9766-ME-0027 (INO-02-013)	9766-ME-0029 (MA527 Amendment 1)	9766-ME-0030 and amendment (INO-04-004)	9766-ME-0040 (PA055)
Autosampler storage stability (re-injection reproducibility)	(b) (4)			
Processed sample stability				
Freeze and thaw stability				
Stability of stock solution	(b) (4)			
Stability IS stock solution				
Test Facility				
	Not evaluated	Not evaluated	Not evaluated	Not evaluated

3. LABELING RECOMMENDATIONS

The label will be filed in DARRTS separately after agreement is reached with the sponsor on the specific wording.

4. Individual Study Reviews

Available separately

5. Pharmacometric Review

See below

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

Application Number	NDA 207500 and NDA 207501
Compound	(b) (4) (Cresemba®); 100 mg capsule and 200 mg IV infusion
Indication	Treatment of invasive aspergillosis and invasive mucormycosis
Submission Date	July 04, 2014
Applicant	Astellas, Inc.
Pharmacometrics Reviewer	Dhananjay D. Marathe, PhD
Pharmacometrics Team Leader	Jeffrey Florian, PhD

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1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions:

1.1.1 What are the characteristics of the exposure-response (E-R) relationships for efficacy and safety for isavuconazole? Is the proposed dosing for isavuconazole appropriate?

In the pivotal phase 3 study 9766-CL-0104, flat exposure-response (E-R) relationships were identified for efficacy and safety variables of interest within the isavuconazole exposure range observed with the proposed dosing regimen after adjusting for other study variable. The efficacy variables used for this analysis were imputed all-cause mortality before day 42 and at the end of treatment (day 84) based on both the safety population and FDA-mITT population. The safety variables used for the analysis were selected adverse events of interest e.g. anxiety, nausea, headache, pruritus, fatigue and liver function test signal of ALT elevation to ≥ 3 x ULN. Individual predicted C_{trough} at Day 7 based on a population pharmacokinetic analysis was used as the isavuconazole exposures metric since near steady state C_{trough} concentrations are expected to be achieved by this time using the Phase 3 loading and maintenance dosing regimen. Overall, the exposure-response analyses support the proposed isavuconazole dosing regimen for the overall population.

The subgroup of patients categorized as Asians (either based on race or country/region of treatment) had increased mortality as compared to non-Asians in the isavuconazole treatment arm, while a similar analysis for comparator voriconazole arm did not show a mortality difference with respect to race/region. The apparent higher mortality in the Asian population is highly influenced by the results in enrolled population in South Korea (KOR) and removal of this country during sensitivity analysis resulted in resolution of the discrepancy in mortality between Asians vs. non-Asians for isavuconazole treatment arm. Thus, the observed mortality differences are likely not attributable to race or region-specific differences in disease/drug/background standard-of-care effects and therefore no action is recommended for isavuconazole treatment for the subgroup of Asian population.

Please refer to the section 2.2.4.1 and section 2.2.4.2 in the Clinical Pharmacology Question Based Review (QBR) for details of evaluation of E-R relationship for efficacy and E-R relationship for safety, respectively.

1.1.2 Are the labeling claims of no dose adjustment for intrinsic factors of race, age, bodyweight and gender appropriate?

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

Please refer to the sections 2.3.1 and 2.3.2.1 through 2.3.2.5 of Clinical Pharmacology QBR for additional details about differences in isavuconazole exposure and response to isavuconazole treatment with these factors.

1.1.3

(b) (4)

(b) (4)

(b) (4)

1.2 Recommendations

The Division of Pharmacometrics in the Office of Clinical Pharmacology has reviewed NDA 207500 and NDA 207501 and has the following recommendations:

- Based on flat E-R relationship for efficacy and safety with isavuconazole exposures in the pivotal Phase 3 study, the proposed dosing regimen for Isavuconazole is acceptable for the overall population.
- No dose modifications are required based on age, weight, gender or race.
-  (b) (4)

1.3 Label Statements

Please refer to labeling recommendations in Clinical Pharmacology QBR.

2 PERTINENT REGULATORY BACKGROUND

Isavuconazonium sulfate is a water-soluble triazole antifungal agent that is being developed by Astellas, Inc. for use in adult patients for the treatment of life-threatening invasive fungal infections. It is available as a sterile lyophilized powder for iv infusion and as hard capsules for oral administration. Isavuconazole is the active moiety of this product, which inhibits the CYP450 dependent lanosterol-14 α -demethylase in yeasts and molds. In vivo, isavuconazole reduced tissue fungal burden and/or increased the survival rate in animal models of *Aspergillus* spp., *R. oryzae*, or *Candida* spp. fungal infections. The Applicant states that, like other triazoles, the pharmacodynamic parameter AUC/MIC correlated best with treatment outcome. In vivo and in vitro dynamic models utilizing both wild-type and isolates with elevated MICs to triazoles or well-characterized mutations in the target gene demonstrated that efficacy could be optimized by increasing the isavuconazole concentrations. In this submission, the Applicant is seeking indication for treatment of invasive aspergillosis and invasive mucormycosis for patients ≥ 18 years of age.

Invasive aspergillosis is treated with systemic antifungal agents, such as polyenes, mold active triazoles and echinocandins. Amphotericin B deoxycholate (AmB) was the first line of therapy for many years. The current treatment guidelines by Infectious Diseases Society of America (IDSA) recommend voriconazole as first-line therapy. For patients who are intolerant to or progress on voriconazole, there is little consensus for the next treatment option. The addition of another agent or a switch to a different drug class for salvage therapy may be considered, with l-AmB (lipid formulations of AmB), caspofungin or posaconazole as potential agents, either as monotherapy or in combination.

The invasive mucormycosis treatment is multimodal and includes treatment of the underlying condition, surgical debridement and antifungal therapy. AmB is the only antifungal approved for its treatment. But recent guidelines issued by 3rd European Conference on Infections in Leukemia (ECIL 3) and the European Society of Clinical Microbiology and Infectious Diseases/European Confederation of Medical Mycology (ESCMID/ECMM) recommend use of l-AmB as first line therapy, with posaconazole and a combination of a polyene and an echinocandin being recommended as salvage therapy options.

The clinical development program for isavuconazole submitted data from 2 pivotal Phase 3 studies and 2 key Phase 2 studies (**Table 1**).

Table 1: Overview of pivotal and key phase 2/3 studies

Parameter	Phase 3 Studies		Phase 2 Studies	
	9766-CL-0104 (WSA-CS-004)	9766-CL-0103 (WSA-CS-003)	9766-CL-0101 (WSA-CS-001)	9766-CL-0102 (WSA-CS-002)
Design	Double-blind, randomized, noninferiority study to evaluate efficacy and safety of ISA vs VRC for the primary treatment of IFD caused by <i>Aspergillus</i> spp. or other filamentous fungi	Open-label, non-comparative study to evaluate the safety and efficacy of ISA for the treatment of invasive aspergillosis in patients with renal impairment or in patients with IFD caused by rare moulds, yeasts or dimorphic fungi	Randomized, double-blind, phase 2, parallel group, noninferiority study to compare the efficacy and safety of 3 oral dosing regimens of ISA to a standard oral FLU regimen for the treatment of patients with uncomplicated esophageal candidiasis	Open-label, multicenter study of the safety and efficacy of escalating intravenous and oral isavuconazole in the prophylaxis of patients undergoing chemotherapy for AML
No. of Sites	102	34	8	3
Countries with Sites that Enrolled Patients	Argentina, Australia, Belgium, Brazil, Canada, Chile, China, Egypt, France, Germany, Hungary, India, Israel, Italy, Malaysia, Mexico, The Netherlands, New Zealand, Poland, Russia, South Korea, Spain, Switzerland, Thailand, Turkey and the United States	Belgium, Brazil, Germany, India, Israel, Lebanon, Mexico, Russia, South Korea, Thailand and the United States	South Africa	Germany
Treatment Groups	ITT: ISA (n = 258) SAF: ISA (n = 257)	ITT: VRC (n = 258) SAF: VRC (n = 259)	ITT: ISA A (n = 40) ISA B (n = 40) ISA C (n = 41) FLU D (n = 38)	Safety Population: Group 1: (n = 11) Group 2: (n = 12)
Loading Dose	ISA 200 mg administered q8h IV for 2 days	VRC 6 mg/kg administered q12h IV for 1 day	ISA A: 200 mg day 1 ISA B: 400 mg day 1 ISA C: 400 mg day 1 FLU D: 200 mg day 1	Group 1: 400/200/200 mg day 1, 200/200 mg day 2 Group 2: 800/400/400 mg day 1, 400/400 mg day 2
Maintenance Dose	200 mg once per day IV or oral	4 mg/kg q12h IV or 200 mg q12h oral	ISA A: 50 mg/day ISA B: 400 mg/week ISA C: 100 mg/day FLU D: 100 mg/day	Group 1: 200 mg/day Group 2: 400 mg/day
Patient Population	Patients with IFD caused by <i>Aspergillus</i> or other filamentous fungi	Renally impaired (creatinine clearance < 50 mL/min) patients with invasive aspergillosis and patients with IFD caused by other rare moulds, yeasts or dimorphic fungi	Patients with uncomplicated esophageal candidiasis	Neutropenic AML patients who were entering first induction treatment or subsequent chemotherapy and had not experienced a prior invasive fungal infection
Primary efficacy endpoint	Crude rate of all-cause mortality through day 42	DRC-assessed overall response at day 42	Endoscopically confirmed clinical response at EOT	Rate of microbiological success (absence of break-through fungal infections and lack of need for other systemic AFT)
Secondary efficacy variables	- Key secondary: DRC-assessed overall response at EOT - All-cause mortality through day 84 - DRC-assessed overall response at days 42 and 84 - Clinical, mycological and radiological response at EOT, and days 42 and 84	- DRC-assessed overall response at EOT and day 84 - DRC-assessed clinical, mycological and radiological success at EOT and days 42 and 84 - Survival rate by days 42, 84, 120 and 180	- Overall therapeutic response at EOT - Microbial response at EOT - Relapse rate at the follow-up and late follow-up visits in patients assessed as a success (cure) at EOT, after a 14-day or 21-day treatment regimen	none

AFT: antifungal therapy; AML: acute myeloid leukemia; DRC: Data Review Committee; EOT: end of treatment; FLU: fluconazole; IFD: invasive fungal disease; ISA: isavuconazole; ITT: intent-to-treat; MIC: minimum inhibitory concentration; NRI: nonrenally impaired; RI: renally impaired; SAF: safety analysis set; VRC: voriconazole.

Source: Applicant's Clinical Overview Report, Table 1, Page 12-13

Adverse events (AEs) of clinical interest for isavuconazole that we focused on in this review included pruritus, anxiety, nausea, headache, and fatigue, all of which had slightly higher incidences in isavuconazole arm compared to voriconazole arm in the Phase 3 study. Liver aminotransferases (ALT elevations) were also evaluated as a part of this review, although the incidences of ALT elevations were lower in isavuconazole arm than voriconazole arm in the Phase 3 study.

The Applicant provided pharmacometric reports for population PK models, and limited exposure-response analyses results for efficacy in pivotal Phase 3 study 9766-CL-0104. Population pharmacokinetic/pharmacodynamics modeling activities assessed the influence of various continuous covariates (age, weight, height, body mass index [BMI], creatinine clearance and liver chemistries) and categorical covariates (race, sex, differences between patients and healthy subjects) on the parameters of the models and provided individual exposure variables for subsequent exposure-response analyses. Population pharmacokinetic modeling was also performed to determine pharmacokinetic differences between Asian and Western subjects. Exposure-response analyses were conducted using pharmacokinetic data from 232 isavuconazole treated patients in Study 9766-CL-0104 to assess if there was a relationship between any exposure parameter and response.

(b) (4)

3 RESULTS OF APPLICANT'S ANALYSIS AND REVIEWER'S COMMENTS

3.1 Dose Selection

The Applicant used the following loading and maintenance regimen in pivotal Phase 3 studies:

- Days 1-2: IV infusions of 200 mg isavuconazole *q8h*
- Days 3-end of treatment (EOT): Maintenance dose of 200 mg isavuconazole *qd*

Briefly, the Applicant justified the Phase 3 dose selection as follows:

- The i.v. and oral formulations were interchangeable since oral bioavailability was ~98%.
- *In vitro*, an isavuconazole MIC of 1-2 µg/mL for *Aspergillus* species represents a biological breakpoint.
- *In vivo*, isavuconazole was as efficacious as itraconazole or voriconazole at comparable dose levels in neutropenic rats or mice. In neutropenic infected mice, at the efficacious dose of 25 mg/kg, the plasma (trough) levels of isavuconazole at the end of the treatment were around MIC of the *Aspergillus flavus* strain (1 µg/mL) used for disseminated aspergillosis.
- Thus, for *Aspergillus* species with isavuconazole MIC up to 2 µg/mL, it was deemed important to maximize both the exposure to isavuconazole (AUC/MIC) and the trough levels. Therefore, a daily dose regimen was preferred over an intermittent schedule.
- The half-life of isavuconazole (~130 h) is greater than the 24-hour dosing interval. The assessment of isavuconazole predose trough concentrations indicated that near steady state conditions of isavuconazole are achieved in ~14 days of once daily oral and IV dosing of isavuconazonium (Study 9766-CL-0003). To achieve steady-state levels more rapidly,

within 3-4 days, a loading dose regimen on days 1 and 2 was proposed, based on simulations and observed data after IV administration to healthy volunteers.

- With the Phase 3 dose regimen stated above, isavuconazole predose plasma concentrations were predicted to be at or near steady-state on day 3 with trough levels of ~3 µg/mL, which is above the targeted MIC values of 1-2 µg/mL. These levels were well tolerated in the Phase 2 study.

Reviewer's comments: The selection of dosing regimen to rapidly achieve near steady state isavuconazole concentrations above MIC of Aspergillus species in patients seems reasonable. Also from E-R for efficacy and safety perspective, the proposed dosing regimen seems reasonable from the reviewer's analysis results of the Phase 3 results described in section 1.1.1.

3.2 Population Pharmacokinetic Analysis

A brief synopsis of Applicant's population pharmacokinetic (Pop-PK) analyses for isavuconazole is given below:

Objective: To develop a Pop-PK model using PK data from Phase 1 and Phase 3 studies and to identify the covariates that affect isavuconazole pharmacokinetics.

Methods: Data from nine Phase 1 studies and one Phase 3 study were pooled from subjects administered single and multiple, oral and IV doses of isavuconazonium that range from 40 mg to 400 mg. Population models were developed in Nonlinear Mixed-Effect Modeling (NONMEM) version 7.2 and the First Order Conditional Estimation (FOCE) method was used to analyze the data. All random effects were treated as log-normally distributed. The Ln-Ln transformation of both the model and the data was used to stabilize the residual variance. The covariates examined included various continuous covariates (age, weight, height, lean body mass, BMI, creatinine CL, liver function tests) and categorical covariates (race, sex, differences between patients and healthy subjects, CYP3A concomitant medications). Absolute bioavailability was fixed to 1 based on previous non-compartmental analyses and was needed to resolve identifiability issues. Stepwise covariate modeling (SCM) was performed in Perl-speaks-NONMEM (PsN) by using the forward selection ($\alpha = 0.01$) and backward elimination ($\alpha = 0.001$) method.

Results: A total of 6363 concentration records (5828 from Phase 1 studies and 535 from the Phase 3 study) from 189 healthy subjects and 232 patients were used for modeling purpose. A 2-compartment model with Weibull absorption function and first order (FO) elimination adequately described plasma isavuconazole concentrations. The population mean estimates of CL were 2.39 L/h with a volume of distribution at steady-state of approximately 450 L. Covariate influences of race on CL, and BMI and difference between patients and healthy subjects on peripheral volume of distribution (Vp) were included in the best model. The covariate relationship was modeled as follows:

$$CL = \theta_1 * (1 + \theta_{9_{\text{race}}})$$

$$V_p = \theta_4 * (1 + \theta_4) * (1 + \theta_{10} * (\text{BMI} - 24.80))$$

Asian patients had approximately 40% decreased CL compared to Caucasian patients. Vp increased with BMI and was also higher in patients as compared to healthy subjects. A 2-compartment model adequately described the data. No relevant pharmacokinetic differences were observed between patients and healthy subjects.

Final parameter estimates from the final best population PK model for isavuconazole are summarized in **Table 2**.

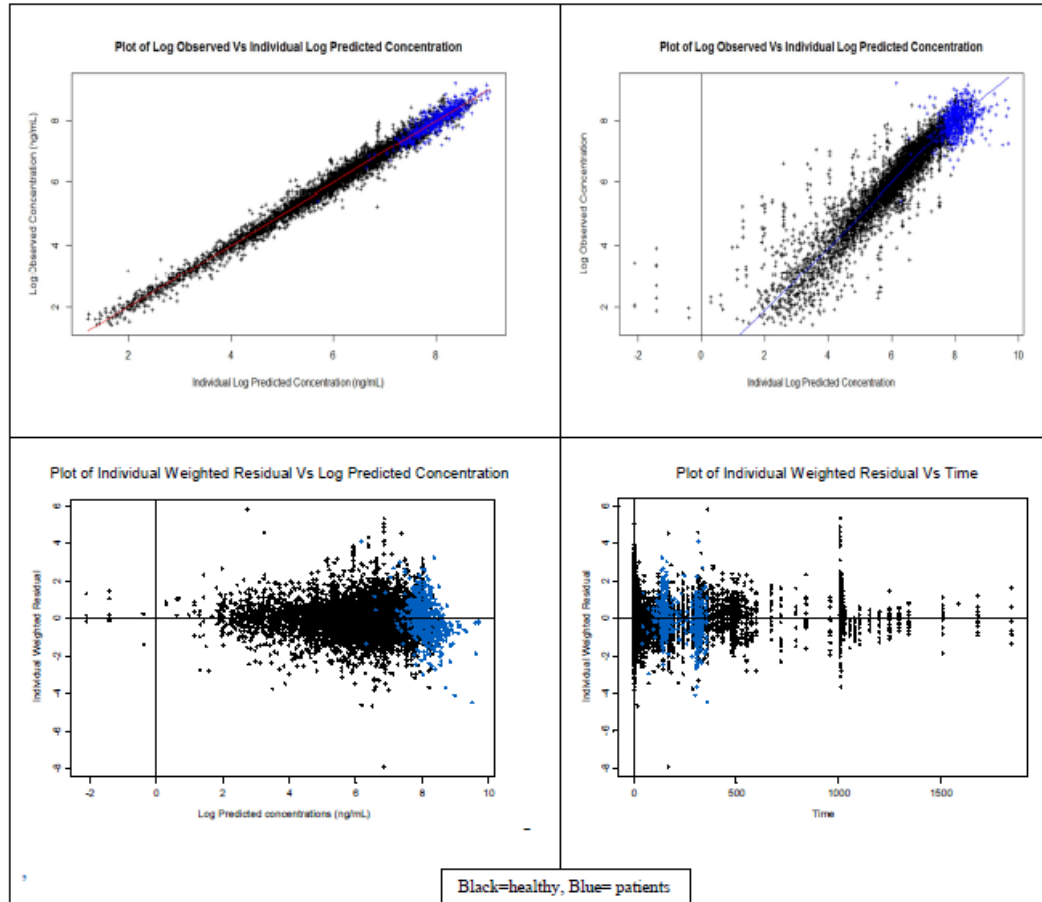
Table 2: Pharmacokinetic Parameter Estimates and Variability Estimates of the Final POP-PK Models

Parameter	Units	Value	SE	% RSE	Bootstrap Mean	Bootstrap 95 % CI	Shrinkage (%)
θ1 (CL, Caucasian)	ml/hr	2390	58.7	2.5	2380	2260 - 2500	
θ2(V2)	ml	49200	1590	3.2	49120	45910 - 52470	
θ3 (Q)	ml/hr	25500	1080	4.1	26640	24530 - 28720	
θ4 (V3)	ml	40200	16600	4.1	402610	370550 - 443210	
Weibull Absorption Parameters							
-θ5 (KAMAX)		1.09	0.09	8.4	1.09	0.91 – 1.32	
θ6 (RA)		0.72	0.02	4.1	0.72	0.66 – 0.78	
θ7(GAM1)		4.89	0.237	4.8	4.87	4.38 – 5.32	
θ8 (CL, Asian)		-0.367	0.06	17	-0.358	-0.470 - -0.227	
θ9 BMI on Vp		0.060	0.002	3.6	0.061	0.048 – 0.073	
θ10 SP on Vp		-0.352	0.29	8.2	-0.353	-0.416 - -0.290	
Variability (%)							
CL		43.13				36.74 – 50.29	15
Vp		35.07				30.33 – 39.74	23
RA		40.37				34.92 – 44.15	47
Q		49.89				42.54 – 58.13	32
GAM1		45.71				36.60 – 54.31	57
Residual Error							
σ ²		45.05	0.004	2.3	44.83	43.93 – 45.93	

Source: Applicant's Population PK Study Report, Table 4, Page 21

The goodness of fit (Observed vs individual predicted concentrations etc.) plots are provided in **Figure 1**.

Figure 1: Goodness-of-Fit Diagnostic Plots for the Final Pop-PK Model



Source: Applicant's Population PK Study Report, Figure 3, Page 20

Reviewer's comments: The Applicant's Pop-PK model provides reasonable description of drug concentrations for individual predictions (observed vs. individual predicted concentrations). Visual inspection shows that the model reasonably predicts individual data over a range of concentrations.

(b) (4)

- Please refer to the section 2.4.5 of Clinical Pharmacology QBR for the details about reviewer's analysis for evaluation of breakpoint criteria.

3.4 Exposure-Response Analysis

Brief synopsis of Applicant's exposure-response (E-R) analysis for efficacy is given below:

Primary exposure parameters (AUC, C_{ss}, C₇, C₁₄ and CLD) were evaluated against mortality at day 42, DRC- adjudicated overall response and DRC- adjudicated clinical response. The analysis was performed on both ITT and mITT patients. Patient 249 (WSACS004-3204-08) was excluded from the analysis due to extremely low clearance/high AUC values as compared to remaining patients, and therefore, was considered an outlier. None of the primary exposure parameters were found to be statistically significant for any of the efficacy endpoints. In most models the duration of therapy (D_{THER}) was the only statistically significant covariate (p<0.05). In some models, either HEMAL or SGM was significant either alone or in combination with D_{THER}. The results for ITT population are summarized in **Table 3**.

Table 3: Exposure-Response Results for efficacy for the ITT Population

Patient Population	Endpoint	Exposure Parameter	Exposure Parameter Statistically Significant	Significant covariate	P value
ITT	Mortality	AUC	No	D _{THER}	<0.0001
		C _{ss}	No	D _{THER}	<0.0001
		C ₇	No	D _{THER}	<0.0001
		C ₁₄	No	D _{THER}	<0.0001
		CLD	No	D _{THER}	<0.0001
ITT	Overall Response Modeled as Categorical	AUC	No	HEMAL SGM	0.039 0.0186
		C _{ss}	No	HEMAL SGM	0.068 0.0186
		C ₇	No	HEMAL SGM	0.039 0.0186
		C ₁₄	No	HEMAL SGM	0.039 0.0186
ITT	Clinical Response Modeled as Categorical	AUC	No	D _{THER}	<0.0001
		C _{ss}	No	D _{THER}	<0.0001
		C ₇	No	D _{THER}	<0.0001

		C14	No	DTher	<0.0001
ITT	Overall Response Modeled as Binary	AUC	No	DTher HEMAL SGM	<0.0001 0.0262 0.0260
ITT	Overall Response Modeled as Binary	Css	No	DTher HEMAL SGM	<0.0001 0.0262 0.0260
		C7	No	DTher HEMAL SGM	<0.0001 0.0262 0.0260
		C14	No	DTher HEMAL SGM	<0.0001 0.0262 0.0260
ITT	Clinical Response Modeled as Binary	AUC	No	DTher	<0.0001
		Css	No	DTher	<0.0001
		C7	No	DTher	<0.0001
		C14	No	DTher	<0.0001

Source: Applicant's Population PK Study Report, Table 7, Page 24-25

Reviewer's comments:

- The Applicant stated that duration of exposure is the only significant covariate for mortality and that none of the primary exposure parameters were found to be statistically significant for any of the efficacy endpoints. The Applicant conducted analysis in a multivariate fashion and in this scenario the inclusion of duration of exposure in a multivariate analysis could falsely mask the potential trends in efficacy (mortality) with exposure parameters because of following reasons:

- If a patient dies early on therapy, he will have lower duration of therapy.
- If the patient shows a treatment failure he would discontinue on therapy and might probably die earlier than the patients who are still continuing on therapy.

Hence the E-R analyses were also performed by the reviewer without the inclusion of duration of therapy. Individual predicted C_{trough} at Day 7 (C7) based on a population pharmacokinetic analysis was used as the isavuconazole exposures metric since near steady state C_{trough} concentrations are expected to be achieved by this time using the Phase 3 loading and maintenance dosing regimen. In such analysis, the patients who have at least 7 days of therapy or beyond are evaluated, which can reduce the potential bias that can be introduced by early on-treatment mortality (<day 7) which may actually be occurring as a result of advanced/terminal disease at the trial recruitment rather than inadequate efficacy of therapy. The results of reviewer's analysis of E-R relationship for efficacy are described in section 2.2.4.1 of the Clinical Pharmacology Question Based Review (QBR).

- The Applicant did not carry out independent safety related E-R analyses. The results of reviewer's analysis of E-R relationship for safety are described in section 2.2.4.2 of the Clinical Pharmacology Question Based Review (QBR).
- Based on flat E-R relationship for efficacy and safety with isavuconazole exposures in the pivotal Phase 3 study, the proposed dosing regimen for isavuconazole is acceptable for the overall population.
- None of the covariates of age, gender, weight or race require dose adjustment based on exposure since the overall E-R relationship for efficacy and safety was flat within the concentration range achieved in the pivotal Phase 3 study 9766-CL-0104. Please refer to the sections 2.3.1 and 2.3.2.1 through 2.3.2.5 of Clinical Pharmacology QBR for the details about differences in isavuconazole exposure and response to isavuconazole treatment with these intrinsic factors.

4 LISTING OF ANALYSES DATASETS, CODES AND OUTPUT FILES

Table 4: Analysis Data Sets

Study Number/Context	Name	Link to EDR
Subject level demographics for Study 9766-CL-0104	ADSL.xpt	\\cdsesub1\evsprod\NDA207500\0000\m5\datasets\9766-cl-0104\analysis\adam\datasets\adsl.xpt
PKPD dataset for efficacy E-R analysis	PKPD xpt	\\cdsesub1\evsprod\nda207500\0000\m5\datasets\pop-pk-data\analysis\adam\datasets\pkpd.xpt
AE dataset	ADAE xpt	\\cdsesub1\evsprod\NDA207500\0000\m5\datasets\9766-cl-0104\analysis\adam\datasets\adae.xpt
Lab chemistry dataset	ADLBCH xpt	\\cdsesub1\evsprod\NDA207500\0000\m5\datasets\9766-cl-0104\analysis\adam\datasets\adlbch.xpt
MIC and Clinical response dataset	PKMIC.xpt	\\cdsesub1\evsprod\NDA207500\0000\m5\datasets\pk-mic\analysis\adam\datasets\pkmic.xpt

Table 5: Codes and Output Files

Description	File Name\Location in \\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Isavuconazonium_NDA207500_207501_DDM\ER_Analyses\codes\
E-R analysis for efficacy and safety	ER_isavuconazole.sas
Subgroup analysis for Asians vs. Non-Asians	asian_nonasian_mortality_comparison.sas
Relationship of Clinical response to MIC and AUC/MIC	PK_MIC_isavuconazole.sas

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAKSHINA M CHILUKURI
12/08/2014

DHANANJAY D MARATHE
12/08/2014

JEFFRY FLORIAN
12/08/2014

PHILIP M COLANGELO
12/09/2014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	207500 and 207501	Brand Name	CRESEMBA
OCP Division (I, II, III, IV, V)	IV	Generic Name	Isavuconazonium
Medical Division	DAIP	Drug Class	Azole
OCP Reviewer	Dakshina M. Chilukuri	Indication(s)	Treatment of invasive aspergillosis and invasive mucormycosis
OCP Team Leader	Philip Colangelo	Dosage Form	IV infusion and capsules
Pharmacometrics Reviewer	TBD	Dosing Regimen	Loading Dose: 200 mg every 8 hours, for 48 hours (6 total doses), via oral or IV administration Maintenance Dose: 200 mg once per day via oral or IV administration, starting 12 to 24 hours after the last loading dose
Date of Submission	July 8, 2014	Route of Administration	IV and oral
Estimated Due Date of OCP Review	December 8, 2014	Sponsor	Astellas
Medical Division Due Date	TBD	Priority Classification	Priority
PDUFA Due Date	March 8, 2015		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies to be reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:	x	2	1	9766-CL-0016 Oral 9766-CL-0050 IV
Isozyme characterization:	x	9	8	9766-ME-1008 9766-ME-0021 9766-ME-0035 9766-ME-1007 9766-ME-1009 9766-ME-1021 9766-ME-1027 9766-ME-1005 9766-ME-1004

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA

Transporter Studies	x	7	6	9766-ME-1010 9766-ME-1025 9766-ME-1026 9766-ME-1031 9766-ME-1006 9766-ME-1022 9766-ME-1023
Other In vitro studies	x	2	1	9766-ME-0004 (in vitro conversion of isavuconazonium) 9766-ME-0005(in vitro conversion of 2 diastereomers of isavuconazonium)
Blood/plasma ratio:				
Plasma protein binding:	x	2	2	9766-ME-1011 9766-ME-1028
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	2	2	9766-CL-0001 (SD, Oral) 9766-CL-0002 (SD, IV)
multiple dose:	x	1	1	9766-CL-0003 (MD, IV and oral)
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	31	24	
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	x	1		9766-CL-0038 (PK study in Chinese subjects)
gender:	x	1		9766-CL-0041 (Effect of young adult vs. elderly subjects and male vs. female)
pediatrics:				
geriatrics:	x	1		9766-CL-0041 (Effect of young adult vs. elderly subjects and male vs. female)
renal impairment:	x	1	1	9766-CL-0018
hepatic impairment:	x	2	2	9766-CL-0008 9766-CL-0014
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	x	1	1	E/R evaluation produced one report with data from 3 studies
Population Analyses -				
Data rich:				
Data sparse:	x	5	5	9766-PK-0005 9766-PK-0004 9766-PK-0003 9766-PK-0001 9766-PK-0002
II. Biopharmaceutics				
Absolute bioavailability	x	1	1	9766-CL-0010
Relative bioavailability -				
solution as reference:	x	1		9766-CL-0013
alternate formulation as reference:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA

Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	x	2	1	9766-CL-0015 (pivotal food effect study) 9766-CL-0013 (EU) (exploratory food effect)
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies	x	2		9766-CL-0004 and 9766-CL-0017 (2 QT studies will be reviewed by QT-IRT)
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		74	56	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			N/A	The oral formulation used in the clinical trials is the same formulation that is proposed to be marketed
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			N/A	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA

Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X		
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X		
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			N/A
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			N/A
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X		
General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			N/A

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
__YES__.

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
 NONE

 Reviewing Clinical Pharmacologist

 Date

 Team Leader/Supervisor

 Date

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/s/

DAKSHINA M CHILUKURI
08/07/2014

PHILIP M COLANGELO
08/07/2014