

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207500Orig1s000 / 207501Orig1s000**

**OTHER REVIEW(S)**

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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**Date of This Memorandum:** March 4, 2015

**Requesting Office or Division:** DAIP (Division of Anti-Infective Products)

**Application Type and Number:** NDA 207500 and NDA 207501

**Product Name and Strength:** Cresemba (Isavuconazonium Sulfate) capsules, 186 mg  
Cresemba (Isavuconazonium Sulfate) for injection, 372 mg

**Submission Date:** February 27, 2015

**Applicant/Sponsor Name:** Astellas Pharma

**OSE RCM #:** 2014 – 1389-01  
2014 – 1393-01

**DMEPA Primary Reviewer:** Jacqueline Sheppard, PharmD

**DMEPA Acting Team Leader:** Vicky Borders-Hemphill, PharmD

**DMEPA Associate Director:** Irene Z. Chan, PharmD, BCPS

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#### 1 PURPOSE

The Division of Anti-Infective Products (DAIP) requested that we review the revised container label, carton labeling, and Prescribing Information (PI) (see Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review<sup>1</sup> and e-mail communication to Astellas Pharmaceuticals dated February 25, 2015, and they also reflect additional recommendations conveyed by the Cresemba review team (see Section 2 Regulatory History below).

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<sup>1</sup> Sheppard J. Label and Labeling Review for Cresemba (NDAs 207500 and 207501). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 Jan 21. 18 p. OSE RCM No.: 2014-1389 and 2014-1393.

## 2 REGULATORY HISTORY

Astellas proposes the introduction of a new anti-fungal product to the market for the treatment of invasive aspergillosis and invasive mucormycosis. The non-proprietary name of the product was originally submitted by Astellas as (b) (4) with a corresponding capsule strength of (b) (4) mg and powder for injection strength of (b) (4) mg per vial based (b) (4). At the time of DMEPA's previous review of the labels and labeling, there were ongoing discussions to determine the appropriate non-proprietary name and strength for this product according to policy and regulations, which in turn impacts the dosage and administration instructions in the PI and container labels and carton labeling for the product. When we conducted our previous label and labeling review, we were informed by CMC that the non-proprietary name should be (b) (4).

(b) (4) Since our previous review, several meetings have been held to further discuss the non-proprietary name and strength of this product due to concerns regarding risk for confusion and medication errors.

The drug substance is a sulfate salt of isavuconazonium. Isavuconazonium is a pro-drug that is hydrolyzed in the body to form isavuconazole, an active metabolite. (b) (4)

(b) (4) According to the USP policy on Salt Nomenclature, when an active ingredient is a salt, the non-proprietary name and strength should be representative of the active moiety<sup>2</sup>. The active moiety for this product is isavuconazonium. (b) (4)

(b) (4) Because Astellas also proposed to include the strength of the active metabolite, isavuconazole, which they believed to be a more clinically meaningful expression, this would essentially result in the presence of (b) (4) (see equivalency statement in previous paragraph).

The Cresemba review team recognized that the presence of essentially (b) (4) could be confusing. DMEPA's position at this point in time was that if (b) (4) then presenting based on the active moiety with an equivalency statement for the sulfate salt would likely be the approach to both meet regulation and policy with the least risk for medication errors in the long run as this product proliferates in the market.

After several meetings between DAIP, DMEPA, the Office of Pharmaceutical Science (OPS), and other disciplines on the Cresemba review team to discuss ways to mitigate dosing confusion and reduce the number of strength statements from (b) (4) the issue was

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<sup>2</sup> USP General Chapters <1121> Nomenclature; Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations

presented at the February 13, 2015 Regulatory Briefing. During the regulatory briefing, DAIP indicated that this drug has been discussed extensively in the literature with 95 publications using the term “isavuconazole” to describe the active ingredient with its corresponding strengths. DAIP indicated that providers who are likely to prescribe this product will prescribe based on isavuconazole described in the literature and that dosing errors will occur if the strength of the active metabolite, isavuconazole, is not prominently displayed throughout labels and labeling. Thus, DAIP strongly felt that the equivalency statement for isavuconazole needed to be present. DMEPA indicated that the presence of multiple strength presentations/equivalency statements could lead to medication errors. OPS indicated that [REDACTED] (b) (4) an exception would have to be made to the salt policy. There was no clear decision made regarding the non-proprietary name and strength during the regulatory briefing.

Subsequently, another meeting was held between OND leadership, senior management for DAIP and OPS, and the Cresemba review team. During this meeting, OND, DAIP, and OPS agreed that Cresemba would be an exception to the USP policy on Salt Nomenclature and FDA would allow the non-proprietary name and strength to be presented based on isavuconazonium sulfate along with an equivalency statement with the name and strength of the active metabolite, isavuconazole. This position was conveyed to Astellas by teleconference, resulting in the submission of revised labels and labeling on February 23, 2015.

During further internal discussions, DMEPA shared our position that the isavuconazole equivalency statement, if it is included, should not be the most prominent expression of strength in labels and labeling and that dosing based on milligrams of isavuconazonium sulfate should be emphasized to minimize the risk for dosing confusion.

On February 27, 2015 during a teleconference, Astellas indicated agreement with [REDACTED] (b) (4) the strength of the product to reflect the salt, isavuconazonium sulfate, with a [REDACTED] (b) (4) capsule strength of 186 mg and powder for injection strength of 372 mg.

### 3 DISCUSSION

Our evaluation of the revised container label and carton labeling are acceptable from a medication error perspective given the decision made to include the isavuconazole equivalency statement. We note that the [REDACTED] (b) (4) back configuration for the oral capsules was not provided in this submission for review. We confirmed per electronic communication with Astellas Pharmaceuticals on February 26, 2015, that they have chosen to [REDACTED] (b) (4) [REDACTED]. We therefore have no recommendations concerning that package configuration.

We do, however, maintain our concerns surrounding the extensive use of the isavuconazole equivalency statement in the Dosage and Administration section of the PI. Additionally, we are concerned with the emphasis on dosing by number of vials or capsules instead of milligrams in the dosing table in Section 2. While the use of a dosing table has many positive attributes including increased readability, the table in its most currently proposed form from Astellas marries the dosage to a package size or units (1 vial or 2 capsules instead of 372 mg) and has

the mg dosage in parentheses. Astellas did this to emphasize dosing by number of vials and capsules instead of mg of isavuconazonium sulfate, indicating that this would simplify the dosing regimen. As the most prominent value is 1 vial or 2 capsules, we believe this will drive prescribers to write for 1 vial or 2 capsules. If in the future the Applicant develops an additional strength for the injection or capsule or additional indications with varying doses, then the potential for medication errors would be potentiated by emphasizing the number of vials and capsules in medication orders instead of the total mg dose. This will be a habit that will be difficult to curb if already ingrained in prescribers. We recommend that the mg of isavuconazonium sulfate remain as the primary expression of dosage and be placed first and more prominently in applicable cells within the dosage table. We provide recommendations to minimize confusion and promote the safe use of the product in section 4.1.

Throughout the revised PI there are references to dosing based on the isavuconazole equivalence. We are concerned this may promote the prescribing of this product by isavuconazole instead of isavuconazonium sulfate, which can result in dosing errors. Our postmarket experience with Cerebyx (fosphenytoin) illustrates the risk for confusion and medication errors when healthcare providers are faced with equivalency statements and attempt to prescribe, dispense, or administer doses based on them.<sup>3</sup> The confusion due to Cerebyx dosing and equivalency to phenytoin has led to significant dosing errors with serious outcomes including death. The prominent display of the isavuconazole equivalency throughout the labels and labeling may lead to the same types of errors seen with Cerebyx (fosphenytoin). Astellas and the Division (DAIP) believe that the prevalence of literature expressing the drug as isavuconazole forces the Agency to present both the salt and equivalency statement throughout the labels and labeling. We acknowledge that when this product is first introduced into the market, those individuals that have read the literature may initially experience confusion and confirmation bias may lead them to prescribe based on isavuconazole. However, providing dosage instructions that reflect isavuconazole will reinforce this prescriber behavior. It is DMEPA's position that dosing based on milligrams of isavuconazonium sulfate should be reinforced to prescribers. While we are not indicating the PI cannot refer to the equivalency between isavuconazonium sulfate and isavuconazole (e.g., in the clinical trials section), we believe the goal of the labeling should be to drive prescribing behavior toward dosing in milligrams of isavuconazonium sulfate. For those prescribers that are yet unfamiliar with Cresemba and future prescribers in succeeding generations, there will be no confirmation bias to impact prescribing behavior. However, given the Division's decision to include isavuconazole equivalency statements throughout the labels and labeling, we

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<sup>3</sup> Crandall A. Medication Error Review for Cerebyx and Phenytoin Sodium (NDA 020450 and ANDAs 077481, 078126, 078137, (b) (4), 078476, 078736, 089521, 089744, 040573, 040573, 084307, 040781). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2010 Oct 1. 43 p. OSE RCM No.: 2010-571.

recommend that these statements be used as minimally as possible and are not overly prominent.

#### **4 CONCLUSION & RECOMMENDATIONS**

We conclude that the proposed insert labeling can be improved to promote the safe use of the product. We provide recommendations for consideration by the Division in Section 4.1 below. We find the container labels and carton labeling acceptable at this time and do not have any further recommendations for them.

##### **4.1 COMMENTS TO THE DIVISION**

###### **A. Highlights of Prescribing Information and Full Prescribing Information, Dosage and Administration (Section 2)**

1. Throughout the revised PI there are references to dosing based on the isavuconazole equivalence. We are concerned this may promote the prescribing based on isavuconazole for this product and result in dosing errors. Dosing of Cresemba should be based on the approved strength of the product and not the equivalency of the active metabolite. Therefore, we recommend that these statements be used as minimally as possible and are not overly prominent. We have made revisions to the Dosage and Administration section of DAIP's working document to improve clarity and minimize the risk for confusion for the Division to consider in keeping with this recommendation.
2. We note references to dosing based on package size or units (1 vial or 2 capsules instead of 372 mg) in the dosing table of the Full Prescribing Information which may promote prescribers to write for 1 vial or 2 capsules instead of the dose in milligrams of isavuconazonium sulfate. If in the future, the Applicant develops an additional strength for the injection or capsule or additional indications with varying doses, then the potential for medication errors would be potentiated by emphasizing the number of vials and capsules in medication orders instead of the total mg dose. We recommend that the mg of isavuconazonium sulfate remain as the primary expression of dosage and be placed first in applicable cells within the dosage table.

If you have further questions or need clarifications, please contact Karen Townsend, OSE project manager, at 301-796-5413.

**APPENDIX A. LABEL AND LABELING SUBMITTED ON MARCH 3, 2015**

**CAPSULE CARTONS**

4- Pack cartons of 14 oral capsules (56 Count) Carton Labeling

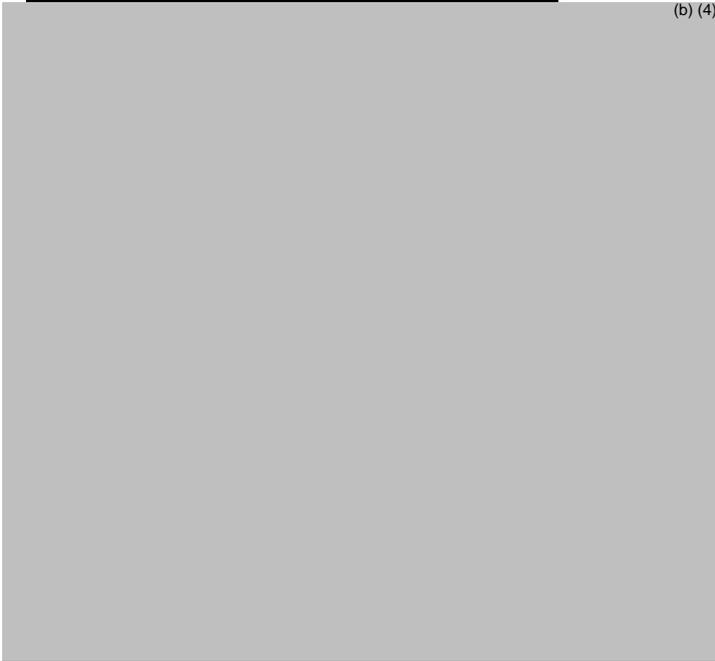


14 Count Cresemba Oral Capsule Blister Carton Labeling



**CAPSULE CONTAINER**

Cresemba Oral Capsule Blister Pack Label



(b) (4)

**INJECTION CARTON**



(b) (4)

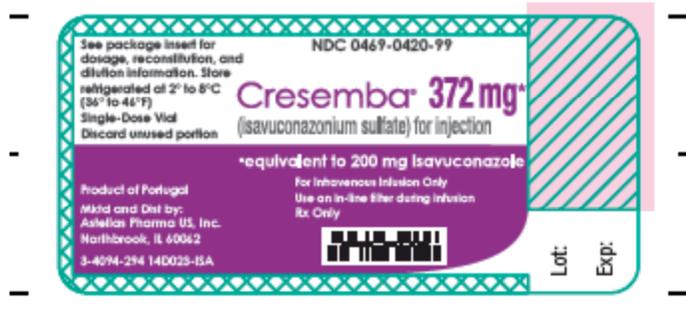
Cresemba for Injection Single Vial Carton Labeling

(b) (4)

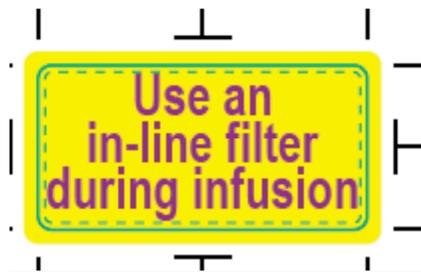


**INJECTION CONTAINER**

Cresemba for Injection vial label



**INFUSION BAG STICKER**



## Dosage Table – DMEPA Proposal

CRESEMBA (isavuconazonium sulfate) is the prodrug of isavuconazole, an azole antifungal drug. Prescribe CRESEMBA as shown in Table 1 below.

**Table 1: Dosage Regimen for CRESEMBA**

	Loading Dose	Maintenance Dose**
CRESEMBA for Injection 372 mg* of isavuconazonium sulfate per vial		(b) (4)
CRESEMBA Capsules 186 mg** of isavuconazonium sulfate per capsule		

\*372 mg of isavuconazonium sulfate is equivalent to 200 mg of isavuconazole

\*\*186 mg of isavuconazonium sulfate is equivalent to 100 mg of isavuconazole

\*\*\*Start maintenance doses 12 to 24 hours after the last loading dose

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JACQUELINE E SHEPPARD  
03/04/2015

BRENDA V BORDERS-HEMPHILL  
03/04/2015

IRENE Z CHAN  
03/04/2015



3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A prospective study over a five-year period on the *in vitro* susceptibility of target fungi to isavuconazole.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

A study of the mechanisms of resistance to isavuconazole if such isolates are identified during the five-year surveillance study

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Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

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Other

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5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)



8. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
  
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
  
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

9. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A carcinogenicity study should be conducted in mice.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

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Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

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Other

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10. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)



13. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
  
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
  
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

14. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A carcinogenicity study should be conducted in rats. It should be a traditional 2-year carcinogenicity study in rat.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

---

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

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Other

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15. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA/BLA #                      NDA 207500, CRESEMBA (isavuconazonium sulfate) Capsules, 186 mg  
Product Name:                NDA 207501, CRESEMBA (isavuconazonium sulfate) for Injection, 372 mg

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PMR/PMC Description:        2872-4:    Establish a registry to collect and analyze clinical efficacy-related outcome data on patients treated with isavuconazonium sulfate who have invasive mucormycosis or infection with non-fumigatus aspergillus species.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>03/31/2016</u>
	Interim Report:	<u>06/30/2018</u>
	Interim Report:	<u>03/31/2019</u>
	Interim Report:	<u>03/31/2020</u>
	Study Completion:	<u>01/31/2022</u>
	Final Report Submission:	<u>01/31/2023</u>
	Other:	_____

16. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Invasive mucormycosis (IM) and invasive aspergillosis (IA) are devastating fungal infections with predictable, high rates of mortality. IM has an incidence rate of 1.7 per 1,000,000 population, and IA 12.4 per 1,000,000 population. CRESEMBA has been granted both qualified infectious disease product (QIDP) and orphan status for both indications. Data for drug efficacy for IM was based upon 37 individuals. The IA trial was a prospective, randomized, double-blind, noninferiority trial with 258 subjects receiving study drug. This PMC seeks to establish a registry, with the goal to gather additional efficacy-related outcome data for infections due to a range of Mucorales and <sup>(b) (4)</sup> *Aspergillus* species.

17. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

18. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

19. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A (b) (4) registry as a post-marketing commitment for CRESEMBA-treated invasive mucormycosis and invasive aspergillosis due to (b) (4) species of *Aspergillus*.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- 
- Other  
Registry study to collect efficacy-related outcomes in additional cases of invasive fungal infections
- 

20. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ALISON K RODGERS  
03/03/2015

JOSEPH G TOERNER  
03/03/2015

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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**Date of This Memorandum:** February 25, 2015  
**Requesting Office or Division:** DAIP (Division of Anti-Infective Products)  
**Application Type and Number:** NDA 207500 and NDA 207501  
**Product Name and Strength:** Cresemba (Isavuconazonium Sulfate) capsules, 186.3 mg  
Cresemba (Isavuconazonium Sulfate) for injection, 372.6 mg  
**Submission Date:** February 23, 2015  
**Applicant/Sponsor Name:** Astellas Pharma  
**OSE RCM #:** 2014 – 1389-01  
2014 – 1393-01  
**DMEPA Primary Reviewer:** Jacqueline Sheppard, PharmD  
**DMEPA Team Leader:** Vicky Borders-Hemphill, PharmD

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#### 1 PURPOSE OF MEMO

The Division of Anti-Infective Products (DAIP) requested that we review the revised container label, carton labeling, and Prescribing Information (PI) (see Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review and also include the revised strength statement and presentation based on the revised established name.<sup>1</sup>

#### 2 DISCUSSION

The revised container label, carton labeling, and Prescribing Information are unacceptable from a medication error perspective. The recommended revisions requested in OSE review #2014-

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<sup>1</sup> Sheppard J. Label and Labeling Review for Cresemba (NDAs 207500 and 207501). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 Jan 21. 18 p. OSE RCM No.: 2014-1389 and 2014-1393.

1389 were not fully implemented nor did the sponsor provide their rationale for not implementing them. Thus, we reiterate these recommendations in section 3.2.

We provide recommendations addressing our concern that the equivalency statement is more prominent than the primary strength statement on container labels and carton labeling and poses risk for dosing medication errors, specifically under dose errors. (b) (4)

(b) (4) he primary strength along with the proprietary name and established name must be the most prominent information on the container labels and carton labeling. We recommend revisions to the presentation of these strength statements to accommodate this concern. Additionally, throughout the PI there are references to dosing in isavuconazole equivalence which may promote the prescribing of the incorrect strength for this product and result in dosing errors. Our experience with Cerebryx (fosphenytoin) provides a historical reference into the dangers of having prescribers dose with an alternate strength expression.<sup>2</sup> Fosphenytoin was to be dosed in terms of its phenytoin equivalent (PE) instead of the mg dosage of fosphenytoin. This expression of strength was chosen to avoid confusion yet post-marketing cases describe inconsistent use of the mg PE nomenclature by physicians, pharmacists, and nurses who did not know whether to interpret the physician's order as converted to mg PE or to convert it themselves during the transcription process. This confusion led to significant dosing errors with serious outcomes including death. Developing product strength or expressing the strength in a manner that is incongruent with the dosage and administration of the product complicates the calculating or determination of dosage and has led to dosing errors. There has been a reported medication error wherein lithium was overdosed due to the presentation of two dosage strengths (mEq and mg). The error resulted in the patient requiring treatment in the critical care unit.<sup>3</sup> We recommend that these isavuconazole equivalence statements be used as minimally as possible in the PI.

We note that the (b) (4) pack configuration for the oral capsules was not provided in this submission for review. We provide recommendations to reduce redundancy, improve communication of important information to minimize confusion and improve readability in sections 3.1 and 3.2.

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<sup>2</sup> Crandall A. Medication Error Review for Cerebryx and Phenytoin Sodium (NDA 020450 and ANDAs 077481, 078126, 078137, (b) (4) 078476, 078736, 089521, 089744, 040573, 040573, 084307, 040781). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2010 Oct 1. 43 p. OSE RCM No.: 2010-571.

<sup>3</sup> Institute for Safe Medication Practices. Lithium dosed in Mg or mEq. ISMP Med Saf Alert Acute Care. 2006;11(8).

### **3 CONCLUSION & RECOMMENDATIONS**

We conclude that the proposed labels and labeling can be improved to reduce redundancy, increase the readability and prominence of important information and to promote the safe use of the product.

#### **3.1 COMMENTS TO THE DIVISION**

DMEPA provides the following comments for the Division to consider implementing prior to approval of this NDA:

##### **A. Highlights of Prescribing Information and Full Prescribing Information, Dosage and Administration Sections**

1. We note references to dosing in isavuconazole equivalence which may promote the prescribing of the incorrect strength for this product and result in dosing errors. Dosing of Cresemba must use the primary strength and instruct a dosage regimen that is congruent with the primary strength presentation on the container labels and carton labeling. As minimally as possible, use the equivalence statement to describe the relationship of isavuconazole to isavuconazonium sulfate to mitigate dosing confusion. We have made preliminary revisions to the Dosage and Administration section of DAIP's working document to improve clarity and readability of important information (see Appendix A).

#### **3.2 COMMENTS TO THE APPLICANT**

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

##### **A. All Container Labels and Carton Labeling**

1. Revise the proprietary name from appearing in all caps, "CRESEMBA", to appear in title case, "Cresemba", to improve readability. Words set in title case form recognizable shapes, making them easier to read than the rectangular shape formed by words set in all upper case letters.<sup>4</sup>

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<sup>4</sup>Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

2. Increase the prominence of the primary strength statement and decrease the prominence of the equivalency statement. As presented the equivalency statement competes with the primary strength presentation and poses risk for dosing errors. The primary strength along with the proprietary name and established name must be the most prominent information on the container labels and carton labeling.
3. Add an asterisk after the primary strength statement and before the equivalency statement to link the two strength statements.

**B. Oral Capsules Blister Pack Label**

1. Ensure that the lot number and expiration date appear on each individual blister for the blister pack.
2.  (b) (4)

**C. Powder for Injection Container Label**

1. Provide a mockup sample of the proposed sticker to be applied to the infusion bag to remind users of the requirement to administer with the use of an in-line filter with the submission of revised container labels and carton labeling.

If you have further questions or need clarifications, please contact Karen Townsend, OSE project manager, at 301-796-5413.

**APPENDIX A. LABEL AND LABELING SUBMITTED ON FEBRUARY 23, 2015**

**CAPSULE CARTONS**

4- Pack cartons of 14 oral capsules (56 Count) Carton Labeling



14 Count Cresemba Oral Capsule Blister Carton Labeling



**CAPSULE CONTAINER**

**Cresemba Oral Capsule Blister Pack (7 capsules each) Label**

(b) (4)



**INJECTION CARTON**

(b) (4)



Cresemba for Injection Single Vial Carton Labeling

(b) (4)



**INJECTION CONTAINER**

Cresemba for Injection vial label



**PRESCRIBING INFORMATION**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JACQUELINE E SHEPPARD  
02/25/2015

BRENDA V BORDERS-HEMPHILL  
02/25/2015

**M E M O R A N D U M**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**CLINICAL INSPECTION SUMMARY**

DATE: January 16, 2015

TO: Alison Rodgers, Regulatory Health Project Manager  
Edward Weinstein, M.D., Ph.D. Medical Officer  
Division of Anti-infective Drug Products

FROM: Antoine El-Hage, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 207500/207501

APPLICANT: Astelas Pharma Global Development, Inc.

DRUG: Cresemba {Isavuconazonium sulfate (BAL8557)}

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority review  
INDICATION: Treatment of Invasive Aspergillosis and Mucormycosis in adults  
CONSULTATION REQUEST DATE: August 4, 2014  
DIVISION ACTION GOAL DATE: March 8, 2015  
PDUFA DATE: March 8, 2015  
INSPECTION SUMMARY DUE DATE: February 8, 2015

## I. BACKGROUND:

The Applicant submitted two NDAs to support the use of isavuconazole (ISA) for the treatment of invasive fungal disease caused by aspergillus species (b) (4) in adult male and female patients. The frequency of invasive fungal disease has increased in the recent years and is a major cause of morbidity and mortality among immunocompromised subjects. Mucormycosis is thought to be under-diagnosed because of its similarity to aspergillosis in clinical presentation. Invasive aspergillosis and mucormycosis are difficult to treat with a high mortality rate in the most severe immunocompromised patients. Because of high toxicity with current antifungal agents, there is an urgent need for effective and safe antifungal agents that can be administered both orally and intravenously with limited toxicity.

The Applicant sponsored two pivotal clinical studies in support of the applications: Protocols WSA-CS-003 and WSA-CS-004 to treat subjects with invasive fungal disease (IFD) and mucormycosis.

Protocols: WSA-CS-004 entitled “ A Phase III, Double-Blind, Randomized Study to Evaluate Safety and Efficacy of BAL8557 Versus Voriconazole for Primary Treatment of Invasive Fungal Disease Caused by Aspergillus Species or Other Filamentous Fungi”, and

WSA-CS-003 entitled “Open-Label Study of Isavuconazole in the Treatment of Patients With Aspergillosis and Renal Impairment or Patients With Invasive Fungal Disease Caused by Rare Molds, Yeasts or Dimorphic Fungi”.

### **Protocol WSA-CS-004**

The objective of this study was to compare all-cause mortality through Day 42 following primary treatment with isavuconazole versus voriconazole (VRC) in patients with IFD caused by aspergillus species or other filamentous fungi

The secondary objectives of this study were: 1) to compare the effect of treatment on all-cause mortality rate at Day 84, overall outcome at Day 42, and end of treatment and Day 84, mycological response at Day 42 and Day 84, and 2) to characterize the safety and tolerance of treatment with ISA.

This protocol was a randomized, multicenter, double-blind, non-inferiority, comparative group study of ISA versus VRC. A total of approximately 510 subjects were enrolled to receive either ISA or VRC in a 1:1 ratio stratified by three geographic regions (USA, Canada and Europe), whether or not they have undergone allergenic bone marrow transplant (BMT)/ hematopoietic stem cell transplantation (HSCT) and whether or not they have an uncontrolled malignancy, defined as the absence of complete remission at randomization. Subjects were treated up to a maximum of 84 days. All subjects received study medication had their visits

performed as scheduled. Follow-up visits took place 4 weeks after the last administration of study medication, and did occur before or after Day 42 and /or Day 84.

### **Protocol WSA-CS-003**

The primary objective of this study was to describe the safety and efficacy of ISA in the treatment of invasive aspergillosis in patients with renal impairment or in patients with IFD caused by rare molds, yeast, or dimorphic fungi.

The secondary objectives of this study were: 1) to determine clinical and mycological response rate by pathogen and 2) to evaluate survival status at Days 42, 84, 120, and 180.

This protocol was an open label, multicenter study of ISA. In addition to the treatment schedule, a follow-up Visit 8 weeks after EOT was made if abnormalities, such as adverse events were still ongoing at the 4 week follow-up Visit. Approximately 150 subjects were enrolled to ensure having a sample size of at least 30 subjects with renally impaired condition with IFD, as well as adequate numbers of subjects with proven or probable zygomycosis. Subjects received a loading dose of ISA followed by a maintenance dose. The duration of therapy was limited to 180 days depending on the severity of the IFD and the clinical response. A loading dose of ISA was given at 8 hours intervals during the first 48 hours followed by a maintenance dose from Day 3 onwards.

The review division requested inspection of six clinical investigators for the pivotal studies noted above because data from the studies are considered essential to the approval process. These sites were targeted for inspection due to 1) enrollment of a relatively large number of subjects with a treatment effect that was greater than average submitted to these original NDAs (two trials) for a 2-NME drug regimen. The trials differ in one or more of the following aspects: patient population, diagnosis, and one is an open label. The reasons selection of sites across multiple trials was necessary was to evaluate the various regimens and population proposed for inclusion in labeling”, and 2) the need to determine if sites conducted the trial ethically and were in compliance with GCP and local regulations. It is for these reasons that it is critical that international sites be included in the inspection.

**II. RESULTS (by protocol/site):**

<b>Name of CI, Location, and Site #</b>	<b>Protocol and # of subjects randomized</b>	<b>Inspection Dates</b>	<b>Final Classification</b>
Issam Raad, M.D. 1515 Holcombe Blvd Houston, Tx 77030 Site# 118	WSA-CS-004 and 003 Number of subjects: 24 WAS-CS-003 5 subjects	10/7-27/2014	Pending (preliminary classification VAI)
Werner Heinz, M.D Oberduerrbacher Atrasse 6 Studienambulanz Hematologie/Onkologie Wyerzburg, By 97080 DEU Western Europe Site #4910	WSA-CS-004 Number of subjects: 23	11/3-7/2014	Pending (preliminary classification VAI)
Francisco Marty, M.D. 75 Francis Street Boston, MA 2115 Site #115	WSA-CS-003 Number of subjects: 14 and  WSA-CS-004 9 subjects	9/7-11/2014	Pending (preliminary classification NAI)
Telles F.de Quieroz, M.D Rua General Carneiro 181 Curitiba, PR 80060-150 Brazil Site #5503	WSA-CS-003 8 subjects  WSA-CS-004 8 subjects	11/3-7/2014	Pending (preliminary classification NAI)
Dominik Selleslag, M.D. Ruddershove 10 Brugge 8000 Belgium Site #3206	WSA-CS-004 Number of Subjects 35	11/3-7/2014	Pending (preliminary classification VAI)

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; the Establishment Inspectional Report (EIR) has not been received from the field and complete review of EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

**1. Johan Maretens, M.D.  
Herestraat 49, Belgium**

- a. What Was Inspected:** This inspection was performed as a data audit for NDAs 207-500/207501 Study Protocol WSA-CS-004. At this site, a total of 60 subjects were screened, one subject was reported as a (skipped) screen failure, 59 subjects were randomized into the study, 25 subjects completed both treatment and study requirement including follow-up visits, five subjects completed treatment but not end of study requirements (three died before the F/U visit), 13 subjects did not complete the treatment but returned to complete the study F/U visit, 15 subjects did not complete the treatment and did not return for the F/U visit (died before follow-up visits), and one subject withdrew consent. A total of 17 subjects died before the follow-up visits/during the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for all subjects were reviewed and compared to data listings. The review included drug accountability records, drug dispensing records, inclusion/exclusion criteria, vital signs, IRB records, sponsor correspondence, and adverse events. Source documents for 13 subjects verified eligibility criteria, protocol deviations, and prohibited medications and were compared to case report forms and data listings including for primary efficacy endpoints and adverse events listings. The field investigator “reported that the inspection was difficult because most of the source documents were scanned and kept electronically and were made available for review; this took too much time due to translation. The information provided had multiple changes made to the data over time. The changes were a result of the remonitoring of the data by Asetella <sup>(b) (4)</sup> after Astellas took over the study”. In addition, our field investigator reported that “The clinical investigators were asked to review data they had previously collected and reported, including a review of the CT scans, and reevaluate their assessments in accordance with the most recent protocol. For example, they may have assessed the subject’s outcome in 2008, but the assessment choices in the CRF may have changed since then. So they were asked to assess the subject’s data using the 2011 definitions. This was all documented at both study sites in Belgium. The doctors were given written questions regarding the data, and they answered the questions, signed and dated the updated information. That final, revised case report form data was verified and matched the data listings”.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Maertens. Although no FDA 483 was issued to the clinical investigator, our FDA investigator presented and discussed the following items:

**Protocol Deviations:**

According to the protocol, patients should be excluded with evidence of moderate to severe renal dysfunction with calculated clearance of Cl/cr <50 or dialysis or likely required dialysis.

Subject 004-3204-01 was enrolled with a creatinine clearance of approximately 38 ml/min. The subject was diagnosed with bacterial pneumonia and was taken off the study due to the need for hemodialysis. The subject died (b) (6) days later.

Subject 004-3204-60 was enrolled with a creatinine clearance of 42.4 ml/min. The staff claimed they made an error in calculation by excluding the age. The subject later died from hypoglycemia.

According to the protocol the infusion duration was 2 hours for the first 24 hours (3 doses) and one and half hours thereafter. At least 5 subjects (03, 27, 35, 53, 55, and 59) had their infusion duration less than an hour. Only Subject #55 died before follow-up visit.

Subject 004-3206-11 received phenobarbital, a prohibited medication, while on study medication. In addition, the protocol required a negative pregnancy test at screening for enrollment. Subject 004-3204-30, a female of childbearing potential, did not have a pregnancy test and no documentation to show if the test was in fact done. The subject was 30 years of age.

#### **Inadequate Drug Accountability Records**

Three subjects 34, 41 and 58 were infused with the incorrect assigned study drugs isavuconazole vs voriconazole.

#### **Inadequate Drug Infusion Records**

For at least five subjects (#35, 42, 46, 50, 57 and 59), the infusion start and volume was either missing or there was no documentation to show the start and end times. For example, Subject #35 received the day 5 and the day 6 infusions on July 19-20, 2008. On both days, the dose 2 infusion documentation was missing the start time. Out of 39 infusions documented between July 14, 2008 and August 1, 2008, there were two missing infusion start times, one infusion end time, six missing the volume given, and 23 of the entries are on records with no identification of the subject being infused”.

There were no unreported deaths and no evidence of under-reporting of adverse events. There were time limitations to the inspection due the necessity for translation .

- c. **Assessment of Data Integrity:** While the above findings represent regulatory violations, they are unlikely to have a significant impact on data integrity or the efficacy results. Although rapid infusion of study drug may pose a safety risk for allergic reactions), none were reported. In OSI’s discussion with the DAIP team, DAIP noted that the above regulatory deficiencies are noncritical. The remaining data generated by this site are considered reliable and appear acceptable in support of the pending applications.

**2. Isam Raad, M.D.**  
**Houston, TX 77030**

- a. What Was Inspected:** This inspection was performed as a data audit for NDAs 207500/207501 and inspected Study Protocols WSA-CS-03 and WSA-CS004.

For study protocol WSA-CS-03: At this site a total of 55 subjects were screened, 51 subjects were reported as screen failures, four subjects were randomized into the study, three subjects died, and one subject completed the study. For study WSA-CS-004: At this site a total of 230 subjects were screened, 206 subjects were reported as screen failures, 24 subjects were enrolled, five subjects died, four subjects withdrew consent, 10 subjects were reported as having insufficient therapeutic response, and five subjects completed the study. Review of the Informed Consent Documents, for the majority of subjects records reviewed, verified that all subjects signed informed consent forms prior to enrollment.

The medical records/source documents for four subjects (WSA-CS-003) and 13 subjects (WSA-CS-004) were reviewed. The medical records/source documents for enrolled subjects for certain visits were reviewed including drug accountability records, vital signs, IRB files, financial disclosures, inclusion/exclusion criteria, prior and concomitant medications, and adverse events reporting. The field investigator compared the source documents/endpoint values to the data listings for primary efficacy endpoints, and no discrepancies were noted.

- b. General Observations/Commentary:** At the conclusion of the inspection, a 2-item Form FDA 483 was issued to Dr. Raad. Our investigator presented and discussed the inspectional observations with the clinical investigator. The discussion included the failure to document the review of documents in order to assess the clinical significance of laboratory results and adverse events, and the failure to report all adverse events to the IRB in a timely manner. For example,

Study WSA-CS-003: Subject #118004 experienced three adverse events; respiratory failure, ST segment elevation, and sepsis that were not reported to the IRB.

Study WSA-CS-004: Subjects 118018, 118019 and 118020 experienced confusion, hyperbilirubinemia; multi-organ failure; and death, respectively. These events were not reported to the IRB according to the protocol.

In general, the medical records reviewed were found to be difficult to read in order to review the records and be able to perform adequate data verifiable. In addition, our investigator noted that there was no documentation to show that the staff/associates who were assisting with the investigation received adequate training regarding their obligations. Furthermore, Subject #118010 did not meet the inclusion criterion for “probably” invasive fungal disease which requires one host factor, one clinical factor, and one mycological factor; the latter was not present diagnosis of fungal disease prior to randomization. There was no evidence of under-reporting of adverse events to the sponsor or the agency. There were no known limitations to the inspection.

- c. **Assessment of Data Integrity:** Although minor regulatory deviations were noted at this site, the findings appear to be isolated and unlikely to impact the outcome of the study. The data in support of the clinical efficacy and safety at this site are considered reliable and may be used in support of the pending applications

**3. Wener Heinz, M.D.  
Wuerzburg, By 97080**

- a. **What Was Inspected:** This inspection was performed as a data audit for NDAs 207500 and 207501 and inspected Study Protocol WSA-CS-004. At this site, a total of 25 subjects were screened, two subjects were reported as screen failures, 23 subjects were randomized into the study, four subjects died before completing the follow-up visits, one subject withdrew consent due to neurological condition, and 18 subjects completed treatment. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for seven subjects were reviewed. The review included primary/secondary endpoints, informed consent, drug accountability records, vital signs, IRB records, prior and current medications, and inclusion/exclusion criteria. Source documents were compared to data listings for primary efficacy endpoints and adverse events listing. The field investigator found insufficient information was recorded at the time of enrollment to determine if the subjects were in fact eligible for entry into the study at this site. In addition, the investigator noted that subject hospital records were reviewed at a later date by a team of individuals to document incidents of adverse events.

- b. **General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr.Heinz. However, minor deficiencies were discussed with the clinical investigator as follows:

**Protocol deviations:**

Subject #20 was enrolled in the study while on the prohibited concomitant medication rapamune/sirolimus. There was no documentation to show that the medication had been changed by the clinical investigator prior to enrollment in the study.

**Inadequate record keeping:**

Subject #5 was given the wrong investigational product; source documents do not support whether an attempt was made to provide the correct product immediately after the incident was detected.

Inconsistencies were noted with documentation recorded for infusion times. For example, review of the infusion logs indicate that the time points of infusions were amended to reflect a total time interval period required by the protocol. The infusion times listed for Subjects #5, 14, and 20 were changed with no explanation provided to meet the infusion times required by the protocol.

Review of records revealed that the site delayed reporting of adverse events after an audit was performed by the sponsor. For example, Subject #5 experienced a “mood alteration” occurring between 4/19/08 through 4/22/08 which was not documented until 10/16/2012.

In general, there was limited documentation to demonstrate that the clinical investigator reviewed the work of rotating physicians, nurses administering care to subjects, that vital signs were always documented, informed consent contact information was provided, and that subjects received all the investigational product during treatment. The remaining records reviewed were verifiable based on the information available at the site. There were known time limitations to the inspection due to the need for translation. There were no unreported deaths and no evidence of under-reporting of adverse events at this site.

- c. Assessment of Data Integrity:** Although minor deviations were noted at this site, the findings appear to be isolated instances, and it is unlikely that these findings would significantly impact the outcome of the study. Overall, the data submitted in support of the clinical efficacy and safety are considered reliable and may be used in support of the pending applications.

#### **4. Francisco Marty, M.D. Boston, MA 2115**

- a. What Was Inspected:** This inspection was performed as a data audit for NDAs 207500/207501 and inspected Study Protocols WSA-CS-003 and WSA-CS-004. **For study WSA-CS-003:** At this site, a total of 14 subjects were screened and enrolled, five subjects completed the study, and 9 subjects who did not complete the study died before completing the follow-up visits.

**For Study WSA-CS-004;** at this site, nine subjects were screened and enrolled, five subjects completed the study, and four subjects died. Any subject who did not complete the study died prior to having their follow-up visits. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for 14 subjects (WSA-CS-003) and nine subjects enrolled in Study (WSA-CS-004) were reviewed. The review included randomization, adverse events, and concomitant medication for all 23 subjects. The records for all 23 subjects compared source documents to electronic case report forms and to data listings including primary efficacy endpoints and adverse event reporting. In addition, the review included drug accountability records, inclusion/exclusion criteria, vital signs, IRB records, sponsor correspondence, and adverse events.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Marty. The medical records were found to be in order,

organized, and the data verifiable. There was no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

- c. **Assessment of Data Integrity:** Overall, the data generated in support of the clinical efficacy and safety at Dr. Marty's site is considered reliable and may be used in support of the pending application.

**5. Telles Fihio Flavio de Quieroz, M.D.  
Curitiba, Brazil 80060-900**

- a. **What was inspected:** This inspection was performed as a data audit for NDAs 207500/207501 and inspected Study Protocols WSA-CS-004 and WSA-CS-003.  
**For protocol WSA-CS-004:** At this site, a total of 10 subjects were screened, two subjects were reported as screen failures, eight subjects were randomized into the study, and four subjects completed the study. Four subjects who did not complete the study had died. Review of the Informed Consent Documents for all subjects verified that all subjects signed informed consent forms prior to enrollment.

**For protocol WSA-CS-003:** At this site, a total of eight subjects were screened, eight were randomized, seven subjects completed the study, and one subject was discontinued from the study.

The medical records/source documents for all subjects enrolled were reviewed. The review included drug accountability records, vital signs, IRB files, primary efficacy endpoints, inclusion/exclusion criteria, study procedures, randomization, laboratory results, myocardial and radiological assessments, monitoring procedures, and use of concomitant medications. Source documents were compared to CRFs and data listings, to include primary efficacy endpoints and adverse events. No deficiencies were noted.

- b. **General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Quieroz. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.
- c. **Assessment of Data Integrity:** The data generated in support of the clinical efficacy and safety at Dr. Quieroz's site is reliable and may be used in support of the pending applications.

**6. Dominik Selleslag, M.D.  
Brugge 8000, Belgium**

- a. **What was inspected:** This inspection was performed as a data audit for NDAs 207500/207501 and inspected Study WSA-CS-004. At this site, a total of 43 subjects were screened, eight subjects were reported as screen failures, 35 subjects were randomized into the study, 26 subjects completed the study, and nine subjects died before completing the study. Review of the Informed Consent Documents for six subjects verified that the subjects signed informed consent forms prior to enrollment.

The medical records/source documents for six subjects were reviewed to include informed consent, randomization, treatment, and drug dispensing records. For the remaining 29 subjects the review included eligibility criteria, drug accountability records, vital signs, inclusion/exclusion criteria, study procedures, and use of concomitant medications. Source documents were compared to CRFs and data listings, to include primary efficacy endpoints and adverse events reporting. The field investigator “reported that the inspection was difficult because most of the source documents were scanned and kept electronically and were made available for review; this took too much time due to translation. The changes were a result of the re-monitoring of the data by Asetella/ (b) (4) after Astellas took over the study”. Our field investigator reports that “The clinical investigators were asked to review data they had previously collected and reported, including a review of the CT scans, and reevaluate their assessments in accordance with the most recent protocol. For example, they may have assessed the subject’s outcome in 2008. The clinical investigators were asked to assess the subject’s data using the 2011 definitions. This was all documented at both study sites in Belgium. The doctors were given written questions regarding the early recorded data to be answered. The team reviewed the records in order to answer the questions by signing and dating the final records. Then the CRFs were changed in accordance with those answers. That final, revised case report form data was verified and matched the data listings”.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Selleslag. Although no FDA 483 was issued to Dr. Selleslag, our investigator presented and discussed the following items:

**Protocol Deviations:**

According to the protocol patients should be excluded with evidence of moderate to severe renal dysfunction with calculated creatinine clearance of Cr/cl <50 or dialysis or likely required dialysis.

Subject 320629 was enrolled with a creatinine clearance < than 50 ml/min. due to an error in calculation and the use of ideal body weight instead of actual body weight. The subject completed both treatment and the study. The subject died on (b) (6)

Subject 320614 was enrolled with a creatinine clearance < than 50ml/min and received greater than 4 antifungal doses of systemic antifungal therapy other than fluconazole within 7 days prior to the first administration of study medication. This subject met exclusionary criterion as stated in the protocol which states that “patients who have administered more than four cumulative days of intraconazole, voriconazole, or posaconazole, for any reason, within seven days prior to the first administration should be excluded. In addition, this subject was treated with Caspofungin on the first day of study medication.

Subjects 320602 and 320612 both had negative galactomannan tests and should have been considered as having “possible” invasive fungal disease. These subjects should have been removed from enrollment after seven days because galactomannan tests remained negative. Instead, Subject 320602 remained in the study until the end of treatment and had follow-up visits. In addition, Subject 320612 had neutropenia and remained on the study until he withdrew consent from treatment on (b) (6) prior to completing the study.

Subject 320622 met exclusion criterion #4 which excludes subjects at high risk for QT/QTc prolongation. The screening exam noted the subject had an irregular pulse and an ECG tracing considered to be clinically significant. The subject was taking two atrial fibrillation drugs during the study. The subject did not complete the study medication due to insufficient response.

Subject 320624 did not meet inclusion criteria due to an increase in QTcF of 40 msec from baseline. The subjects’ screening ECG showed a QTcF of 383msec on July 12, 2011. On July 26, 2011, the ECG showed an increase in QTc of 494ms which was determined to be clinically not significant by the clinical investigator. The increase in QTcF by 111 msec was greater than the 40 msec from baseline allowed by the protocol. The subject remained on the study and completed the study.

Subject 320625 started the study on July 15, 2011. On (b) (6) the subject underwent “urgent hemodialysis” due to acute renal failure. The protocol required subjects to discontinue study medication due to dialysis; instead the subject remained in the study and completed treatment.

The medical records reviewed were found adequate and the data verifiable. There was no evidence of under-reporting of adverse events. Subjects who died before completing the study were accurately reported. There were known limitations to the inspection to due language.

- c. **Assessment of Data Integrity:** Although regulatory deviations were noted at this site, the findings appear to be isolated and unlikely to impact the efficacy results. OSI recommends that the review division may wish to exclude certain subjects from the final analyses in support of the application. The remaining data generated at this site in support of the clinical efficacy and safety is considered reliable and may be used in support of the pending applications.

### III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Six clinical investigator sites were inspected in support of this application. The inspection of the four clinical investigators listed above revealed regulatory violations. The pending classification for Drs. Maertens, Raad, Heinz, and Selleslag sites are Voluntary Action Indicated (VAI) and the pending classification for Drs. Marty and Quieroz sites are No Action Indicated (NAI). For the pending classifications, a summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

Overall, while the above findings represent observed regulatory deficiencies, these findings are unlikely to have a significant impact on data acceptability. In OSI's discussion with the review team in DAIP, DAIP noted that the above regulatory deficiencies were noncritical, expressed no concerns and agreed that the data submitted from these six sites are considered acceptable and may be used in support of the pending application.

*{See appended electronic signature page}*

Antoine El-Hage, Ph.D.  
Good Clinical Practice Assessment Branch  
Division Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D. M.P.H.  
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Office of Scientific Investigations

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/s/  
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ANTOINE N EL HAGE  
01/22/2015

SUSAN D THOMPSON  
01/22/2015

KASSA AYALEW  
01/22/2015

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**LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** January 21, 2014

**Requesting Office or Division:** DAIP (Division of Anti-Infective Products)

**Application Type and Number:** NDA 207500 and NDA 207501

**Product Name and Strength:** Cresemba (b) (4) capsules, (b) (4) mg  
Cresemba (b) (4) for injection, (b) (4) mg

**Product Type:** Single Ingredient Product

**Rx or OTC:** Rx

**Applicant/Sponsor Name:** Astellas Pharma

**Submission Date:** July 8, 2014

**OSE RCM #:** 2014 - 1389  
2014 - 1393

**DMEPA Primary Reviewer:** Jacqueline Sheppard, PharmD

**DMEPA Acting Team Leader:** Vicky Borders-Hemphill, PharmD

**DMEPA Associate Director:** Irene Z. Chan, PharmD, BCPS

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## 1 REASON FOR REVIEW

Astellas proposes the introduction of a new anti-fungal product to the market for the treatment of invasive aspergillosis and invasive mucormycosis. This review evaluates proposed container labels and carton and insert labeling for Cresemba (Isavuconazonium) capsules (NDA 207500) and for injection (NDA 207501) for areas of vulnerability that may lead to medication errors in response to a request from the Division of Anti-Infective Products (DAIP).

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B – N/A
Previous DMEPA Reviews	C – N/A
Human Factors Study	D – N/A
ISMP Newsletters	E – N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Astellas Pharma, Inc submitted NDAs for Cresemba (isavuconazonium) capsules and powder for injection. The capsules and powder for injection share the same indication, (b) (4). However, the for injection product is a lyophilized powder for intravenous infusion that forms visible particulates after the reconstituted solution is further diluted. The diluted solution must be gently mixed and handled to reduce formation of particulates and administered through an infusion set with an in-line filter to remove any isavuconazole particulates from the infusion solution. Thus, DMEPA requested the Applicant to conduct a use-risk analysis to identify potential errors associated with the reconstitution, dilution, and administration of Cresemba injection. A description of tasks, potential errors or omissions, and mitigation strategies submitted in the Applicant’s use-risk analysis is provided in Appendix F.

The Cresemba (Isavuconazole) use-risk analysis identified steps that represent areas of potential error or omission that have the potential to result in the increased formation of isavuconazole particulate. These errors were identified from clinical trial data. The Applicant determined that the Critical tasks include:

1. withdrawing of the reconstituted solution from the vial to add to the intravenous bag
2. mixing the intravenous bag containing drug product and inspecting for particulates
3. determining if visible particulates matches the description in product labeling
4. transporting the infusion bag to the floor under ambient conditions
5. selecting infusion sets with inline filters, [REDACTED] (b) (4)

Potential mitigation strategies proposed by Astellas include enhanced product labeling that alerts about the correct reconstitution and infusion diluents, enhanced visual inspection of the particulates, and instructions to use gentle mixing and avoid the use of a pneumatic tube system. The Applicant will also provide a warning sticker to be applied to the infusion bag to remind users of the requirement to administer with the use of an in-line filter, and a PharmAlert newsletter will be distributed that will include the requirement for utilization of an in-line filter and dilution and transportation recommendations.

We discuss the critical tasks below and describe strategies in the proposed label and labeling that we find acceptable to mitigate risks related to these errors. However, in addition to these strategies, we recommend the placement of a statement on the principal display panel (PDP) of the injection carton label to alert users to carefully read the preparation and administration instructions before using Cresemba to reduce the risk of particulate formation and the administration of particulates to the patient (see section 4.1).

1. The Applicant considers withdrawing of the reconstituted solution from the vial to add to the intravenous bag a critical task. If the incorrect infusion diluent is chosen during this task, there is a risk for product degradation and increased particulate formation. Section 2 in the Full Prescribing Information provides clear information about compatible diluent information. We find this acceptable.
2. Mixing of the infusion bag was assessed as having a high risk for error. During the mixing process and subsequent inspection for particulates, users must be careful to not subject the bag to vigorous mixing to minimize the risk for increased formation of isavuconazole particulates. Section 2 in the Full Prescribing Information clearly instructs users to avoid unnecessary shaking. We find this acceptable.

3. Failure to distinguish isavuconazole particulates from non-isavuconazole particulates was assessed as having a medium risk for error. Users must be able to effectively identify isavuconazole particulates or risk infusing solution containing non-isavuconazole particulates. Astellas' proposed mitigation strategy to ensure the standard visual inspection of intravenous preparations is to describe the isavuconazole particulate in greater detail. Section 2 in the Full Prescribing Information details the isavuconazole particulates for the users so they may differentiate said particles from non-isavuconazole isolates. We find this acceptable.
4. Transporting the infusion bag to the floor under ambient conditions is required to minimize shaking that can result in increased formation of particulates. Section 2 in the Full Prescribing Information clearly instructs users to avoid the use of pneumatic transport systems and use care when transporting the product. We find this acceptable.
5. The use of a dedicated line or separation of Cresemba from other infusions was assessed as having low to medium risk of error. Infusion of Cresemba with other medications risks an increase in particulate levels. Section 2 of the Full Prescribing Information provides instruction to not co-infuse Cresemba with other medications. We find this acceptable.

Administration of the infusion solution with the use of an inline filter was assessed as having a low to medium risk for error. Users must choose and use an appropriate filter to administer Cresemba. The risk of administration of particulates to the patient may occur if this step is omitted. Section 2 of the Full Prescribing Information instructs users to use an inline filter and dictates the appropriate size of the required filter. Additionally, the statement "Use an in-line filter during infusion" is provided on the vial container label and the carton labeling; however, we believe this can be made more prominent (see discussion below). The Applicant also proposes to provide a sticker to be placed on each infusion bag to remind users to use an in-line filter. While the use of warning stickers is limited as it dependent upon users remembering to place the sticker and also correctly placing the sticker on the bag without obscuring important information, data obtained from the 1995 FDA mandate for labeling stickers on Vincristine showed a reduction in errors.<sup>1</sup> Thus, we find the use of the sticker acceptable. However, we request that the Applicant provide a mockup sample of the proposed supplied warning sticker for our review to determine if the size and proposed placement of the sticker introduces risk for medication errors (see Section 4.1).

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<sup>1</sup> Cohen, M (2007). The Role of Drug Packaging and Labeling in Medication Errors. In *Medication Errors* (2<sup>nd</sup> Ed, pp 133-134). Washington DC: American Pharmacists Association.

DMEPA performed a risk assessment of the proposed container label, carton labeling, and prescribing information for the injection and the capsule from a medication error perspective. We identified areas of the carton labeling and container labels that can be revised to increase clarity, improve readability, add important critical information, or increase prominence of important information (See section 4.2). For all container labels and carton labeling, we recommend revision to the product name and equivalency statement on the carton labeling and container labels in accordance with guidelines from the Chemistry and Manufacturing Controls (CMC) policy on salt nomenclature for both the capsule and injection. On the vial container label, the statement, “Use an in-line filter during infusion”, may be made prominent by relocating it to the PDP to appear under the strength statement. On the oral capsule blister pack label, we recommend the revision of the desiccant statement to add “Do not eat” to mitigate inadvertent ingestion of the desiccant. On the oral capsule blister carton labeling, we recommend relocation and revision of the net quantity statement to mitigate dosing confusion and to add the package type to provide important information. On the oral capsules 4- (b) (4) pack carton labeling, we recommend revisions to the contents statement to increase prominence, (b) (4)

Additionally, we performed a risk assessment of the proposed PLR conversion prescribing information to identify areas of improvement for readability. We noted the use of error-prone abbreviations in the Dosage and Administration section and recommend these are removed and replaced with their intended meanings. These changes were added to DAIP’s working version of prescribing information that is currently undergoing revision.

## **4 CONCLUSION & RECOMMENDATIONS**

The proposed labels and labeling for Cresemba may be improved to communicate important use information and to improve prominence of important product information. We recommend the following revisions be implemented prior to the approval of the NDA.

### **4.1 RECOMMENDATIONS FOR APPLICANT/SPONSOR**

#### **A. All Container Labels and Carton Labeling**

1. Revise the proprietary name from appearing in all caps, “CRESEMBA”, to appear in title case, “Cresemba”, to improve readability. Words set in title case form recognizable shapes, making them easier to read than the rectangular shape formed by words set in all upper case letters.<sup>2</sup>

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<sup>2</sup>Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

**B. Oral Capsules Blister Pack Label**

1. Revise the statement from “ [REDACTED] (b) (4) ” to read “Contains desiccant to protect from moisture. Do not open. Do not eat.” to alert patients that the desiccant should not be eaten.
2. Revise the product name and equivalency statement from “Cresemba [isavuconazonium sulfate] capsules equivalent to 100 mg isavuconazole 100 mg” to read [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED] (b) (4)
3. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product barcode to each individual unit dose per 21CFR 201.25(c)(2).
4. Ensure that the lot number and expiration date appear on each individual blister for the blister pack.

**C. Oral Capsule Blister Carton Labeling – 14 count**

1. See B.2.
2. Revise the usual dosage statement from [REDACTED] (b) (4) to “See prescribing information” in accordance with 21 CFR 201.55.
3. Remove the designation [REDACTED] (b) (4) after the net quantity statement as this is confusing [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]

4. Relocate the net quantity statement towards the bottom of the principal display panel. The current location competes for prominence with the strength and labeling equivalency statement.
5. Add the package type to the principal display panel (i.e., Unit-dose blister) to appear prior to the net quantity statement to identify how the medication should be safely handled and used.

**D. Oral Capsule Blister Carton Labeling – 4 pack cartons**

1. See B.2. Remove the second equivalency statement that appears in the colored box.
2. See C.2.
3. Revise the contents statement from [REDACTED] (b) (4) to read “Contents: 4 cartons each containing one unit dose blister pack of 14 capsules”. Increase the font size of the contents statement to reduce the risk of confusion between the 56 count [REDACTED] (b) (4)



**F. Powder for Injection Container Label**

1. Revise the product name and equivalency statement from “Cresemba [isavuconazonium sulfate] for injection equivalent to 200 mg isavuconazole” to read [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

2. Relocate the statements, “For Intravenous Infusion Only” and “Use an in-line filter during Infusion” to appear on the principal display panel under the strength and equivalency statements
3. Add “Discard unused portion” statement to the side panel to appear under the “Single Use Vial” statement
4. Provide a mockup sample of the proposed sticker to be applied to the infusion bag to remind users of the requirement to administer with the use of an in-line filter with the submission of revised container labels and carton labeling.

**G. Powder for Injection Carton Labeling**

1. See F.1.
2. Add a statement to appear under the inline filter statement on the principal display panel similar to “Carefully read the Preparation and Administration Instructions prior to Use.” to alert users to review important information which will mitigate the risk of particulate formation.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Cresemba that Astellas Pharma submitted on July 8, 2014.

<b>Table 2. Relevant Product Information for Cresemba</b>	
<b>Active Ingredient</b>	Isavuconazonium Sulfate
<b>Indication</b>	Treatment of invasive aspergillosis and invasive mucormycosis
<b>Route of Administration</b>	Oral; intravenous
<b>Dosage Form</b>	Capsules; injection
<b>Strengths</b>	186.3 mg capsules 372.6 mg injection
<b>Dose and Frequency</b>	Loading dose: (b) (4) mg every 8 hours for 6 doses via oral or intravenous administration Maintenance dose: (b) (4) mg once per day via oral or intravenous route starting 12 to 24 hours after the last loading dose
<b>How Supplied</b>	Capsules: 7 count blister pack Injection: 372.6 mg vials
<b>Storage</b>	Capsules: Controlled Room Temperature Injection: lyophilized powder should be stored refrigerated between 2-8°C. Reconstituted solution can be stored for 6 hours at room temperature or 24 hours refrigerated between 2-8°C.

## APPENDIX F . Drug Product Use-Related Risk Analysis

Table 3 presents areas of potential error or omission with the qualitative risk level for Cresemba Injection that Astellas Pharma submitted on October 10, 2014.

Table 3

Process step number	Process step description	Potential errors or omissions	Risk for error or omission	Mitigation of potential error	Potential consequences of error or omission
4	Reconstitute drug product with SWFI, shake and inspect for particulate	Incorrect reconstitution diluent used	Low	Current label instructions 1) to use SWFI and 2) that reconstituted solution should be clear and free of visible particulate	None: Precipitate would be observed in reconstituted solution, which would be discarded
7	Withdraw reconstituted solution from vial and add to IV bag	Incorrect bag size (i.e. less than 250 mL) used	Low	Current label instructions to use 250 mL infusion bag	Potential risk for infusion related reactions: CRESEMBA should be (b) (4)
7	Withdraw reconstituted solution from vial and add to IV bag	Use of diluent other than specified in product labeling	Med	Current label instructions to use 0.9% sodium chloride injection or 5% dextrose injection mitigate this risk and additional label instructions are proposed† to emphasize that only these two infusion diluents should be used	Potential risk for product degradation and increased particulate formation
8	Mix IV bag containing drug product and inspect for particulate	IV bag is subjected to vigorous mixing	High	Additional label instructions are proposed† for gentle mixing or rolling the IV bag	Increased formation of particulate
10	Does particulate match description in product label?	Non-isavuconazole particulate is not detected	Med	Additional label instructions are proposed† to support in the standard visual inspection of IV preparations by describing the isavuconazole particulate in more detail	Potential for infusion solution containing non-isavuconazole particulate
15	Transport infusion bag to floor under ambient conditions	Infusion bag is transported using a pneumatic tube system or in a way that causes shaking or vibration	High	Additional label instructions to avoid vibration during transportation and to not use a pneumatic tube system are proposed†	Increased particulate count
17	Store infusion bag at room temperature	Infusion bag is stored longer than the allowed maximum time	Low	Current label instructions to administer drug within 6 hours at ambient temperature	Potential risk for product degradation and increased particulate formation

Process step number	Process step description	Potential errors or omissions	Risk for error or omission	Mitigation of potential error	Potential consequences of error or omission
19	Collect infusion set with inline filter, (b) (4) infusion bag, (b) (4)	Infusion set without inline filter is used	Med	Current label instructions to use an inline filter for administration mitigate this risk. Proposed sticker to be applied to infusion bag in pharmacy as a reminder of the requirement that CRESEMBA for injection must be administered through an in-line filter	Potential for infusion solution with increased particulate levels to be administered
19	Collect infusion set with inline filter, (b) (4) infusion bag, (b) (4)	Infusion set with incorrect filter (incorrect pore size) is used	Low	Current label instructions to use inline filter with pore size 0.2 to 1.2 µm	Potential for infusion solution with increased particulate levels to be administered
20	Connect infusion set to patient	Connection is made distal to the inline filter	Low	Additional label instructions are proposed† to not co-infuse CRESEMBA with other medications or to use a separate line for infusion	Potential for infusion solution with increased particulate levels to be administered

## APPENDIX G. LABELS AND LABELING

### G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>3</sup> we reviewed the following Cresemba labels and labeling submitted by Astellas on October 10, 2014 and revisions to the Division of Anti-Infective Products Working Document on December 16, 2014.

- Container label
- Carton labeling
- Prescribing Information

<sup>3</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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01/21/2015

BRENDA V BORDERS-HEMPHILL  
01/22/2015

IRENE Z CHAN  
01/22/2015

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** November 20, 2014

**To:** Alison Rodgers, Regulatory Project Manager  
Division of Anti-Infective Products

**From:** Christine Corser, Regulatory Review Officer  
Office of Prescription Drug Promotion

**Subject:** **NDA #207500, 207501**  
**CRESEMBA<sup>®</sup> (isavuconazonium) capsules and injection**

---

As requested in your consult dated August 19, 2014, OPDP has reviewed the proposed draft labeling for CRESEMBA<sup>®</sup> (b) (4) capsules and injection.

OPDP's comments on the PI are based on the substantially complete version of the labeling titled, "isavuconazole-redline-uspi-07oct2014.docx," which was received via email from DAIP on November 7, 2014.

OPDP's comments on the PI are provided in the attached, clean version of the labeling.

OPDP has also reviewed the proposed carton and container labels that were submitted to FDA on July 8, 2014 (e.g., CRESEMBA 100 mg (b) (4) 4 pack carton, (b) (4) CRESEMBA 100 mg Blister Carton, CRESEMBA 100 mg Blister Package, CRESEMBA 200 mg (b) (4) Vial Carton, CRESEMBA 200 mg Individual Vial Carton, and CRESEMBA 200 mg Vial Label). OPDP has reviewed these proposed carton and container labeling from a promotional perspective, and has no comments at this time.

Thank you for the opportunity to review and provide comments on the proposed PI and carton/container labeling. If you have any questions about OPDP's comments, please contact Christine Corser at 6-2653 or [Christine.corser@fda.hhs.gov](mailto:Christine.corser@fda.hhs.gov).

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CHRISTINE G CORSER  
11/20/2014

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: November 18, 2014

To: Sumathi Nambiar, MD, MPH  
Director  
**Division of Anti-Infective Products (DAIP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Marcia Williams, PhD  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Shawna Hutchins, MPH, BSN, RN  
Acting Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Christine Corser, PharmD, RAC  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): CRESEMBA (isavuconazonium)

Dosage Form and Route: Capsules, for oral administration  
For injection, for intravenous (IV) administration

Application Type/Number: NDA 207500 (capsules)  
NDA 207501 (IV)

Applicant: Astellas Pharma US Inc.

## 1 INTRODUCTION

On July 07, 2014, Astellas Pharma US Inc., submitted for the Agency's review an original New Drug Application (NDA 207500) for CRESEMBA (isavuconazonium) Capsules, for oral administration, and an original New Drug Application (NDA 207501) for CRESEMBA (isavuconazonium) For injection, for intravenous administration, indicated for the treatment of invasive aspergillosis and invasive mucormycosis in patients 18 years of age and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anti-Infective Products (DAIP) on July 30, 2014, and August 19, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for CRESEMBA (b) (4) Capsules, for oral administration and CRESEMBA (b) (4) Injection, for intravenous administration.

## 2 MATERIAL REVIEWED

- Draft CRESEMBA (b) (4) PPI received on July 07, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 07, 2014.
- Draft CRESEMBA (b) (4) Prescribing Information (PI) received on July 07, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 07, 2014.
- Approved VFEND (voriconazole) comparator labeling dated April 07, 2014.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SHAWNA L HUTCHINS  
11/18/2014

CHRISTINE G CORSER  
11/18/2014

MARCIA B WILLIAMS  
11/18/2014

LASHAWN M GRIFFITHS  
11/18/2014

## Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

<b>IND or NDA</b>	NDA 207500 & NDA 207501
<b>Brand Name</b>	Cresemba
<b>Generic Name</b>	isavuconazole
<b>Sponsor</b>	Astellas Pharma US Inc
<b>Indication</b>	Treatment of invasive aspergillosis and invasive mucormycosis
<b>Dosage Form</b>	Capsule for oral administration (NDA 207500) Injection for i.v. (NDA 207501)
<b>Drug Class</b>	Anti-fungal
<b>Therapeutic Dosing Regimen</b>	200 mg/day preceded by a loading dose of 200 mg 3 times a day for 2 days
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	Not established
<b>Submission Number and Date</b>	SDN 001; 8 Jul 2014
<b>Review Division</b>	DAIP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

### 1 SUMMARY

#### 1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of isavuconazole (200 mg and 600 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between isavuconazole (200 mg and 600 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the  $\Delta\Delta\text{QTcF}$  for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 3, indicating that assay sensitivity was established.

In this randomized, double-blind, placebo and active controlled, parallel study, 160 healthy subjects received isavuconazole 200 mg, isavuconazole 600 mg, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

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

Treatment	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Isavuconazole 200 mg	2	-13.1	(-18.1, -8.1)
Isavuconazole 600 mg	2	-24.6	(-29.8, -19.3)
Moxifloxacin 400 mg	2	11.0	(6.1, 15.9)

The suprathreshold dose (600 mg) produces mean  $C_{\text{max}}$  values of 2.7-fold the mean  $C_{\text{max}}$  for the therapeutic dose (200 mg). These concentrations are above those for the predicted worst case scenario (drug interaction with ketoconazole) and show that at these concentrations there are no detectable prolongations of the QT-interval. The  $C_{\text{max}}$  concentration of isavuconazole following i.v. administration is similar to the  $C_{\text{max}}$  following oral administration at the same dose.

## 1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

- At a dose 3 times the recommended therapeutic maintenance dose, isavuconazonium capsule did not prolong the QT interval to any clinically relevant extent. In fact, a dose-and-concentration-related shortening of the QTc interval was observed with isavuconazole, probably correctly attributed by the sponsor to slight block of the calcium channel.
- Because of the significant higher exposure of isavuconazonium and BAL8728 following intravenous administration compared to that isavuconazonium after oral administration, the results from this capsule TQT study cannot be adequately applied to intravenous administration, although QT prolongation with intravenous administration is unlikely based on the results from study 9766-CL-0004, and, even if there were some inhibition of IKr or hERG at higher exposure, the earlier onset calcium current block would render it benign.
- There is also a small effect (about 10 ms at the highest tested exposure) reducing the PR interval. We do not believe this is clinically relevant. If the sponsor performs a study with intravenous administration, it will be of interest to see the PR results.

## 2 PROPOSED LABEL

Following proposed labeling information is provided by the sponsor related to cardiac Electrophysiology:

### 5 WARNINGS AND PRECAUTIONS

(b) (4)

## 12 CLINICAL PHARMACOLOGY

### 12.2 PHARMACODYNAMICS

#### *Pharmacokinetic/Pharmacodynamic relationship*

#### *Cardiac Electrophysiology*

(b) (4)

Isavuconazole resulted in dose-related shortening of the QTc interval. For the (b) (4) dosing regimen, the least squares mean (LSM) difference from placebo was -13.1 (b) (4) msec at 2 hours postdose [90% CI: -17. (b) (4), -9.1 (b) (4) msec]. Increasing the dose to (b) (4) resulted in an LSM difference from placebo of -24. (b) (4) msec at 2 hours postdose [90% CI: -28.7 (b) (4) - 20.4 (b) (4)].

#### 2.1 QT-IRT RECOMMENDATIONS

*Our recommendations are suggestions only. We defer final labeling decisions to the review division.*

#### 12.2 Pharmacodynamics

#### Cardiac Electrophysiology

(b) (4)

We do not believe any further concern about other drugs that shorten QT is indicated.

## 3 BACKGROUND

### 3.1 PRODUCT INFORMATION

Isavuconazonium sulfate (BAL8557-002) is a water-soluble triazole antifungal agent that is being developed for use in adult patients for the treatment of life-threatening invasive fungal infections. Isavuconazonium sulfate is available as a sterile lyophilized powder for intravenous infusion and as hard capsules for oral administration. Isavuconazole is the active moiety of isavuconazonium sulfate.

Following intravenous administration, isavuconazonium is rapidly and quantitatively converted to the active moiety isavuconazole and its cleavage product BAL8728 by enzymatic hydrolysis.

Isavuconazonium sulfate is considered a Class I (high solubility and high permeability) compound in the Biopharmaceutical Classification System (BCS). The prodrug (isavuconazonium sulfate) is highly soluble, with a solubility > 1.0 g/mL in any of the pH conditions tested (pH 1, 3, 5 and 7). After oral administration, isavuconazonium predominantly undergoes chemical hydrolysis in the gastrointestinal lumen and is not detected in plasma. The active moiety (isavuconazole) is highly permeable; the mean absolute bioavailability of isavuconazole after a single oral dose of isavuconazonium sulfate hard capsule (equivalent to 400 mg isavuconazole) was approximately 98%, demonstrating complete absorption. The inactive cleavage product, BAL8728, was undetectable in plasma or close to the LLOQ in plasma of healthy subjects after oral administration of isavuconazonium.

### **3.2 MARKET APPROVAL STATUS**

Isavuconazole is not approved for marketing in any country.

### **3.3 PRECLINICAL INFORMATION**

The nonclinical safety profile of isavuconazole was comparable to other azoles, and no notable findings were observed to contraindicate evaluation of isavuconazonium in humans. Isavuconazole inhibited the human ether-a-go-go related gene potassium current at a concentration inducing 50% inhibition (IC<sub>50</sub>) of 5.82 μM, which is 34-fold the human non-protein bound C<sub>max</sub> at the clinical maintenance dose of 200 mg/day (derived from the mean steady-state C<sub>max</sub> in healthy volunteers taking 200 mg eq. isavuconazole once daily [7.50 μg/mL] in Study 9766-CL-0017 and an unbound fraction set to 0.01). A second in vitro ion channel study confirmed this finding but also showed that isavuconazole inhibited the L-type calcium channel (hCav1.2) with an IC<sub>50</sub> of 6.57 μM (38-fold the human non-protein bound C<sub>max</sub> at the clinical maintenance dose of 200 mg/day). This ion channel finding is consistent with the QT interval corrected using Fridericia's correction formula (QTcF) interval shortening reported in the clinical thorough QT (TQT) study. QTcF shortening was not observed in monkeys at a human equivalent doses up to 2.2-fold the clinical maintenance dose. Intravenous administration of isavuconazonium to monkeys at human equivalent doses up to 2.2-fold the clinical maintenance dose resulted in transient and reversible decreases in systolic and diastolic blood pressure during the infusion period. In addition, an increase in heart rate (HR) was noted for the highest dose tested.

### **3.4 PREVIOUS CLINICAL EXPERIENCE**

Isavuconazole has been clinical evaluated in 2166 subjects, including 1322 subjects in 40 Phase 1 studies, 182 subjects in 2 Phase 2 studies and 662 subjects in 2 Phase 3 studies. Of these 2166 subjects, 1692 received at least one dose of isavuconazole including 1145 subjects in Phase 1 studies, 144 subjects in the Phase 2 studies and 403 subjects in Phase 3 studies.

In the isavuconazole clinical program, Torsade de Pointes (TdP) was identified as an Event of Interest. It was assessed by utilizing the TdP MedDRA SMQ (broad).

In the phase 3 controlled study [9766-CL-0104], isavuconazole vs voriconazole), there was a numerically lower proportion of isavuconazole-treated patients (5.8%) compared to

voriconazole-treated patients (7.3%) who experienced TEAEs in the torsade de pointes SMQ. The more common events that occurred in  $\geq 1\%$  of patients in either the isavuconazole or voriconazole treatment groups, respectively, were syncope (2.7% vs 0.8%), loss of consciousness (1.2% vs 0), ECG prolonged QT (0.8% vs 3.1%) and cardiac arrest (0.4% vs 2.3%). Loss of consciousness and syncope were reported in a higher proportion of isavuconazole-treated patients compared to voriconazole-treated patients, while QT prolongation and cardiac arrest were reported in a lower proportion of isavuconazole- than voriconazole-treated patients.

In the 10 isavuconazole-treated patients with events of syncope or loss of consciousness, these events occurred from 2 to 24 days after the last dose of isavuconazole in 3 patients, concurrent with additional illnesses in 2 patients and during treatment with concomitant medications in 5 patients.

In the overall isavuconazole population in the combined phase 2 and 3 studies, 3.5% of patients experienced TEAEs in the torsade de pointes SMQ, with syncope being the most frequently occurring event (1.6%).

In the phase 1 studies, there were no TEAEs in the torsade de pointes SMQ.

Electrocardiographic assessments with particular emphasis on QT interval were evaluated in a TQT study [9766-CL-0004] at subclinical doses utilizing both oral and intravenous routes of administration. There was no apparent difference in QTcF results between the PO or IV treatment phase, nor between the 100-mg steady state or 150-mg steady-state dose level. No subject had a QTcF value above 500 ms at any time. No subject had a change in QTcF  $\geq 60$  ms at any time. Qualitative analysis revealed slight changes of repolarization, described as decreases in T wave amplitude after dosing, compared with pre-dose ECGs. No seizure, sudden cardiac death or ventricular arrhythmia was reported. Isavuconazole shortens QTc by  $\sim 15$  ms.

### **3.5 CLINICAL PHARMACOLOGY**

Appendix 6.1 summarizes the key features of drug's clinical pharmacology.

## **4 SPONSOR'S SUBMISSION**

### **4.1 OVERVIEW**

The QT-IRT reviewed the protocol prior to conducting this study under IND 72953. The sponsor submitted the study report 9766-CL-0017 for isavuconazole, including electronic datasets and waveforms to the ECG warehouse.

### **4.2 TQT STUDY**

#### **4.2.1 Title**

A phase 1, randomized, double-blind, placebo and active controlled, parallel study to evaluate the effect of repeat doses of isavuconazole on cardiac repolarization in healthy adult subjects

#### **4.2.2 Protocol Number**

9766-CL-0017

#### **4.2.3 Study Dates**

09 Mar 2012 -- 09 Jul 2012

#### **4.2.4 Objectives**

The primary objective was to evaluate the effect of steady-state isavuconazole levels on QTcF interval (Fridericia's Correction) at 200 and 600 mg versus placebo in healthy adult subjects.

The secondary objectives were to evaluate safety, tolerability and pharmacokinetics of isavuconazole and possible metabolite(s) in healthy adult subjects.

#### **4.2.5 Study Description**

##### **4.2.5.1 Design**

This is a randomized, double-blind, placebo and active controlled, parallel study.

##### **4.2.5.2 Controls**

The sponsor used both placebo and positive (moxifloxacin) controls.

##### **4.2.5.3 Blinding**

The positive (moxifloxacin) control was not blinded. All other treatments were administered blinded using a double dummy approach.

#### **4.2.6 Treatment Regimen**

##### **4.2.6.1 Treatment Arms**

There were 4 treatment arms (Table 2). On day 1, subjects were randomized to 1 of 4 treatment groups. On days 1 and 2, study drug was administered orally 3 times daily, every 8 hours. On days 3 through 13, study drug was administered orally once daily in the morning; dosing occurred at the same time as the morning dose on day 1.

**Table 2: Dose Regimen by Treatment Group  
(Sponsor's Table)**

Day	Treatment Groups			
	Isavuconazole		Placebo (n = 40)	Moxifloxacin (n = 40)
	200 mg (n = 40)	600 mg (n = 40)		
Days 1-2	200 mg oral isavuconazole tid	200 mg oral isavuconazole tid	placebo oral tid	placebo oral tid
Days 3-12	200 mg oral isavuconazole qd	600 mg oral isavuconazole qd	placebo oral qd	placebo oral qd
Day 13	200 mg oral isavuconazole	600 mg oral isavuconazole	placebo oral	400 mg oral moxifloxacin

#### 4.2.6.2 Sponsor's Justification for Doses

The therapeutic dose of isavuconazole being evaluated in the phase 3 studies was 200 mg/day preceded by a loading dose of 200 mg 3 times a day for 2 days. The 200 mg daily and the 600 mg daily regimens were predicted to have a mean C<sub>max</sub> of 5.2 and 15.6 mg/mL, respectively. The highest daily dose that could be safely administered to healthy volunteers based on the Threshold of Toxicological Concern (TTC) was 600 mg per day and was the basis for the suprathreshold dose. In addition, the choice of the 600 mg dose was based on a review of an acceptable incidence of gastrointestinal adverse events (AEs) (i.e., nausea, vomiting and diarrhea) that may lead to discontinuation and still allow for the target number of evaluable subjects. It was expected that the metabolite(s), if present, and the pharmacologically active isavuconazole would be at or near steady state at the 200 mg (clinical dose) and 600 mg dose by day 13.

*Reviewer's Comment: The selected doses for the study appear to be reasonable. DDI studies indicate that a strong CYP3A inhibitor, ketoconazole increased the isavuconazole AUC by 422% but C<sub>max</sub> only by 9%. Because of the significantly higher increase in AUC the concomitant use of ketoconazole with isovuconazole was contraindicated.*

*Lopinavir/ritonavir increased the C<sub>max</sub> and AUC of isavuconazole by 74% and 96%, respectively. Thus choice of 600-mg as a suprathreshold dose to evaluate the effect of isavuconazole on QTc prolongation seems reasonable.*

#### 4.2.6.3 Instructions with Regard to Meals

Doses will be administered with or without food. Meals are to be consumed and doses taken at the same time on each occasion.

*Reviewer's Comment: Since no significant effect of food was observed with administration of single dose of isavuconazonium sulfate (400 mg eq.), the dosing instruction regarding food consumption appears reasonable.*

#### 4.2.6.4 ECG and PK Assessments

Triplicate 12-lead safety ECGs, recorded approximately 1 minute apart, were obtained during screening and day -3, which were used to determine study eligibility, and on days 4, 7, 10 and 14 or at early termination. Continuous 12-lead ECG were recorded for

approximately 24 hours on day -2 and day -1 (baseline) and on day 13, starting approximately 1 hour prior to the planned dosing time. On day -2 continuous ECGs were recorded for approximately 24 hours to familiarize the subjects with the study procedure; these ECGs were not extracted for analysis. ECG recordings were extracted for interval analysis on days -1 and 13.

Blood samples for the determination of plasma concentrations of isavuconazole and its metabolite(s) were collected at the following time points: days 11 and 12 (within 15 minutes prior to dosing); day 13 (predose [0 hour] and 1, 2, 3, 4, 8, 10, 12, 20 and 24 hours after study drug administration. Blood samples for determination of plasma concentrations of moxifloxacin were collected at the following time points: day 13 (predose [0 hour] and 1, 2, 3, 4, 8, 10, 12, 20 and 24 hours after study drug administration.

*Reviewer's Comment: Tmax was around 3 [2-4] hours postdose following 200 mg of isavuconazole and 4 hours [2-4] hours post-dose following 600 mg of isavuconazole. The timing of ECG/PK sampling was able to capture potential effects at Tmax and delayed effects over 24 hours*

#### **4.2.6.5 Baseline**

Time-matched average values on day -1 were used as baselines.

#### **4.2.7 ECG Collection**

Intensive 12-Lead Holter monitoring will be used to obtain digital ECGs. Standard 12-Lead ECGs will be obtained while subjects are recumbent.

#### **4.2.8 Sponsor's Results**

##### **4.2.8.1 Study Subjects**

A total of 161 healthy subjects were enrolled and randomized into 1 of the 4 treatment groups. A total of 148 (91.9%) subjects completed the study and 13 subjects discontinued. A total of 160 subjects were included in the safety analysis set, 109 subjects were included in the pharmacokinetic analysis set, and 148 subjects were included in the ECG analysis set.

##### **4.2.8.2 Statistical Analyses**

###### **4.2.8.2.1 Primary Analysis**

The sponsor's assessment was based on time-matched change from baseline in QTcF using analysis of covariance by time point with treatment as a fixed effect and baseline as a covariate. The sponsor's results of primary analysis are displayed in Table 3.

Multiple doses of 200 mg and 600 mg of isavuconazole did not prolong the QTcF interval. For the isavuconazole 200 mg and 600 mg treatment groups, the mean change from placebo baseline-adjusted in QTcF decreased by 9 to 13 ms and by 19 to 25 ms, respectively, within 1 hour and 24 hours postdose.

**Table 3: Statistical Analysis of Time-Matched Change from Baseline in QTcF Between Treatment and Placebo at Each Time Point on Day 13 (Sponsor's Results)**

Parameter	Placebo	Isavuconazole	
		200 mg	600 mg
<b>-0.75 hours</b>			
n	39	35	32
Difference (treatment – placebo)	--	-8.79	-19.75
90% CI of difference	--	(-12.50, -5.08)	(-23.55, -15.95)
<b>-0.50 hours</b>			
n	39	37	32
Difference (treatment – placebo)	--	-9.02	-22.59
90% CI of difference	--	(-12.77, -5.28)	(-26.48, -18.70)
<b>-0.25 hours</b>			
n	39	37	32
Difference (treatment – placebo)	--	-10.02	-21.65
90% CI of difference	--	(-13.90, -6.13)	(-25.69, -17.62)
<b>1 hour</b>			
n	39	37	32
Difference (treatment – placebo)	--	-10.90	-21.83
90% CI of difference	--	(-14.75, -7.05)	(-25.85, -17.81)
<b>2 hours</b>			
n	38	37	32
Difference (treatment – placebo)	--	-13.10	-24.56
90% CI of difference	--	(-17.07, -9.13)	(-28.71, -20.41)
<b>3 hours</b>			
n	39	37	32
Difference (treatment – placebo)	--	-11.62	-24.25
90% CI of difference	--	(-15.78, -7.46)	(-28.60, -19.90)
<b>4 hours</b>			
n	39	37	32
Difference (treatment – placebo)	--	-12.26	-24.41
90% CI of difference	--	(-16.19, -8.33)	(-28.48, -20.33)
<b>8 hours</b>			
n	38	37	32
Difference (treatment – placebo)	--	-10.24	-22.38
90% CI of difference	--	(-14.35, -6.12)	(-26.65, -18.10)
<b>12 hours</b>			
n	39	37	31
Difference (treatment – placebo)	--	-9.01	-18.89
90% CI of difference	--	(-12.61, -5.41)	(-22.70, -15.08)
<b>24 hours</b>			
n	38	37	32
Difference (treatment – placebo)	--	-12.51	-22.36
90% CI of difference	--	(-16.83, -8.19)	(-26.95, -17.78)

*Reviewer's Comments: please see the reviewer's analysis in section 5.2.*

#### **4.2.8.2.2 Assay Sensitivity**

Assay sensitivity was assessed at 2 hours, the median  $t_{max}$  for moxifloxacin. The lower bound of the maximum treatment difference from placebo for moxifloxacin at the nominal assessment time was greater than 5 ms, the assay sensitivity was confirmed.

The sponsor's assay sensitivity analysis is displayed in the following table.

**Table 4: Statistical Analysis of Time-Matched Change From Baseline in QTcF Between Moxifloxacin and Placebo at 2 hours (Sponsor's Results)**

Parameter 2 hour time point	Placebo	Moxifloxacin
		400 mg
n	38	40
Difference (treatment – placebo)	--	11.03
90% CI of difference	--	(7.14, 14.92)

*Reviewer's Comments: please see the reviewer's analysis in section 5.2.*

#### 4.2.8.2.3 Categorical Analysis

No subjects had QTcF > 450 msec or an increase from baseline >30 msec in the isavuconazole treatment groups. However, a decrease from baseline in QTcF of greater than 30 ms was observed in 13 (40.6%) subjects in the isavuconazole 600 mg treatment group, 7 (18.9%) subjects in the isavuconazole 200 mg treatment group and 1 (2.6%) subject in the placebo group.

No subjects in the study had an increase or decrease from baseline in QTcF greater than 60 ms on day 13.

#### 4.2.8.3 Clinical Pharmacology

##### 4.2.8.3.1 Pharmacokinetic Analysis

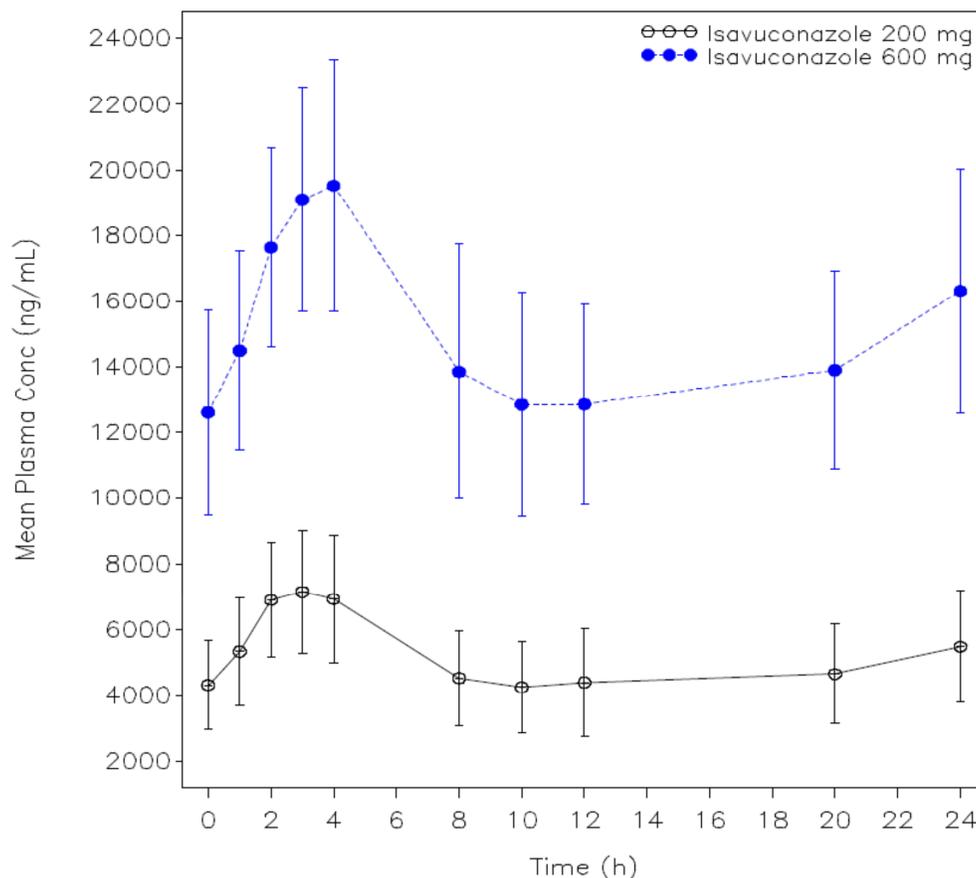
The PK analysis results for isavuconazole are presented in Table 5 and Figure 1. C<sub>max</sub> and AUC values in the thorough QT study were 2.7-fold and 2.9-fold, respectively, higher following administration of 600 mg of isavuconazole compared with 200 mg of isavuconazole, the intended clinical dose.

**Table 5. PK Parameters for Isavuconazole**

Parameter Statistic	Isavuconazole 200 mg Day 13 (n = 37)	Isavuconazole 600 mg Day 13 (n = 32)
<b>C<sub>max</sub> (ng/mL)</b>		
Mean	7499	20028
SD	1893.3	3584.3
%CV	25.2	17.9
Median	7668	19978
Min - Max	2854 – 11144	13425 – 29068
<b>t<sub>max</sub> (h)</b>		
Median	3.000	4.000
Min - Max	2.0 – 4.0	2.0 – 4.0
<b>AUC<sub>24</sub> (h•ng/mL)</b>		
Mean	121402	352805
SD	35768.8	72018.5
%CV	29.5	20.4
Median	117244	344524
Min - Max	39079 - 182318	233486 - 545638

*Source: Table 7 in sponsor's Safety Report, Page 46*

**Figure 1. Mean (SD) plasma concentration of isavuconazole for the 200 and 600 mg treatment groups on day 13**



Source: Figure 2 in sponsor's Safety Report, Page 45

#### **4.2.8.3.2 Exposure-Response Analysis**

There was a negative relationship between ddQTcF and isavuconazole plasma concentrations with predicted mean ddQTcF at the mean C<sub>max</sub> for the 200 mg and 600 mg treatment groups of -13.84 and -26.80, respectively.

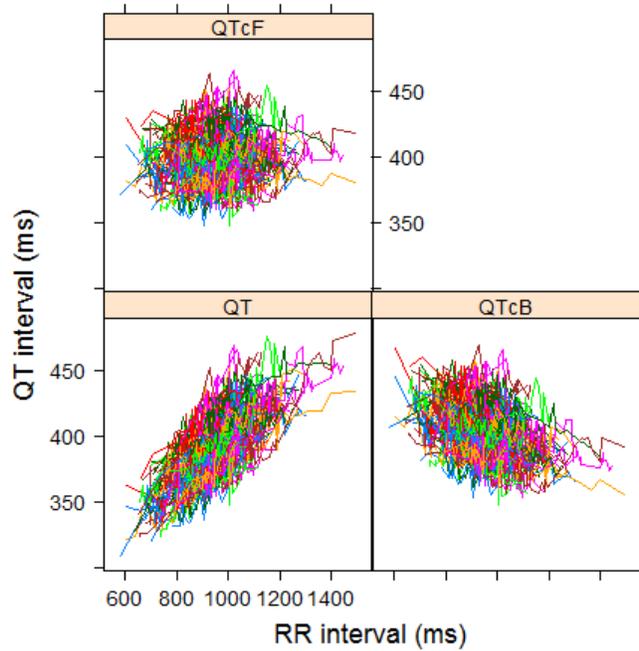
Reviewer's Analysis: A plot of  $\Delta\Delta QTc$  vs. drug concentrations is presented in Figure 4.

## **5 REVIEWERS' ASSESSMENT**

### **5.1 EVALUATION OF THE QT/RR CORRECTION METHOD**

The relationship between different correction methods and RR is presented in Figure 2. This statistical reviewer used QTcF for the primary statistical analysis.

**Figure 2: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)**



## 5.2 STATISTICAL ASSESSMENTS

### 5.2.1 QTc Analysis

#### 5.2.1.1 The Primary Analysis for Isavuconazole

The statistical reviewer used ANCOVA model and least square estimator by time to analyze the  $\Delta$ QTcF effect based on ECG analysis set. The model includes treatment as a fixed effect and baseline QTcF as a covariate. The analysis results are listed in the following tables.

**Table 6: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Treatment Group = Isavuconazole 200 mg x 13 days**

Time (hour)	$\Delta$ QTcF (ms) Isavuconazole 200 mg	$\Delta$ QTcF (ms) Placebo	$\Delta\Delta$ QTcF (ms) Isavuconazole 200 mg	
	LSmean	LSmean	LSmean	90% CI
-0.75	-7.3	1.7	-8.8	(-13.5, -4.1)
-0.5	-5.9	3.5	-9.0	(-13.7, -4.3)
-0.25	-7.6	2.6	-10.0	(-14.9, -5.1)
1	-8.4	3.1	-10.9	(-15.7, -6.1)
2	-11.0	2.5	-13.1	(-18.1, -8.1)
3	-8.4	3.8	-11.6	(-16.9, -6.4)
4	-8.8	3.9	-12.3	(-17.2, -7.3)
8	-5.1	5.7	-10.2	(-15.4, -5.1)
12	-8.9	0.4	-9.0	(-13.5, -4.5)
24	-2.6	9.8	-12.5	(-17.9, -7.1)

**Table 7: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Treatment Group = Isavuconazole 600 mg x 13 days**

Time (hour)	$\Delta$ QTcF (ms) Isavuconazole 600 mg	$\Delta$ QTcF (ms) Placebo	$\Delta\Delta$ QTcF (ms) Isavuconazole 600 mg	
	LSmean	LSmean	LSmean	90% CI
-0.75	-18.1	1.7	-19.7	(-24.5, -15.0)
-0.5	-19.1	3.5	-22.6	(-27.5, -17.7)
-0.25	-19.0	2.6	-21.7	(-26.7, -16.6)
1	-18.8	3.1	-21.8	(-26.9, -16.8)
2	-22.2	2.5	-24.6	(-29.8, -19.3)
3	-20.5	3.8	-24.3	(-29.7, -18.8)
4	-20.4	3.9	-24.4	(-29.5, -19.3)
8	-17.2	5.7	-22.4	(-27.7, -17.0)
12	-18.6	0.4	-18.9	(-23.7, -14.1)
24	-12.2	9.8	-22.4	(-28.1, -16.6)

The largest time-matched mean difference between isavuconazole 200 mg and placebo, and isavuconazole 600 mg and placebo were -13.1 ms with a 90% CI of -18.1 to -8.1 ms and -24.6 ms with a 90% CI of -29.8 to -19.3 ms, respectively, indicating no QTc prolonging effect.

### 5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 8. The largest unadjusted 90% lower confidence interval was 6.1 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval was 5.1 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

**Table 8: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Moxifloxacin**

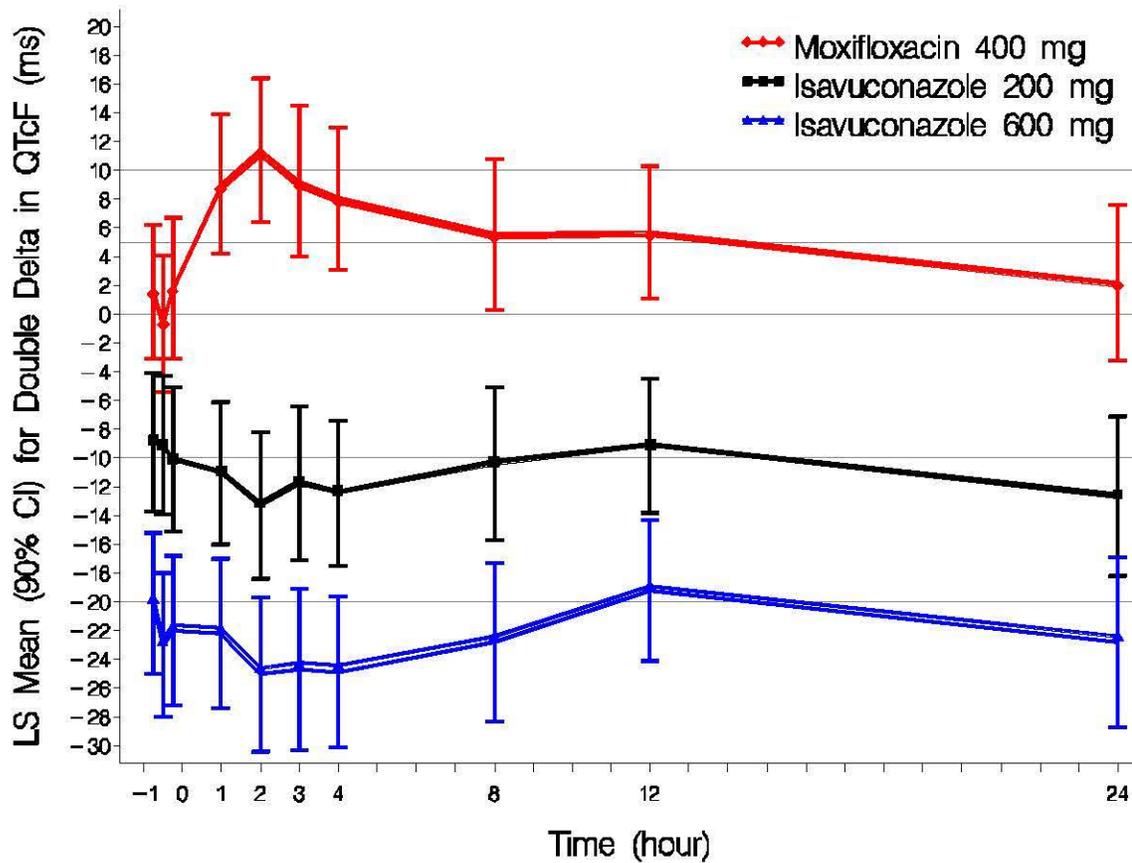
Time (hour)	$\Delta$ QTcF (ms) Moxifloxacin 400 mg	$\Delta$ QTcF (ms) Placebo	$\Delta\Delta$ QTcF (ms) Moxifloxacin 400 mg		
	LSmean	LSmean	LSmean	90% CI	Adjust 90% CI*
-0.75	3.1	1.7	1.4	(-3.1, 5.9)	(-4.1, 6.9)
-0.5	2.5	3.5	-0.7	(-5.4, 3.9)	(-6.4, 4.9)
-0.25	4.3	2.6	1.6	(-3.2, 6.4)	(-4.2, 7.5)
1	11.4	3.1	8.7	(4.0, 13.4)	(2.9, 14.5)
2	13.3	2.5	11.0	(6.1, 15.9)	(5.1, 17.0)
3	12.1	3.8	8.9	(3.8, 14.0)	(2.6, 15.2)
4	11.3	3.9	7.8	(2.9, 12.6)	(1.9, 13.7)
8	10.3	5.7	5.3	(0.2, 10.4)	(-0.9, 11.6)
12	5.6	0.4	5.5	(1.0, 10.0)	(-0.0, 11.0)
24	11.6	9.8	2.0	(-3.3, 7.3)	(-4.4, 8.5)

\* Bonferroni method was applied for multiple endpoint adjustment for 3 time points.

### 5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

The following figure displays the time profile of  $\Delta\Delta$ QTcF for different treatment groups. (Note: CIs are all unadjusted including moxifloxacin)

Figure 3: Mean and 90% CI  $\Delta\Delta$ QTcF Timecourse



### 5.2.1.4 Categorical Analysis

Table 9 lists the number of subjects as well as the number of observations whose QTcF values were  $\leq 450$  ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

**Table 9: Categorical Analysis for QTcF**

Treatment Group	Total N		QTcF $\leq$ 450 ms		450<QTcF $\leq$ 480 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	160	1590	160 (100%)	1590 (100%)	0 (0.0%)	0 (0.0%)
Placebo	39	387	39 (100%)	387 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	40	397	35 (87.5%)	382 (96.2%)	5 (12.5%)	15 (3.8%)
Isavuconazole 200 mg	37	368	37 (100%)	368 (100%)	0 (0.0%)	0 (0.0%)
Isavuconazole 600 mg	32	319	32 (100%)	319 (100%)	0 (0.0%)	0 (0.0%)

\*This table and later categorical analyses were based on safety analysis set.

Table 10 lists the categorical analysis results for  $\Delta$ QTcF. No subject's change from baseline was above 60 ms.

**Table 10: Categorical Analysis of  $\Delta$ QTcF**

Treatment Group	Total N		$\Delta$ QTcF $\leq$ 30 ms		30< $\Delta$ QTcF $\leq$ 60 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Placebo	39	385	36 (92.3%)	381 (99.0%)	3 (7.7%)	4 (1.0%)
Moxifloxacin 400 mg	40	397	36 (90.0%)	391 (98.5%)	4 (10.0%)	6 (1.5%)
Isavuconazole 200 mg	37	367	37 (100%)	367 (100%)	0 (0.0%)	0 (0.0%)
Isavuconazole 600 mg	32	312	32 (100%)	312 (100%)	0 (0.0%)	0 (0.0%)

Table 11 lists the number of subjects as well as the number of observations whose change from baseline in QTcF decreased over 30 ms. No subject's change from baseline in QTcF decreased more than 60 ms.

**Table 11: Categorical Analysis of  $\Delta$ QTcF (Decrease)**

Treatment Group	Total N		-60 $\leq\Delta$ QTcF<-30 ms		$\Delta$ QTcF<-60 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Placebo	39	385	1 (2.6%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	40	397	1 (2.5%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Isavuconazole 200 mg	37	367	7 (18.9%)	7 (1.9%)	0 (0.0%)	0 (0.0%)
Isavuconazole 600 mg	32	312	13 (40.6%)	46(14.7%)	0 (0.0%)	0 (0.0%)

### 5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 12. The largest time-matched mean difference between isavuconazole 200 mg and placebo, and isavuconazole 600 mg and placebo were 2.8 bpm with a 90% CI of 0.0 to 5.5 bpm and 7.0 bpm with a 90% CI of 4.1 to 9.9 bpm, respectively.

The outlier analysis results for HR are presented in Table 13.

**Table 12: Analysis Results of  $\Delta$ HR and  $\Delta\Delta$ HR**

Time (hour)	Isavuconazole 200 mg			Isavuconazole 600 mg		
	$\Delta$ HR LSmean (bpm)	$\Delta$ HR LSmean Placebo (bpm)	$\Delta\Delta$ HR LSmean (90% CI) (bpm)	$\Delta$ HR LSmean (bpm)	$\Delta$ HR LSmean Placebo (bpm)	$\Delta\Delta$ HR LSmean (90% CI) (bpm)
-0.75	1.5	-0.8	2.4 (-0.4, 5.3)	4.2	-0.8	4.5 (1.6, 7.5)
-0.5	2.1	-0.4	2.3 (-0.7, 5.4)	3.7	-0.4	3.3 (0.2, 6.5)
-0.25	2.2	0.0	1.9 (-1.2, 5.1)	4.9	0.0	4.1 (0.8, 7.4)
1	1.6	0.9	0.9 (-1.9, 3.8)	5.4	0.9	3.8 (0.8, 6.8)
2	3.1	0.3	2.8 (0.0, 5.5)	7.7	0.3	7.0 (4.1, 9.9)
3	1.9	-0.1	2.6 (-0.1, 5.3)	6.1	-0.1	5.9 (3.1, 8.7)
4	0.6	-0.3	1.3 (-1.9, 4.4)	6.0	-0.3	5.6 (2.3, 9.0)
8	-0.3	3.3	-2.4 (-6.2, 1.4)	2.8	3.3	-0.9 (-4.9, 3.0)
12	-1.9	-0.3	-1.3 (-4.3, 1.7)	2.1	-0.3	1.3 (-1.9, 4.5)
24	-8.5	-8.1	0.1 (-3.1, 3.3)	-1.6	-8.1	4.9 (1.5, 8.3)

**Table 13: Categorical Analysis for HR**

	Total N	HR $\leq$ 100 bpm	HR $>$ 100 bpm	HR $>$ 45 bpm	HR $\leq$ 45 bpm
Treatment Group	Subj. #	Subj. #	Subj. #	Subj. #	Subj. #
Baseline	160	159 (99.4%)	1 (0.6%)	157 (98.1%)	3 (1.9%)
Placebo	39	39 (100%)	0 (0.0%)	38 (97.4%)	1 (2.6%)
Moxifloxacin 400 mg	40	40 (100%)	0 (0.0%)	39 (97.5%)	1 (2.5%)
Isavuconazole 200 mg	37	37 (100%)	0 (0.0%)	37 (100%)	0 (0.0%)
Isavuconazole 600 mg	32	32 (100%)	0 (0.0%)	32 (100%)	0 (0.0%)

### 5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 14. The largest time-matched mean difference between isavuconazole 200 mg and placebo, and isavuconazole 600 mg and placebo were -6.7 ms with a 90% CI of -10.9 to -2.6 ms and -12.8 ms with a 90% CI of -16.2 to -9.4 ms, respectively.

The outlier analysis results for PR are presented in Table 15.

**Table 14: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR**

Time (hour)	Isavuconazole 200 mg			Isavuconazole 600 mg		
	$\Delta$ PR LSmean (ms)	$\Delta$ PR LSmean Placebo (ms)	$\Delta\Delta$ PR LSmean (90% CI) (ms)	$\Delta$ PR LSmean (ms)	$\Delta$ PR LSmean Placebo (ms)	$\Delta\Delta$ PR LSmean (90% CI) (ms)
-0.75	0.0	3.9	-4.7 (-8.6, -0.7)	-5.5	3.9	-10.1 (-14.2, -6.0)
-0.5	-1.0	3.0	-4.7 (-8.4, -1.1)	-7.3	3.0	-11.0 (-14.8, -7.2)
-0.25	-0.9	4.5	-5.9 (-9.2, -2.6)	-7.9	4.5	-12.8 (-16.2, -9.4)
1	-1.8	4.2	-6.7 (-10.6, -2.9)	-7.4	4.2	-12.2 (-16.2, -8.2)
2	-0.7	5.0	-6.2 (-9.5, -2.9)	-6.0	5.0	-11.4 (-14.9, -8.0)
3	-1.1	4.3	-6.0 (-9.9, -2.0)	-7.4	4.3	-12.2 (-16.4, -8.1)
4	-2.5	3.5	-6.7 (-10.9, -2.6)	-7.4	3.5	-11.5 (-15.8, -7.2)
8	-2.4	3.1	-6.1 (-10.1, -2.2)	-6.6	3.1	-10.4 (-14.5, -6.3)
12	-3.3	1.8	-5.6 (-9.8, -1.4)	-7.1	1.8	-9.4 (-13.8, -5.0)
24	-2.9	3.4	-6.7 (-10.7, -2.6)	-6.6	3.4	-10.4 (-14.7, -6.1)

**Table 15: Categorical Analysis for PR**

Treatment Group	Total N		PR $\leq$ 200 ms		PR $>$ 200 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	160	1590	151 (94.4%)	1533 (96.4%)	9 (5.6%)	57 (3.6%)
Placebo	39	387	37 (94.9%)	373 (96.4%)	2 (5.1%)	14 (3.6%)
Moxifloxacin 400 mg	40	397	37 (92.5%)	376 (94.7%)	3 (7.5%)	21 (5.3%)
Isavuconazole 200 mg	37	368	34 (91.9%)	347 (94.3%)	3 (8.1%)	21 (5.7%)
Isavuconazole 600 mg	32	319	32 (100%)	319 (100%)	0 (0.0%)	0 (0.0%)

#### 5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 16. The largest time-matched

mean difference between isavuconazole 200 mg and placebo, and isavuconazole 600 mg and placebo were -3.1 ms with a 90% CI of -4.9 to -1.4 ms and -3.8 ms with a 90% CI of -5.6 to -2.0 ms, respectively.

The outlier analysis results for QRS are presented in

Table 17.

**Table 16: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS**

Time (hour)	Isavuconazole 200 mg			Isavuconazole 600 mg		
	$\Delta$ QRS LSmean (ms)	$\Delta$ QRS LSmean Placebo (ms)	$\Delta\Delta$ QRS LSmean (90% CI) (ms)	$\Delta$ QRS LSmean (ms)	$\Delta$ QRS LSmean Placebo (ms)	$\Delta\Delta$ QRS LSmean (90% CI) (ms)
-0.75	-1.6	1.6	-3.1 (-4.8, -1.3)	-2.4	1.6	-3.8 (-5.6, -2.0)
-0.5	-1.5	1.3	-2.6 (-4.3, -1.0)	-2.1	1.3	-3.2 (-5.0, -1.5)
-0.25	-1.7	1.6	-3.1 (-4.9, -1.4)	-2.2	1.6	-3.6 (-5.4, -1.7)
1	-0.3	1.8	-2.1 (-3.8, -0.4)	-1.4	1.8	-2.9 (-4.7, -1.1)
2	-1.5	1.1	-2.6 (-4.2, -0.9)	-1.9	1.1	-2.8 (-4.6, -1.0)
3	-1.0	1.1	-2.0 (-3.7, -0.4)	-0.9	1.1	-1.9 (-3.6, -0.2)
4	-0.4	0.6	-1.0 (-2.7, 0.6)	-1.9	0.6	-2.3 (-4.0, -0.7)
8	-1.0	1.1	-2.1 (-3.7, -0.4)	-2.6	1.1	-3.5 (-5.3, -1.8)
12	-1.0	0.7	-1.7 (-3.5, 0.0)	-2.1	0.7	-2.5 (-4.3, -0.6)
24	-1.6	0.4	-1.9 (-3.7, -0.1)	-2.5	0.4	-2.6 (-4.5, -0.7)

**Table 17: Categorical Analysis for QRS**

Treatment Group	Total N		QRS $\leq$ 110 ms		QRS $>$ 110 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	160	1590	159 (99.4%)	1582 (99.5%)	1 (0.6%)	8 (0.5%)
Placebo	39	387	39 (100%)	387 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	40	397	40 (100%)	397 (100%)	0 (0.0%)	0 (0.0%)

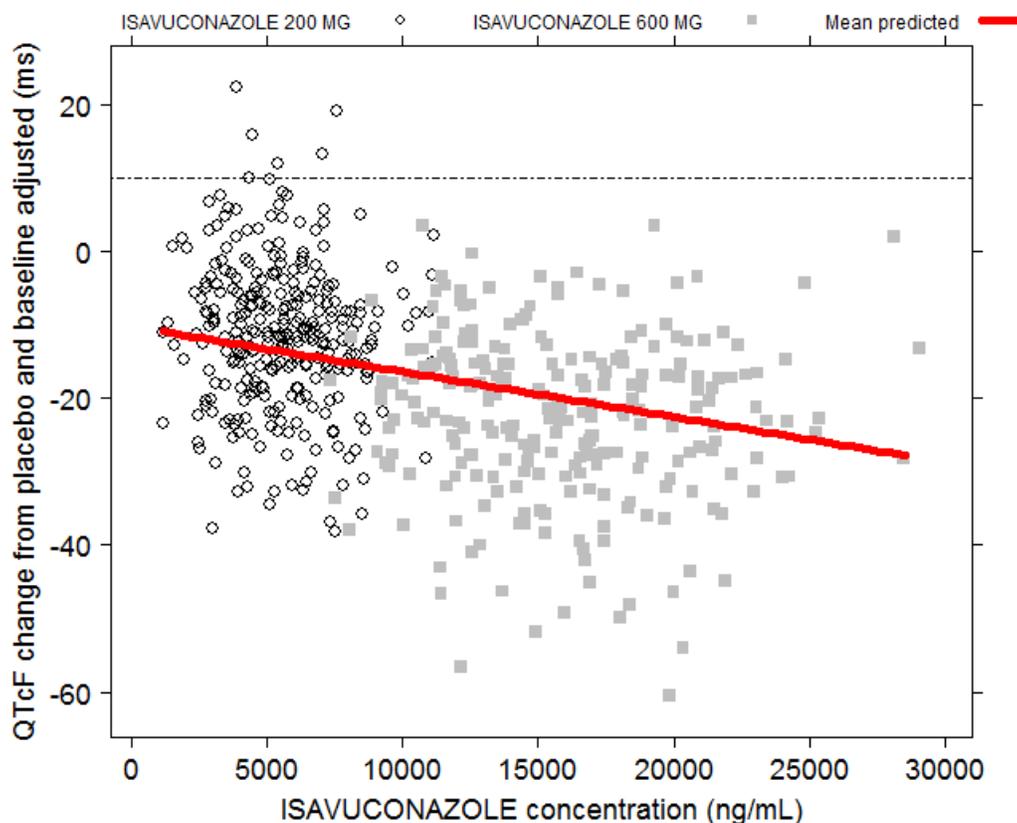
Treatment Group	Total N		QRS≤110 ms		QRS>110 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Isavuconazole 200 mg	37	368	36 (97.3%)	360 (97.8%)	1 (2.7%)	8 (2.2%)
Isavuconazole 600 mg	32	319	32 (100%)	319 (100%)	0 (0.0%)	0 (0.0%)

### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean isavuconazole concentration-time profiles are illustrated in Figure 1 above.

The relationship between  $\Delta\Delta\text{QTcF}$  and isavuconazole concentrations is visualized in Figure 4 with a significant negative exposure-response relationship.

**Figure 4:  $\Delta\Delta\text{QTcF}$  vs. Isavuconazole concentration**



## 5.4 CLINICAL ASSESSMENTS

### 5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

### 5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

### 5.4.3 PR and QRS Interval

Neither PR nor QRS is affected to any clinically relevant extent, but there is a small shortening in PR.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	<p>&lt;Include maximum proposed clinical dosing regimen&gt;</p> <p>Isavuconazonium sulfate is a prodrug containing the active moiety, isavuconazole (ISA). The dosing and administration directions that follow are expressed as isavuconazole mg equivalent. Loading dose: 200 mg every 8 hours, for 48 hours (6 total doses), via oral or IV administration.</p> <p>Maintenance dose: 200 mg once per day via oral or IV administration, starting 12 to 24 hours after the last loading dose.</p>			
Maximum tolerated dose	<p>&lt;Include if studied or NOAEL dose&gt;</p> <p>In healthy volunteers, the highest PO and IV (2-hour infusion) dose investigated in single dose studies was 400 mg ISA administered to healthy male subjects in study [9766-CL-0010].</p> <p>The highest PO repeat dosing of ISA in healthy subjects has been a 200 mg tid ISA loading dose on days 1 and 2, followed by 600 mg once per day ISA for 11 days in tQT study [9766-CL-0017]. At the 600 mg/day dose in the tQT study, there were proportionally more treatment-emergent adverse events than in the therapeutic dose group (isavuconazole 200 mg/day maintenance dose) for the following: headache, dizziness, paresthesia, somnolence, disturbance in attention, dysgeusia, nausea, dry mouth, diarrhea, oral hypoesthesia, vomiting, hot flush, anxiety, palpitations, photophobia and arthralgia. Treatment-emergent adverse events leading to discontinuation of study drug occurred in 7 of 39 (17.9%) subjects in the isavuconazole 600 mg treatment group. This dosing regimen is not considered a well tolerated dose.</p> <p>In patients, the highest dose regimen investigated was 800 mg, followed by 400 mg and 400 mg on day 1, 400 mg BID on day 2 and 400 mg per day from day 3 up to day 28 [9766-CL-0102]. This dose regimen was well tolerated.</p>			
Principal adverse events	<p>&lt;Include most common adverse events; dose limiting adverse events&gt;</p> <p>In the combined single-dose groups in healthy subjects enrolled in phase 1 studies, TEAEs occurring in <math>\geq 5\%</math> of subjects were headache (41/279, 14.7%) and dizziness (14/279, 5.0%). In the combined isavuconazole multiple dose groups, the more frequently reported adverse events (<math>\geq 5\%</math>) headache (141/722, 19.5%), nausea (78/722, 10.8%), diarrhea (63/722, 8.7%), dizziness (61/722, 8.4%), and somnolence (48/722, 6.6%).</p> <p>The highest multiple dose investigated in healthy subjects was 600 mg per day. In this dose group, the most frequently TEAEs that occurred at a higher rate in 4 or more subjects and more frequently than that seen in the other multiple dose groups included hot flush (20/39, 51.3%), nausea (10/39, 25.6%), anxiety (5/39, 12.8%), paresthesia (6/39, 15.4%), dry mouth (5/39, 12.8%), dysgeusia (4/39, 10.3%), hypoesthesia oral (4/39, 10.3%), disturbance in attention (4/39, 10.3%), and palpitations (4/39, 10.3%). In addition, in this dose group, headache was reported by 14/39 (35.9%) and dizziness by 7/39 (17.9%) of subjects [Module 2.7.4, Table 23].</p>			
Maximum dose tested	Single Dose	<p>&lt;Specify dose &gt;</p> <p>400 mg ISA PO or IV in healthy male subjects under fasting conditions [9766-CL-0010].</p>		
	Multiple Dose	<p>&lt;Specify dosing interval and duration&gt;</p> <ul style="list-style-type: none"> <li>200 mg tid ISA loading dose PO on days 1 and 2, followed by 600 mg once per day ISA for 11 days in healthy subjects in tQT study [9766-CL-0017].</li> <li>800 mg, followed by 400 mg and 400 mg on day 1, 400 mg BID on day 2 and 400 mg per day from day 3 up to day 28 in patients [9766-CL-0102].</li> </ul>		
Exposures Achieved at Maximum Tested Dose	Single Dose Mean (%CV) $C_{max}$ and AUC	400 mg PO Dose (n=14) [Study 9766-CL-0010]		
			$AUC_{inf}$ ( $\mu\text{g}\cdot\text{h/mL}$ )	$C_{max}$ ( $\mu\text{g/mL}$ )
		Mean	189.5	3.830
		CV (%)	36.5	21.4
		400 mg IV Dose		
		Mean	193.9	4.849
CV (%)	37.2	13.2		

	Multiple Dose Mean (%CV) C <sub>max</sub> and AUC	600 mg qd PO Dose (n=32) [Study 9766-CL-0017]										
			AUC <sub>24</sub> (µg·hr/mL)	C <sub>max</sub> (µg/mL)								
		Mean	352.8	20.03								
		CV (%)	20.4	17.9								
		800/400/400 mg day 1, 400 mg day 7 (n=10) [Study 9766-CL-0102]										
		Day 1		Day 7								
		AUC <sub>24</sub> (µg·hr/mL)	C <sub>max</sub> (µg/mL)	AUC <sub>24</sub> (µg·hr/mL)								
		Mean	65.64	NA								
		CV (%)	34.5	NA								
				C <sub>max</sub> (µg/mL)								
				113.1								
				7.98								
				17.3								
				35.6								
Range of linear PK	<Specify dosing regimen> There are no relevant deviations from dose proportionality in isavuconazole plasma exposure for both routes of administration [Module 2.7.2, Section 3.6]. In tQT study [9766-CL-0017], isavuconazole AUC <sub>24</sub> and C <sub>max</sub> after 600 mg once daily for 11 days were 2.9- and 2.7-fold higher, respectively, than at 200 mg/day.											
Accumulation at steady state	<Mean (%CV); specify dosing regimen> Mean isavuconazole AUC <sub>24</sub> increased approximately 4- to 5-fold after once daily administration relative to single-dose data for both routes of administration [9766-CL-0003]. This estimation is based on a comparison of mean dose-normalized AUC <sub>24</sub> on day 1 and day 14 (IV)/21 (PO) and assumes approximately dose-proportional pharmacokinetics. Isavuconazole C <sub>max</sub> was approximately 2- to 3-fold higher at steady state compared to a single dose. Dosing regimens studied were: ISA 100 mg PO day 1 and 50 mg qd PO day 2-21; ISA 200 mg PO day 1 and 100 mg qd PO day 2-21; ISA 80 mg IV day 1 and 40 mg qd IV day 2-14; or ISA 160 mg IV day 1 and 80 mg qd IV day 2-14.											
Absorption	Absolute/Relative Bioavailability	<Mean (%CV)> Intact isavuconazonium was generally not detected in plasma or urine after oral administration [Module 2.7.2, Section 2.1.4.4]. The active moiety isavuconazole was completely bioavailable (98%) after oral administration of isavuconazonium sulfate (corresponding to 400 mg isavuconazole) [9766-CL-0010]. The 90% CIs for the oral-to-intravenous ratio for AUC <sub>inf</sub> of isavuconazole (94.4%, 101.3%) were contained in the equivalence limits of 80% to 125%.										
	T <sub>max</sub>	<ul style="list-style-type: none"> <li>• &lt;Median (range) for parent&gt;</li> <li>• &lt;Median (range) for metabolites&gt;</li> </ul> Isavuconazonium t <sub>max</sub> was reached within 0.75 hours after the start of a 1-hour infusion in healthy subjects [Module 2.7.2, Table 11]. Isavuconazonium t <sub>max</sub> could not be determined after oral administration. After oral administration of isavuconazonium in healthy subjects, the active moiety, isavuconazole, generally reached maximum plasma concentrations 2 to 3 hours after single and multiple dosing. Isavuconazole t <sub>max</sub> following 200 and 600 mg qd PO under fasted conditions [Study 9766-CL-0017] are as follows: <table border="1"> <thead> <tr> <th>t<sub>max</sub> (h)</th> <th>200 mg qd (n=37)</th> <th>600 mg qd (n=32)</th> </tr> </thead> <tbody> <tr> <td>Median</td> <td>3.0</td> <td>4.0</td> </tr> <tr> <td>Range</td> <td>2.0 – 4.0</td> <td>2.0 – 4.0</td> </tr> </tbody> </table> T <sub>max</sub> values for the inactive cleavage product BAL8728 were reached towards the end of the infusion after IV administration [9766-CL-0003]. BAL8728 t <sub>max</sub> could not be determined after oral administration. Apart from isavuconazole, no major metabolites have been identified in human plasma, therefore no other metabolites have been monitored in clinical studies.			t <sub>max</sub> (h)	200 mg qd (n=37)	600 mg qd (n=32)	Median	3.0	4.0	Range	2.0 – 4.0
t <sub>max</sub> (h)	200 mg qd (n=37)	600 mg qd (n=32)										
Median	3.0	4.0										
Range	2.0 – 4.0	2.0 – 4.0										
Distribution	Vd/F or Vd	<Mean (%CV)> The volume of distribution after single oral (Vz/F) and IV (Vz) doses in healthy male subjects was large for both PO (159 to 281 L) and IV (265 to 490 L).										

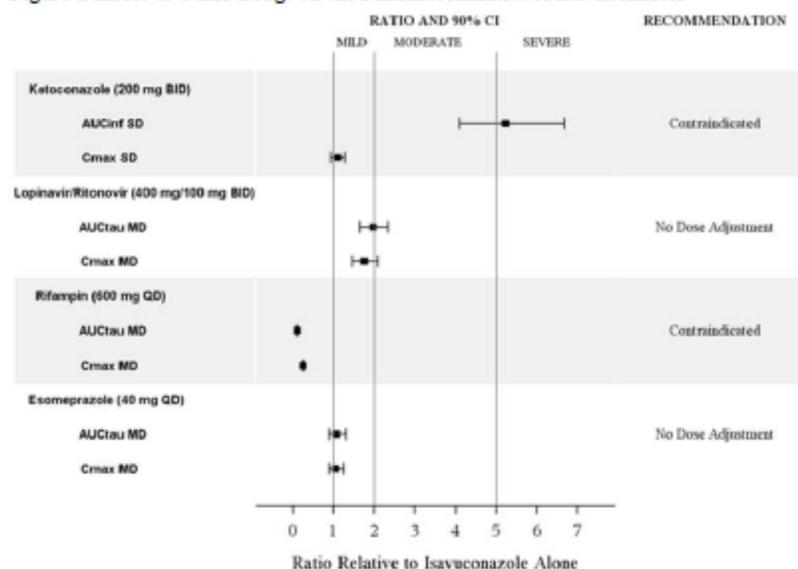
		PO dosing [9766-CL-0001]			IV dosing [9766-CL-0002]		
		100 mg	200 mg	400 mg	40 mg	80 mg	160 mg
		Mean (L)	246.72	280.87	159.44	490.21	405.45
CV (%)	31.8	29.5	26.0	42.9	47.4	40.1	
		Modeling data from 9 phase 1 studies and a phase 3 study generated a volume of distribution at steady-state of approximately 450 L [9766-PK-0005].					
				V <sub>c</sub>	V <sub>p</sub>		
		Mean (L)		49.20	402		
		CV%		NA	35		
		NA: not applicable. Inter-individual variability only on peripheral volume of distribution (V <sub>p</sub> )					
		V <sub>c</sub> : central volume of distribution					
	% bound	<Mean (%CV)>					
		In healthy subjects, isavuconazole was extensively bound (> 99%) to plasma proteins, predominantly to albumin. Binding was independent of concentration over a range of 0.2 to 20 µg/mL in vitro.					
		Dose	Unbound Percentage of Isavuconazole	[9766-CL-0008] (n=8)	[9766-CL-0014] (n=8)	[9766-CL-0018] (n=8)	
		100 mg PO	Mean	0.665	0.125	NA	
			CV (%)	7.6	7.2	NA	
		100 mg IV	Mean	0.691	0.131	NA	
			CV (%)	11.5	9.3	NA	
		200 mg IV	Mean	NA	NA	0.186 - 0.272	
			CV (%)	NA	NA	26.1 - 40.6	
Elimination	Route	<ul style="list-style-type: none"> <li>• &lt;Primary route; percent dose eliminated&gt;</li> <li>• &lt;Other routes&gt;</li> </ul> <p>Following a single oral solution dose of [cyano-<sup>14</sup>C]-labeled isavuconazonium sulfate (target 200 mg eq. of isavuconazole), a mean of 46.1% of the dose was recovered in feces and 45.5% was recovered in urine [9766-CL-0016]. 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%.</p> <p>Isavuconazole accounted for the majority of the radioactivity in feces. The majority of the [cyano-<sup>14</sup>C]-radioactivity recovered in urine was excreted as metabolites of isavuconazole. Renal excretion of isavuconazole itself was less than 1% of the dose administered.</p> <p>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 [9766-CL-0018]. Following intravenous administration of radio-labeled cleavage product, 95% of the total radioactive dose was excreted in the urine [9766-CL-0050].</p> <p>Other routes: Not applicable.</p>					
	Terminal t <sub>1/2</sub>	<ul style="list-style-type: none"> <li>• &lt;Mean (%CV) for parent&gt;</li> <li>• &lt;Mean (%CV) for metabolites&gt;</li> </ul> <p>The population mean half-life of isavuconazole is approximately 130 hours [Study 9766-PK-0005]. The terminal half-life was similar after single and multiple dosing and independent of dose or route of administration (IV vs. oral) (see table below). The variability in isavuconazole t<sub>1/2</sub> in the various studies in healthy subjects may have been due to differences in sampling time and duration.</p>					

		<b>Isavuconazole Terminal <math>t_{1/2}</math> after Fasted Single and Multiple Doses of Isavuconazonium in Healthy Subjects</b>																																																																										
		<b>Dose (mg eq.)</b>	<b>Study</b>	<b>n</b>	<b>Mean (h)</b>	<b>CV (%)</b>																																																																						
		<b>Single Intravenous Doses</b>																																																																										
		40	[9766-CL-0002]	6	81.56	66.0																																																																						
		80		6	92.70	49.6																																																																						
		160		6	83.74	49.8																																																																						
		100	[9766-CL-0008]	8	124.8	30.7																																																																						
		100	[9766-CL-0014]	8	115.7	23.1																																																																						
		200	[9766-CL-0018]	8	125.5	50.4																																																																						
		200	[9766-CL-0018]	8	140.5	55.3																																																																						
		400	[9766-CL-0010]	14	115.0	51.0																																																																						
		<b>Multiple Intravenous Doses</b>																																																																										
		40 qd	[9766-CL-0003]	5	98.09	48.0																																																																						
		80 qd		6	110.4	15.5																																																																						
		150 qd	[9766-CL-0004]	39	115.0	60.1																																																																						
		<b>Single Oral Doses</b>																																																																										
		100	[9766-CL-0001]	6	62.30	33.4																																																																						
		200		6	73.52	16.8																																																																						
		400		3	56.21	4.4																																																																						
		100	[9766-CL-0008]	8	127.9	16.9																																																																						
		100	[9766-CL-0014]	8	121.1	44.7																																																																						
		400	[9766-CL-0010]	14	109.7	31.5																																																																						
		400	[9766-CL-0015]	25	113.4	40.8																																																																						
		<b>Multiple Oral Doses</b>																																																																										
		50 qd	[9766-CL-0003]	6	108.9	42.1																																																																						
		100 qd		6	76.56	28.6																																																																						
		The isavuconazonium half-life was not estimated in pharmacokinetics studies because isavuconazonium plasma concentrations were essentially undetectable after oral administration and typically only quantifiable during the infusion interval. The inactive cleavage product BAL8728 had a terminal half-life of approximately 1 hour after intravenous administration [9766-CL-0018].																																																																										
	CL/F or CL	<p>&lt;Mean (%CV)&gt;</p> <p>The population mean (%CV) estimate of CL was approximately 2.4 L/h (43%) [9766-PK-0005]. Similar values were obtained in individual studies in healthy subjects (see table below).</p> <p><b>Isavuconazole Clearance after Single and Multiple Intravenous Doses of Isavuconazonium in Healthy Subjects</b></p> <table border="1"> <thead> <tr> <th><b>Dose (mg)</b></th> <th><b>Study</b></th> <th><b>n</b></th> <th><b>Mean (L/h)</b></th> <th><b>CV (%)</b></th> </tr> </thead> <tbody> <tr> <td colspan="5"><b>Single Intravenous Doses</b></td> </tr> <tr> <td>40</td> <td>[9766-CL-0002]</td> <td>6</td> <td>4.045</td> <td>41.9</td> </tr> <tr> <td>80</td> <td></td> <td>6</td> <td>3.225</td> <td>26.9</td> </tr> <tr> <td>160</td> <td></td> <td>6</td> <td>2.284</td> <td>19.4</td> </tr> <tr> <td>100</td> <td>[9766-CL-0008]</td> <td>8</td> <td>2.763</td> <td>27.7</td> </tr> <tr> <td>100</td> <td>[9766-CL-0014]</td> <td>8</td> <td>2.788</td> <td>29.7</td> </tr> <tr> <td>200</td> <td>[9766-CL-0018]</td> <td>8</td> <td>2.354</td> <td>35.9</td> </tr> <tr> <td>200</td> <td>[9766-CL-0018]</td> <td>8</td> <td>2.448</td> <td>47.6</td> </tr> <tr> <td>400</td> <td>[9766-CL-0010]</td> <td>14</td> <td>2.305</td> <td>31.5</td> </tr> <tr> <td colspan="5"><b>Multiple Intravenous Doses</b></td> </tr> <tr> <td>40 qd</td> <td>[9766-CL-0003]</td> <td>5</td> <td>3.258</td> <td>48.7</td> </tr> <tr> <td>80 qd</td> <td></td> <td>6</td> <td>2.558</td> <td>28.0</td> </tr> <tr> <td>150 qd</td> <td>[9766-CL-0004]</td> <td>39</td> <td>2.182</td> <td>20.5</td> </tr> </tbody> </table>					<b>Dose (mg)</b>	<b>Study</b>	<b>n</b>	<b>Mean (L/h)</b>	<b>CV (%)</b>	<b>Single Intravenous Doses</b>					40	[9766-CL-0002]	6	4.045	41.9	80		6	3.225	26.9	160		6	2.284	19.4	100	[9766-CL-0008]	8	2.763	27.7	100	[9766-CL-0014]	8	2.788	29.7	200	[9766-CL-0018]	8	2.354	35.9	200	[9766-CL-0018]	8	2.448	47.6	400	[9766-CL-0010]	14	2.305	31.5	<b>Multiple Intravenous Doses</b>					40 qd	[9766-CL-0003]	5	3.258	48.7	80 qd		6	2.558	28.0	150 qd	[9766-CL-0004]	39	2.182	20.5
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Intrinsic Factors	Age	<p>&lt;Specify mean changes in <math>C_{max}</math> and AUC&gt;</p> <p>Isavuconazole <math>AUC_{inf}</math> and <math>AUC_{inf}</math> increased 53% and 64%, respectively, for elderly females compared with nonelderly females. There was no difference in <math>AUC_{inf}</math> between elderly and non-elderly males. There was no difference in <math>C_{max}</math> between elderly and non-elderly subjects [9766-CL-0041].</p>																																																																										
	Sex	<p>&lt;Specify mean changes in <math>C_{max}</math> and AUC&gt;</p>																																																																										

	<p>Isavuconazole <math>AUC_{inf}</math> and <math>AUC_{inf}</math> increased 37% in the elderly females compared with the elderly males while in the non-elderly group; they decreased by 20% and 16%, respectively. There was a 5% decrease in isavuconazole <math>C_{max}</math> of females relative to the males [9766-CL-0041].</p>																																						
Race	<p>&lt;Specify mean changes in <math>C_{max}</math> and AUC&gt;</p> <p>Comparison of Mean Isavuconazole Exposure in Healthy Chinese and Western Subjects after Single- and Multiple-Dose Oral Administration of Isavuconazonium (200 mg eq.) is as follows</p> <table border="1"> <thead> <tr> <th rowspan="2"></th> <th colspan="2">Single Dose</th> <th colspan="2">Multiple Dose</th> </tr> <tr> <th>Chinese Subjects</th> <th>Western Subjects</th> <th>Chinese Subjects</th> <th>Western Subjects</th> </tr> </thead> <tbody> <tr> <td>Study</td> <td>[9766-CL-0038]</td> <td>[9766-CL-0041]</td> <td>[9766-CL-0038]</td> <td>[9766-CL-0017]</td> </tr> <tr> <td><math>C_{max}</math> (ug/mL)</td> <td>3.39</td> <td>2.32</td> <td>8.89</td> <td>7.5</td> </tr> <tr> <td>AUC (ug*h/ mL)</td> <td>116.4</td> <td>96.26</td> <td>140.4</td> <td>121.4</td> </tr> </tbody> </table> <p>A population pharmacokinetic model was developed to assess the pharmacokinetics of isavuconazole between healthy Western and Chinese subjects. Chinese subjects had approximately 50% higher AUC than Western subjects [9766-PK-0004]. Chinese subjects were found to have on average a 40% lower clearance compared to Western subjects (1.6 L/h for Chinese subjects as compared to 2.57 L/h for Western subjects).</p>		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]	$C_{max}$ (ug/mL)	3.39	2.32	8.89	7.5	AUC (ug*h/ mL)	116.4	96.26	140.4	121.4														
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Hepatic & Renal Impairment	<p>&lt;Specify mean changes in <math>C_{max}</math> and AUC&gt;</p> <p><b>Hepatic Impairment</b> Two separate open-label, single-dose, parallel-group studies were conducted to characterize the effect of mild (Child-Pugh class A) to moderate (Child-Pugh class B) hepatic impairment due to cirrhosis caused by alcohol [9766-CL-0008] or hepatitis B and/or C [9766-CL-0014] on the single dose pharmacokinetics of isavuconazole.</p> <p>Mean Ratios of Isavuconazole Total Plasma Pharmacokinetic Parameters in Subjects with Varying Degrees of Hepatic Impairment Compared with Healthy Control Subjects are shown in table below</p> <table border="1"> <thead> <tr> <th rowspan="2">Parameter</th> <th rowspan="2">Extent of impairment</th> <th colspan="4">Ratio (%) Impaired/Normal<sup>a</sup></th> </tr> <tr> <th colspan="2">[9766-CL-0008]</th> <th colspan="2">[9766-CL-0014]</th> </tr> <tr> <th></th> <th></th> <th>IV</th> <th>PO</th> <th>IV</th> <th>PO</th> </tr> </thead> <tbody> <tr> <td rowspan="2"><math>AUC_{inf}</math></td> <td>Mild</td> <td>158.9</td> <td>217.5</td> <td>147.8</td> <td>140.9</td> </tr> <tr> <td>Moderate</td> <td>219.1</td> <td>140.7</td> <td>205.6</td> <td>185.1</td> </tr> <tr> <td rowspan="2"><math>C_{max}</math></td> <td>Mild</td> <td>85.9</td> <td>86.1</td> <td>92.0</td> <td>137.3</td> </tr> <tr> <td>Moderate</td> <td>76.6</td> <td>55.1</td> <td>73.5</td> <td>79.0</td> </tr> </tbody> </table> <p><sup>a</sup>The exponentiated value of the least squares mean based on natural log-transformed data.</p>	Parameter	Extent of impairment	Ratio (%) Impaired/Normal <sup>a</sup>				[9766-CL-0008]		[9766-CL-0014]				IV	PO	IV	PO	$AUC_{inf}$	Mild	158.9	217.5	147.8	140.9	Moderate	219.1	140.7	205.6	185.1	$C_{max}$	Mild	85.9	86.1	92.0	137.3	Moderate	76.6	55.1	73.5	79.0
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		<p>Renal Impairment</p> <p>Mean Ratios of Isavuconazole Total Plasma pharmacokinetics Parameters in Subjects with Varying Degrees of Renal Impairment Compared with Healthy Control Subjects are shown in table below</p> <table border="1" data-bbox="553 331 1339 590"> <thead> <tr> <th rowspan="2">Parameter</th> <th rowspan="2">Extent of impairment</th> <th>Ratio (%) Impaired/Normal<sup>a</sup></th> </tr> <tr> <th>Isavuconazole</th> </tr> </thead> <tbody> <tr> <td>AUC<sub>72</sub></td> <td>ESRD</td> <td>66.34</td> </tr> <tr> <td rowspan="3">AUC<sub>inf</sub></td> <td>Severe</td> <td>100.85</td> </tr> <tr> <td>Moderate</td> <td>104.33</td> </tr> <tr> <td>Mild</td> <td>97.96</td> </tr> <tr> <td rowspan="4">C<sub>max</sub></td> <td>ESRD</td> <td>79.33</td> </tr> <tr> <td>Severe</td> <td>85.57</td> </tr> <tr> <td>Moderate</td> <td>93.32</td> </tr> <tr> <td>Mild</td> <td>104.32</td> </tr> </tbody> </table> <p><sup>a</sup>The exponentiated value of the least squares mean based on natural log-transformed data. The population pharmacokinetic model developed to assess the pharmacokinetics of isavuconazole in healthy subjects, patient with mild, moderate and severe renal dysfunction as well as patients with ESRD [9766-PK-0002] revealed there were no clinically relevant differences in the concentration time profile to steady state of the targeted population.</p>	Parameter	Extent of impairment	Ratio (%) Impaired/Normal <sup>a</sup>	Isavuconazole	AUC <sub>72</sub>	ESRD	66.34	AUC <sub>inf</sub>	Severe	100.85	Moderate	104.33	Mild	97.96	C <sub>max</sub>	ESRD	79.33	Severe	85.57	Moderate	93.32	Mild	104.32
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Extrinsic Factors	Drug interactions	<p>&lt;Include listing of studied DDI studies with mean changes in C<sub>max</sub> and AUC&gt;</p> <p><b>Effect of Other Drugs on Isavuconazole</b></p> <p>Isavuconazole is a substrate of CYP3A4 and CYP3A5.</p> <p><b>Strong CYP3A Inhibitors</b></p> <p>As a strong CYP3A inhibitor, ketoconazole increased the isavuconazole C<sub>max</sub> 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 CYP3A substrate. Concomitant use of isavuconazole with strong CYP3A inhibitors is not recommended with the exception of low dose ritonavir as found in the combination product lopinavir/ritonavir [Module 2.7.2, Section 3.11.1.2].</p> <p>Lopinavir/ritonavir (400 mg/100 mg twice daily) increased the C<sub>max</sub> and AUC<sub>inf</sub> of isavuconazole (clinical dose) 74% and 96%, respectively with concurrent decreases in the mean AUCs of lopinavir and ritonavir by 27% and 31%, respectively. [Module 2.7.2, Section 2.4.17]. No modification of the isavuconazole dose is recommended when the drugs are co-administered [Module 2.7.2, Section 3.11.1.2].</p> <p><b>Strong CYP3A Inducers</b></p> <p>Repeated doses of rifampin (600 mg/day) decreased mean C<sub>max</sub> and AUC<sub>inf</sub> of isavuconazole by 75% and 90%, respectively [Module 2.7.2, Section 3.11.1.2]. Concomitant use of isavuconazonium with strong CYP3A inducers (e.g., rifampin, rifapentin, phenytoin, carbamazepine, phenobarbital and St. John's wort) is contraindicated [Module 2.7.2, Section 3.11.1.2].</p> <p><b>Gastric pH Raising Drugs</b></p> <p>Co-administration of steady state esomeprazole (40 mg daily for 10 days) with steady state isavuconazole resulted in a 7.6% increase in AUC<sub>inf</sub> and a 4.8% increase in the C<sub>max</sub> of isavuconazole compared to isavuconazole alone. These findings indicate that concomitant medications that alter the gastric pH (i.e., proton-pump inhibitors, H<sub>2</sub>-receptor antagonists and antacids) do not significantly affect the pharmacokinetics of isavuconazole [Module 2.7.2, Section 3.11.1.2].</p> <p>The effect of ketoconazole, lopinavir/ritonavir, rifampin, and esomeprazole on the pharmacokinetics of isavuconazole are shown in <a href="#">[Figure 1]</a>.</p>																							

**Figure 1 Effect of Other Drugs on the Pharmacokinetics of Isavuconazole**



Source: [Module 2.7.2, Figure 5]

**Effect of Isavuconazole on Other Drugs**

In vitro, isavuconazole is an inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2C19 and CYP2D6. Isavuconazole is also an inhibitor of P-gp-, BCRP- and OCT2-mediated drug transports [Module 2.7.2, Sections 2.1.5.2 and 3.11.2.1]. In vitro, isavuconazole is also an inducer of CYP1A2, CYP3A4/5, CYP2B6, CYP2C8 and CYP2C9.

The effect isavuconazole on the pharmacokinetics of co-administered drugs were studied after single and multiple doses of isavuconazole in healthy subjects [Module 2.7.2, Section 3.11.2.2].

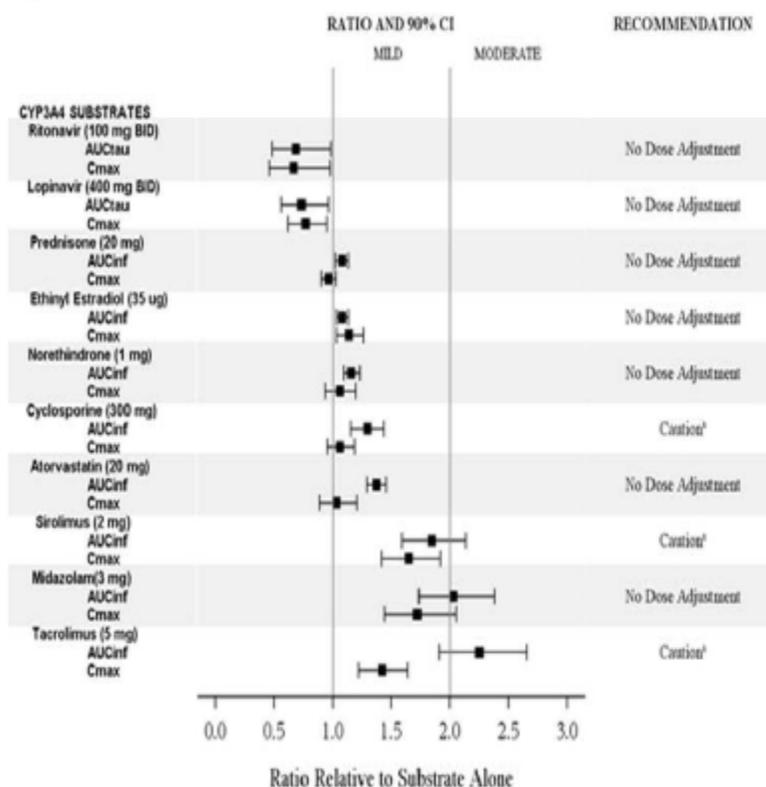
**CYP3A Substrates**

Isavuconazole, at the projected therapeutic dose of isavuconazonium, increased the systemic exposure of sensitive CYP3A substrates midazolam, sirolimus and tacrolimus approximately 2-fold, therefore, isavuconazole can be considered a moderate inhibitor of CYP3A.

Multiple doses of isavuconazonium at the recommended clinical dose increased the C<sub>max</sub> and AUC<sub>inf</sub> of midazolam (clinical dose) by 72% and 103%, respectively, sirolimus (clinical dose) by 65% and 84%, respectively, and tacrolimus (clinical dose) by 42% and 125%, respectively [Module 2.7.2, Section 3.11.2.2].

The effects of isavuconazole on the CYP3A substrates ritonavir, lopinavir, prednisone, ethinyl estradiol, norethindrone, cyclosporine, atorvastatin, sirolimus, midazolam and tacrolimus are show in [Figure 2]. Results can be found in [Module 2.7.2, Section 3.11.2.2].

**Figure 2 Effect of Isavuconazole on Pharmacokinetics of CYP3A Substrates**



Caution<sup>1</sup>: Appropriate therapeutic drug monitoring and dose adjustment of tacrolimus, sirolimus and cyclosporine may be necessary when co-administered with isavuconazole.

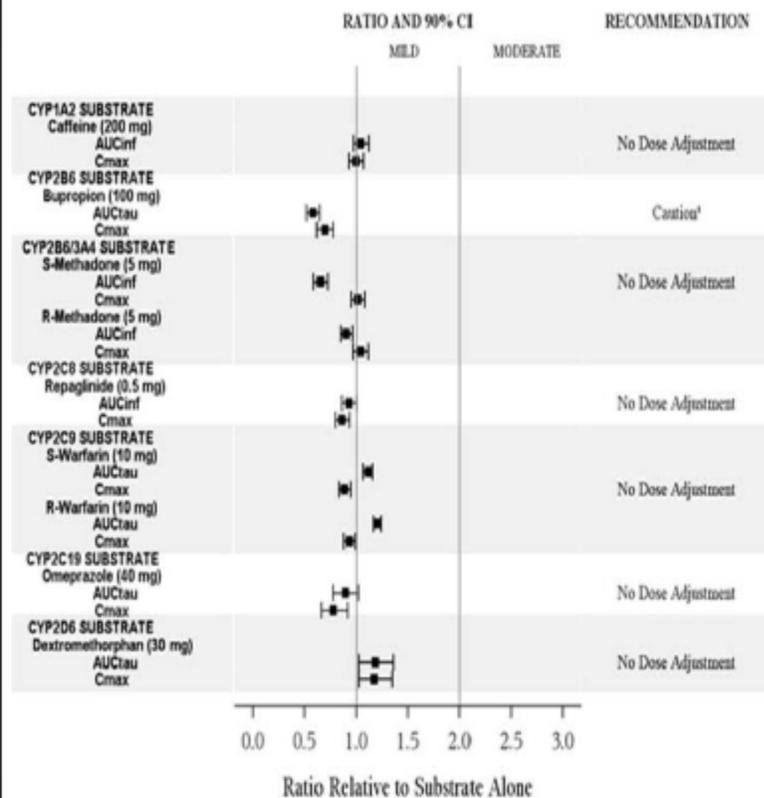
Source: [Module 2.7.2, Figure 6]

**Other CYP Substrates**

Isavuconazonium is a weak inducer of CYP2B6 in vivo. Co-administration of isavuconazonium (200 mg eq. isavuconazole once per day orally) with bupropion resulted in decreased AUC<sub>inf</sub> and C<sub>max</sub> by 42% and 31%, respectively, compared with bupropion alone [Module 2.7.2, Sections 3.11.2.2].

The effects of isavuconazole on the pharmacokinetics of other CYP substrates such as caffeine, bupropion, methadone, repaglinide, warfarin, omeprazole and dextromethorphan are presented in [Figure 3]. Results can be found in [Module 2.7.2, Section 3.11.2.2].

**Figure 3 Effect of Isavuconazole on Pharmacokinetics of Other CYP Substrates**



Caution<sup>1</sup>: Isavuconazole decreased the systemic exposure of bupropion. Caution is advised if isavuconazonium is co-administered with CYP2B6 substrates, especially narrow therapeutic index drugs such as efavirenz and cyclophosphamide.

Source: [Module 2.7.2, Figure 7]

**UGT Substrates**

Co-administration of multiple doses of isavuconazonium (200 mg eq. isavuconazole qd po) with MMF increased the AUC<sub>inf</sub> of the active moiety MPA by 35% and decreased the C<sub>max</sub> by 11% compared to MMF alone [9766-CL-0030]. The AUC<sub>inf</sub> and C<sub>max</sub> of the glucuronide metabolite of MPA, MPAG, decreased by 24% and 32%, respectively [Module 2.7.2, Section 3.11.2.2].

**Transporter Substrates**

Co-administration of isavuconazonium (200 mg eq. isavuconazole qd po) with the P-gp substrate digoxin resulted in a 33% increase in C<sub>max</sub> and a 25% increase in AUC<sub>inf</sub> [9766-CL-0025] compared with digoxin alone [Module 2.7.2, Section 3.11.2.2].

The effects of isavuconazole on the pharmacokinetics of UGT and transporter substrates such as MMF, methotrexate, metformin and digoxin are shown in [Figure 4](#). Results can be found in [Module 2.7.2, Section 3.11.2.2].

Figure 4 Effect of Isavuconazole on the Pharmacokinetics of UGTs and Transporters		
	RATIO AND 90% CI MILD MODERATE	RECOMMENDATION
<b>UDP-GLYCOSYLTRANSFERASE</b> Mycophenolate Mofetil (1 g)-MPAG AUC <sub>0-24</sub> C <sub>max</sub> Mycophenolate Mofetil (1 g)-MPA AUC <sub>0-24</sub> C <sub>max</sub>		Caution <sup>1</sup>
<b>BCRP SUBSTRATE</b> Methotrexate (7.5 mg) AUC <sub>inf</sub> C <sub>max</sub>		No Dose Adjustment
<b>OCT2 SUBSTRATE</b> Metformin (850 mg) AUC <sub>inf</sub> C <sub>max</sub>		No Dose Adjustment
<b>P-gP SUBSTRATE</b> Digoxin (0.5 mg) AUC <sub>0-24</sub> C <sub>max</sub>		Caution <sup>2</sup>
	0.0 0.5 1.0 1.5 2.0 2.5 3.0 Ratio Relative to Substrate Alone	
	Caution <sup>1</sup> Due to the unclear association between MPA pharmacokinetics and MPA-related toxicity, no specific dose recommendation can be made. Patients receiving isavuconazole concurrently with MMF should be monitored for MPA-related toxicities. Caution <sup>2</sup> Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect. BCRP: breast cancer resistance protein; MMF: mycophenolate mofetil; MPA: mycophenolic acid; OCT2: organic cation transporter 2; P-gp: P-glycoprotein; UDP: uridine diphosphate. Source: [Module 2.7.2, Figure 8]	
Food Effects	<Specify mean changes in C <sub>max</sub> and AUC and meal type (i.e., high-fat, standard, low-fat)> Administration of a single dose of isavuconazonium sulfate (400 mg eq.) with a high-fat breakfast did not affect isavuconazole plasma exposure. Mean ratios for isavuconazole C <sub>max</sub> and AUC <sub>inf</sub> with and without food were 91.9% and 109.6%, respectively, with 90% CIs contained entirely within the default no effect boundaries of 80% to 125% [Module 2.7.2, Section 3.10.1].	
Expected High Clinical Exposure Scenario	<Describe worst case scenario and expected fold-change in C <sub>max</sub> and AUC. The increase in exposure should be covered by the supra-therapeutic dose.> Co-administration of ISA at 200 mg per day with the strong CYP3A inhibitor ketoconazole (200 mg/day) led to a 5-fold increase in AUC <sub>inf</sub> of ISA, compared with administration of ISA alone [9766-CL-0040]. Concomitant use of isavuconazole with strong CYP3A inhibitors is contraindicated with the exception of low dose ritonavir as found in the combination product lopinavir/ritonavir. Administration of 600 mg of ISA daily, led to 2.9-fold increase in AUC <sub>inf</sub> of ISA, compared with exposure at the proposed therapeutic dose of 200 mg once per day. In the tQT study the therapeutic dose was the maximum recommended clinical dose of 200 mg/day following a loading dose of 200 mg tid for two days. In this study the suprathreshold dose was three times higher (600 mg/day). The tolerability of the 600 mg/day dose was sufficient to complete the tQT study, but 17% of the subjects discontinued due to an AE. It is unlikely that a higher suprathreshold dose would have been tolerated well enough to complete the study.	

Preclinical Cardiac Safety	<p>&lt;Summarize <i>in vitro</i> and <i>in vivo</i> results per S7B guidance&gt;</p> <p>An initial <i>in vitro</i> assessment of cardiovascular safety was performed in HEK293 cells stably transfected to express the hERG potassium channel. The active moiety, isavuconazole, over a concentration range of 1 to 30 <math>\mu</math>M, resulted in a concentration related inhibition of the hERG current with an <math>IC_{50}</math> of 5.82 <math>\mu</math>M (34-fold higher than the non-protein bound <math>C_{max}</math> at the clinical maintenance dose).</p> <p>A follow up <i>in vitro</i> assessment of the effects of isavuconazole (1 to 30 <math>\mu</math>M) on a panel of cardiomyocyte ion channels was performed <i>in vitro</i> with HEK293 cells or CHO cells transfected with one of the following six potassium channels: hERG potassium channel, hKir2.1, hKir3.1/hKir3.4, Kir6.2/SUR2A, hKv1.5, hKv4.3/KChIP2.2, and hKvLQT1/hmink. In addition, one sodium channel (hNav1.5) and one calcium channel (hCav1.2) were assessed <i>in vitro</i>. The results are listed in the table below.</p> <table border="1" data-bbox="407 485 1338 768"> <thead> <tr> <th>Ion Channel</th> <th><math>IC_{50}</math> (ng/mL)</th> <th><math>IC_{50}:C_{max}</math></th> </tr> </thead> <tbody> <tr> <td>hERG</td> <td>8500</td> <td>113</td> </tr> <tr> <td>hKir2.1</td> <td>&gt;13,118</td> <td>&gt;174</td> </tr> <tr> <td>hKir3.1/3/4</td> <td>&gt;13,118</td> <td>&gt;174</td> </tr> <tr> <td>Kir6.2/SURA</td> <td>&gt;13,118</td> <td>&gt;174</td> </tr> <tr> <td>hKv1.5</td> <td>&gt;13,118</td> <td>&gt;174</td> </tr> <tr> <td>hKv4.3/KChIP2.2</td> <td>&gt;13,118</td> <td>&gt;174</td> </tr> <tr> <td>hKvLQT1/hmink</td> <td>10,505</td> <td>140</td> </tr> <tr> <td>hNav1.5 (Tonic)</td> <td>8,902</td> <td>119</td> </tr> <tr> <td>hNav1/5 (Phasic)</td> <td>6,502</td> <td>87</td> </tr> <tr> <td>hCav1.2</td> <td>2,872</td> <td>38</td> </tr> </tbody> </table> <p>Non-protein bound <math>C_{max}</math> = 75 ng/mL</p> <p>These data suggest the mechanism for the observed QTc shortening observed in the clinical tQT study was inhibition of the L-type calcium channel.</p> <p><i>In vivo</i> cardiovascular assessments were performed in instrumented anesthetized monkeys following single i.v. administration (2.5, 7.5, and 22.5 mg/kg) of the prodrug, isavuconazonium. No significant changes in the QTc interval were noted at any dose tested. A retrospective assessment showed a transient (during the infusion) non-significant (approximately 6%) transient decrease in the QTc interval at the highest dose tested (human equivalent dose 2-fold the clinical maintenance dose). QTc interval shortening was not confirmed in the repeated dose toxicology studies in monkeys at oral doses up to 40 mg/kg.</p>	Ion Channel	$IC_{50}$ (ng/mL)	$IC_{50}:C_{max}$	hERG	8500	113	hKir2.1	>13,118	>174	hKir3.1/3/4	>13,118	>174	Kir6.2/SURA	>13,118	>174	hKv1.5	>13,118	>174	hKv4.3/KChIP2.2	>13,118	>174	hKvLQT1/hmink	10,505	140	hNav1.5 (Tonic)	8,902	119	hNav1/5 (Phasic)	6,502	87	hCav1.2	2,872	38
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hNav1/5 (Phasic)	6,502	87																																
hCav1.2	2,872	38																																
Clinical Cardiac Safety	<p>&lt;Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).&gt;</p> <p><i>Exposure:</i></p> <p>A total of 1049 healthy subjects received at least one dose of isavuconazole in a total of 40 completed phase 1 clinical studies, including single doses of up to 400 mg and multiple doses of up to 600 mg. Additionally, in renally impaired subjects in study [9766-CL-0018], 11 subjects with end-stage renal disease received 2 doses of isavuconazole 200 mg and 21 subjects with various degrees of renal impairment received a single dose of isavuconazole 200 mg. A total of 64 hepatically impaired subjects in studies [9766-CL-0008] and [9766-CL-0014] received a single dose of isavuconazole 100 mg.</p> <p>A total of 144 patients enrolled in the 2 phase 2 studies received maintenance doses of up to 400 mg of isavuconazole.</p> <p>A total of 403 patients with invasive aspergillosis and other filamentous fungi, or rare molds, yeast and dimorphic fungi were enrolled in the 2 phase 3 studies and received at least one dose of isavuconazole 200 mg.</p> <p><i>Cardiac Safety:</i></p> <p>In the isavuconazole clinical program, Torsade de Pointes (TdP) was identified as an Event of Interest. It was assessed by utilizing the TdP MedDRA SMQ (broad).</p> <p>In the phase 3 controlled study [9766-CL-0104], isavuconazole vs voriconazole), there was a numerically lower proportion of isavuconazole-treated patients (5.8%) compared to voriconazole-treated patients (7.3%) who experienced TEAEs in the torsade de pointes SMQ. The more common events that occurred in <math>\geq 1\%</math> of patients in either the isavuconazole or voriconazole treatment groups, respectively, were syncope (2.7% vs 0.8%), loss of consciousness (1.2% vs 0), ECG prolonged QT (0.8% vs 3.1%) and cardiac arrest (0.4% vs 2.3%). Loss of consciousness and syncope were reported in a higher proportion of isavuconazole-treated</p>																																	

	<p>patients compared to voriconazole-treated patients, while QT prolongation and cardiac arrest were reported in a lower proportion of isavuconazole- than voriconazole-treated patients.</p> <p>More details on those patients who experienced a TEAE of syncope or loss of consciousness can be found in [Module 2.7.4, Table 46]. In the 10 isavuconazole-treated patients with events of syncope or loss of consciousness, these events occurred from 2 to 24 days after the last dose of isavuconazole in 3 patients, concurrent with additional illnesses in 2 patients and during treatment with concomitant medications in 5 patients.</p> <p>In the overall isavuconazole population in the combined phase 2 and 3 studies, 3.5% of patients experienced TEAEs in the torsade de pointes SMQ, with syncope being the most frequently occurring event (1.6%).</p> <p>In the phase 1 studies, there were no TEAEs in the torsade de pointes SMQ.</p>
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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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HUIFANG CHEN  
09/29/2014

QIANYU DANG  
09/29/2014

JEE E LEE  
09/29/2014

JIANG LIU  
09/29/2014

MICHAEL Y LI  
09/29/2014

NORMAN L STOCKBRIDGE  
09/29/2014

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 207500	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Cresemba Established/Proper Name: isavuconazonium sulfate Dosage Form: Capsules Strengths: 100 mg		
Applicant: Astellas Pharma US Inc. Agent for Applicant (if applicable): N/A		
Date of Application: July 8, 2014 Date of Receipt: July 8, 2014 Date clock started after UN: N/A		
PDUFA Goal Date: March 8, 2015	Action Goal Date (if different):	
Filing Date: September 6, 2014	Date of Filing Meeting: August 14, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s): Treatment of invasive aspergillosis and invasive mucormycosis in patients 18 years of age and older.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i></b> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> .		
Type of BLA  <b><i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i></b>	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
Review Classification:  <b><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i></b>  <b><i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i></b>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>  <b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other: Qualified Infectious Disease Product (QIDP) Designation	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s): 119307				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>	<input type="checkbox"/>	X		
<b>If yes, explain in comment column.</b>				
<b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</b>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X	<input type="checkbox"/>		

<u>User Fee Status</u>		Payment for this application:		
<i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		<input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required		
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees:  <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears		
<b>505(b)(2)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>(NDAs/NDA Efficacy Supplements only)</b>				
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>				
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>If yes, please list below:</b>				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>				
<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Does another product (same active moiety) have orphan	<input type="checkbox"/>	X		

<p>exclusivity for the same indication? <b>Check the Orphan Drug Designations and Approvals list at:</b>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></p>				
<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><b>If yes, # years requested:</b></p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	<input type="checkbox"/>	X	<input type="checkbox"/>	
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>	<input type="checkbox"/>	X	<input type="checkbox"/>	
<p><b>If yes</b>, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	X	
<p><b>For BLAs:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?</p> <p><i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i></p> <p><i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<b>Format and Content</b>	
<p><b>Do not check mixed submission if the only electronic component is the content of labeling (COL).</b></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>	

<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission</b> , does it follow the eCTD guidance? <sup>1</sup> <b>If not</b> , explain (e.g., waiver granted).	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	X	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:  X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only)  <b>If no</b> , explain.	X	<input type="checkbox"/>		
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes</b> , BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	X	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X	<input type="checkbox"/>	<input type="checkbox"/>	

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>	X	<input type="checkbox"/>		
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	X	<input type="checkbox"/>		
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	X	Electronic submission

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	X	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input type="checkbox"/>	X		Application has orphan designation.
<p><b>If the application triggers PREA</b>, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<input type="checkbox"/>	<input type="checkbox"/>	X	
<p><b>If studies or full waiver not included</b>, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	X	
<p><b>If a request for full waiver/partial waiver/deferral is included</b>, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	X	
<p><b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i></p>	<input type="checkbox"/>	X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	X	<input type="checkbox"/>	<input type="checkbox"/>	

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

REMS	YES	NO	NA	Comment
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	X	<input type="checkbox"/>		
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	X	<input type="checkbox"/>		
Is the PI submitted in PLR format? <sup>4</sup>	X	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<b>X Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	QT Interdisciplinary Review Team
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? <b>Date(s):</b> 12/20/05 <i>If yes, distribute minutes before filing meeting</i>	X	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 10/29/13 ( CMC Pre-NDA), 11/5/13 (Pre-NDA) <i>If yes, distribute minutes before filing meeting</i>	X	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> 6/5/06 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 8-14-14

**NDA #:** 207500

**PROPRIETARY NAME:** Cresemba

**ESTABLISHED/PROPER NAME:** isavuconazonium sulfate

**DOSAGE FORM/STRENGTH:** Capsules, 100 mg

**APPLICANT:** Astellas Pharma US Inc. (Astellas)

**PROPOSED INDICATION(S):** Treatment of invasive aspergillosis and invasive mucormycosis in patients 18 years of age and older.

**BACKGROUND:** The IND for Isavuconazonium Sulfate Intravenous (IND 72593) was submitted on June 9, 2005. An End-of-Phase 2 meeting was held on December 20, 2005. The IND was transferred from Basilea Pharmaceutical International, Ltd. to Astellas on March 12, 2010. IND 119307, for the oral capsule formulation, was submitted on August 9, 2013. A Pre-NDA meeting was held on November 5, 2013. A CMC Pre-NDA meeting was held on October 29, 2013.

NDA 207500 (Capsule) and 207501 (Intravenous) were submitted on July 8, 2014. Both applications and both indications have been granted orphan and Qualified Infectious Disease Product (QIDP) designations.

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Alison Rodgers	Y
	CPMS/TL:	Maureen Dillon-Parker	N
Cross-Discipline Team Leader (CDTL)	John Alexander		Y
Clinical	Reviewer:	Edward Weinstein	Y
	TL:	Elizabeth O'Shaughnessy	Y

Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	Shukal Bala	Y
	TL:	Kerry Snow	Y
Clinical Pharmacology	Reviewer:	Dakshina Chilukuri	Y
	TL:	Philip Colangelo	Y
Biostatistics	Reviewer:	Cheryl Dixon	Y
	TL:	Karen Higgins	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Owen McMaster	Y
	TL:	Wendelyn Schmidt	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Yichin Sun	Y
	TL:	Gene Holbert	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Vinayak Pawar	N
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Steven Hertz	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Aleksander Winiarski	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:	Carolyn Yancey	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		

	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Antoine El Hage	Y
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Dorota Matecka, Shawna Hutchins, Carolyn Yancey, Dhananjay Marathe, Banu Zolnik		
Other attendees	Jennifer Shepherd, Jane Dean, Frances LeSane, Sumathi Nambiar, John Farley, Edward Cox, Susmita Samanta, Karen Townsend, Kelly Cao, Timothy Jancel, Dev Jillapalli		

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<p>X Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no</b>, explain:</p>	<p>X YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p>
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p>X FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIostatistics</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE

<b>Comments:</b>	<input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b>  <b>Comments:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>PRODUCT QUALITY (CMC)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<u><b>Environmental Assessment</b></u>  <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p style="margin-left: 40px;"><b>If no</b>, was a complete EA submitted?</p> <p style="margin-left: 40px;"><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <b>Comments:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<u><b>Quality Microbiology (for sterile products)</b></u>  <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <b>Comments:</b>	<input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b> Seven facilities to be inspected.</p>	<p><input type="checkbox"/> Not Applicable</p> <p>X YES <input type="checkbox"/> NO</p> <p>X YES <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p>X Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<p><input type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES X NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	<p>N/A</p>
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<p>X YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> <li>Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority: Edward Cox, MD, MPH</b></p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): 10/3/14</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional): Post Mid-Cycle Meeting Communication with Applicant: 10/17/14, Wrap-Up: 1/26/15, Late-Cycle Meeting with Applicant : 1/9/15</p> <p><b>Comments:</b></p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter.  <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input type="checkbox"/> Standard Review  <input checked="" type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter

X	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
X	Send review issues/no review issues by day 74
X	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
X	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:  <a href="http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]</p>
<input type="checkbox"/>	Other

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ALISON K RODGERS

09/04/2014

MAUREEN P DILLON PARKER

09/05/2014

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 207501	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Cresemba Established/Proper Name: isavuconazonium sulfate Dosage Form: Powder for Injection Strengths: 200 mg		
Applicant: Astellas Pharma US Inc. Agent for Applicant (if applicable): N/A		
Date of Application: July 8, 2014 Date of Receipt: July 8, 2014 Date clock started after UN: N/A		
PDUFA Goal Date: March 8, 2015		Action Goal Date (if different):
Filing Date: September 6, 2014		Date of Filing Meeting: August 14, 2014
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s): Treatment of invasive aspergillosis and invasive mucormycosis in patients 18 years of age and older.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i></b> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> .		
Type of BLA  <b><i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i></b>	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
Review Classification:  <b><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i></b>  <b><i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i></b>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>  <b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products	

Other (drug/device/biological product)

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other: Qualified Infectious Disease Product (QIDP) Designation	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (*if OTC product*): N/A

List referenced IND Number(s): 72593

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>	<input type="checkbox"/>	X		
<b>If yes, explain in comment column.</b>				
<b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</b>	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment

Is Form 3397 (User Fee Cover Sheet) included with authorized signature?		X	<input type="checkbox"/>		
<b>User Fee Status</b>  <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		<b>Payment for this application:</b>  <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		<b>Payment of other user fees:</b>  <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<b>505(b)(2)</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>(NDAs/NDA Efficacy Supplements only)</b>					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Check the Electronic Orange Book at:</b> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a>					
<b>If yes, please list below:</b>					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></i>	<input type="checkbox"/>	X		
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDAs/NDA efficacy supplements only</i> )  <b>If yes</b> , # years requested:  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	X	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?	<input type="checkbox"/>	X	<input type="checkbox"/>	
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	
<b>For BLAs:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i>  <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) X All electronic <input type="checkbox"/> Mixed (paper/electronic)  X CTD <input type="checkbox"/> Non-CTD

	<input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission</b> , does it follow the eCTD guidance? <sup>1</sup> <b>If not</b> , explain (e.g., waiver granted).	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	X	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:  X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only)  <b>If no</b> , explain.	X	<input type="checkbox"/>		
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes</b> , BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	X	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X	<input type="checkbox"/>	<input type="checkbox"/>	

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>	X	<input type="checkbox"/>		Forms submitted via cross-reference to NDA 207500.
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	X	<input type="checkbox"/>		
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	X	Electronic submission
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff :</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	X	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input type="checkbox"/>	X		Application has orphan designation.
<p><b>If the application triggers PREA</b>, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<input type="checkbox"/>	<input type="checkbox"/>	X	
<p><b>If studies or full waiver not included</b>, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	X	
<p><b>If a request for full waiver/partial waiver/deferral is included</b>, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	X	
<p><b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i></p>	<input type="checkbox"/>	X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Prescription Labeling</b>	<b>X Not applicable/ Note: All labeling submitted to cross-referenced NDA 207500.</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	X	<input type="checkbox"/>		
Is the PI submitted in PLR format? <sup>4</sup>	X	<input type="checkbox"/>		Submitted to NDA 207500.
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<b>X Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	QT Interdisciplinary Review Team
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? <b>Date(s):</b> 12/20/05 <i>If yes, distribute minutes before filing meeting</i>	X	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 10/29/13 ( CMC Pre-NDA), 11/5/13 (Pre-NDA) <i>If yes, distribute minutes before filing meeting</i>	X	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> 6/5/06 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 8-14-14

**NDA #:** 207501

**PROPRIETARY NAME:** Cresemba

**ESTABLISHED/PROPER NAME:** isavuconazonium sulfate

**DOSAGE FORM/STRENGTH:** Intravenous, 200 mg

**APPLICANT:** Astellas Pharma US Inc. (Astellas)

**PROPOSED INDICATION(S):** Treatment of invasive aspergillosis and invasive mucormycosis in patients 18 years of age and older.

**BACKGROUND:** The IND for Isavuconazonium Sulfate Intravenous (IND 72593) was submitted on June 9, 2005. An End-of-Phase 2 meeting was held on December 20, 2005. The IND was transferred from Basilea Pharmaceutical International, Ltd. to Astellas on March 12, 2010. IND 119307, for the oral capsule formulation, was submitted on August 9, 2013. A Pre-NDA meeting was held on November 5, 2013. A CMC Pre-NDA meeting was held on October 29, 2013.

NDA 207500 (Capsule) and 207501 (Intravenous) were submitted on July 8, 2014. Both applications and both indications have been granted Orphan and Qualified Infectious Disease Product (QIDP) designations.

NDA 207501 contains drug product information for the intravenous formulation and incorporates all remaining information via cross reference to NDA 207500.

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Alison Rodgers	Y
	CPMS/TL:	Maureen Dillon-Parker	N
Cross-Discipline Team Leader (CDTL)	John Alexander		Y
Clinical	Reviewer:	Edward Weinstein	Y
	TL:	Elizabeth O'Shaughnessy	Y

Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	Shukal Bala	Y
	TL:	Kerry Snow	N

Clinical Pharmacology	Reviewer:	Dakshina Chilukuri	Y
	TL:	Philip Colangelo	Y
Biostatistics	Reviewer:	Cheryl Dixon	Y
	TL:	Karen Higgins	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Owen McMaster	Y
	TL:	Wendelyn Schmidt	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Nina Ni	Y
	TL:	Gene Holbert	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Vinayak Pawar	N
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Steven Hertz	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Aleksander Winiarski	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:	Carolyn Yancey	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Antoine El Hage	Y
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Dorota Matecka, Shawna Hutchins, Dhananjay Marathe, Banu Zolnik		
Other attendees	Jennifer Shepherd, Jane Dean, Frances LeSane, Sumathi Nambiar, John Farley, Edward Cox, Susmita Samanta, Karen Townsend, Kelly Cao, Timothy Jancel, Dev Jillapalli		

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<p>X Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<p>X YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p>
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p>X FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul>	<p>X YES</p>

<p><b>If no, explain:</b></p>	<input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO X To be determined  Reason:
<ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	X Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	X Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES X NO
<p><b>BIOSTATISTICS</b></p>	<input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<b>Comments:</b>	
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	
<b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	
<b>PRODUCT QUALITY (CMC)</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	
<b><u>Environmental Assessment</u></b>	
<ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>If no</b>, was a complete EA submitted?</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
<b><u>Quality Microbiology (for sterile products)</u></b>	<input type="checkbox"/> Not Applicable
<ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	

<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b> Seven facilities to be inspected.</p>	<p><input type="checkbox"/> Not Applicable</p> <p>X YES <input type="checkbox"/> NO</p> <p>X YES <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p>X Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<p><input type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES X NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	<p>N/A</p>
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<p>X YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority: Edward Cox, MD, MPH</b></p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): 10/3/14</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional): Post Mid-Cycle Meeting Communication with Applicant: 10/17/14, Wrap-Up: 1/26/15, Late-Cycle Meeting with Applicant: 1/9/15</p> <p><b>Comments:</b></p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter.  <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input type="checkbox"/> Standard Review  <input checked="" type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter

X	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
X	Send review issues/no review issues by day 74
X	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
X	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:  <a href="http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]</p>
<input type="checkbox"/>	Other

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/s/  
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ALISON K RODGERS  
09/04/2014

MAUREEN P DILLON PARKER  
09/05/2014

**REGULATORY PROJECT MANAGER  
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW  
OF THE PRESCRIBING INFORMATION**

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 207500 and NDA 207501

**Application Type:** New NDA

**Name of Drug/Dosage Form:** Cresemba (isavuconazonium sulfate), Capsule, 100mg (207500) and Cresemba (isavuconazonium sulfate), Intravenous, 200mg (207501)

**Applicant:** Astellas Pharma USA Inc.

**Receipt Date:** July 8, 2014

**Goal Date:** March 8, 2015

**1. Regulatory History and Applicant's Main Proposals**

These are two related new NDA submissions which reference each other. The injection and the hard capsule are together in one label.

**2. Review of the Prescribing Information**

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

**3. Conclusions/Recommendations**

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by October 10, 2014. The resubmitted PI will be used for further labeling review.

# Selected Requirements of Prescribing Information

## Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

### HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.
- Comment:**
- NO** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.
- Comment:** *The HL is more than one-half page and no waiver was submitted.*
- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
- Comment:**
- NO** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.
- Comment:** *There are some horizontal lines that extend over the entire width of the column and some that do not.*
- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.
- Comment:** *White space is missing before “Dosage Forms and Strengths,” “Contraindications,” and “Drug Interactions.”*
- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.
- Comment:** *“Dosage Forms and Strengths” is missing a reference to section 3.*
- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required

## Selected Requirements of Prescribing Information

• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

**Comment:**

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

**Comment:**

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

**Comment:**

#### Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:** *The approval year is missing. 2015 should be placed as a place holder.*

#### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

**Comment:**

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and

## Selected Requirements of Prescribing Information

other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

**Comment:**

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

**Comment:**

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

**Comment:**

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

**Comment:**

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

**Comment:**

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

**Comment:**

### Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

**Comment:** *The bulleted indications does not line up with the other bullets.*

### Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

**Comment:**

## Selected Requirements of Prescribing Information

### Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

**Comment:**

### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

**Comment:**

### Patient Counseling Information Statement in Highlights

- NO** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

**Comment:** *It should say "See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"*

### Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

**Comment:** *The revision date needs a date and year.*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
*Comment:*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
*Comment:*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

**Comment:**

## Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

*Comment:*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

*Comment:*

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

*Comment:*

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

*Comment:*

#### CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

*Comment:*

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

*Comment:*

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

*Comment:*

#### PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

## Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

#### WARNING: [SUBJECT OF WARNING]

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

#### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

#### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

#### DOSAGE AND ADMINISTRATION

- [text]
- [text]

#### DOSAGE FORMS AND STRENGTHS

[text]

#### CONTRAINDICATIONS

- [text]
- [text]

#### WARNINGS AND PRECAUTIONS

- [text]
- [text]

#### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- [text]
- [text]

#### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

#### 6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

#### 7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

#### 9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

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/s/  
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ALISON K RODGERS

09/04/2014

MAUREEN P DILLON PARKER

09/05/2014