

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207500Orig1s000 / 207501Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 207500

SUPPL #

HFD #

Trade Name Cresemba Capsules, 186 mg

Generic Name isavuconazonium sulfate

Applicant Name Astellas Pharma US Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES X NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES X NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO X

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO X

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO X

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO X

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Alison Rodgers
Title: Regulatory Project Manager
Date: 2-13-15

Name of Office/Division Director signing form: Sumathi Nambiar, MD, MPH
Title: Director, Division of Anti-Infective Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

GAIN Exclusivity Summary

Application Number	NDA 207501
Product Name/Generic/Dosage Form	Cresemba (isavuconazonium sulfate) Powder for Injection, 372 mg
Sponsor	Astellas Pharma US, Inc.

1. Does this product have Qualified Infectious Disease Product (QIDP) designation?

YES	NO
X	

2. Are the indication(s) approved in this NDA or supplement the same as the indication(s) identified in the QIDP designation letter(s)?

YES	NO
X	

3. Has this product previously received a 5-year GAIN exclusivity extension?

YES	NO
	X

Name of person completing form: Alison Rodgers

Title: Regulatory Project Manager

Date: *<see electronic signature>*

Name of Office/Division Director signing form: Sumathi Nambiar, MD, MPH

Title: Director, Division of Anti-Infective Products

Date: *<see electronic signature>*

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

/s/

ALISON K RODGERS
03/09/2015

SUMATHI NAMBIAR
03/09/2015

EXCLUSIVITY SUMMARY

NDA # 207501

SUPPL #

HFD #

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Approval Date, If Known

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505(b)(1)

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YES NO X

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NDA#

NDA#

NDA#

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YES NO

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NDA#

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NDA#

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(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

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Investigation #2 YES NO

Investigation #1
!
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YES ! NO
Explain: ! Explain:

Investigation #2
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Explain: ! Explain:

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YES NO

If yes, explain:

Name of person completing form: Alison Rodgers
Title: Regulatory Project Manager
Date: 2-13-15

Name of Office/Division Director signing form: Sumathi Nambiar, MD, MPH
Title: Director, Division of Anti-Infective Products

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YES	NO
X	

2. Are the indication(s) approved in this NDA or supplement the same as the indication(s) identified in the QIDP designation letter(s)?

YES	NO
X	

3. Has this product previously received a 5-year GAIN exclusivity extension?

YES	NO
	X

Name of person completing form: Alison Rodgers

Title: Regulatory Project Manager

Date: <see electronic signature>

Name of Office/Division Director signing form: Sumathi Nambiar, MD, MPH

Title: Director, Division of Anti-Infective Products

Date: <see electronic signature>

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

/s/

ALISON K RODGERS
03/09/2015

SUMATHI NAMBIAR
03/09/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹		
NDA # 207500 BLA # N/A	NDA Supplement # N/A BLA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: CRESEMBA Established/Proper Name: isavuconazonium sulfate Dosage Form: Capsules		Applicant: Astellas Pharma US Inc. Agent for Applicant (if applicable):
RPM: Alison Rodgers		Division: Anti-Infective Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	For ALL 505(b)(2) applications, two months prior to EVERY action: <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check:	
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>03-08-2015</u> 		X AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		X None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): 1P
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments: QIDP designated

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval 3-6-15
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	X Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	X Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input type="checkbox"/> Included – Please see Package Insert dated 3-5-15.
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input type="checkbox"/> Included – Please see Package Insert dated 7-8-14.
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	X Included
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	3-3-15; 5-12-14 3-2-15; 8-22-14
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: 9-5-14 DMEPA: 3-4-15; 1-22-15 DMPP/PLT (DRISK): 11-18-14 OPDP: 11-20-14 SEALD: None CSS: None Other: None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	9-5-14
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	X Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	X Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes X No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: Product has orphan designation. 	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	3-9-15 (4); 2-23-15 (2); 2-17-15; 2-12-14; 12-11-14 (2); 12-9-14; 11-3-14; 10-28-14; 10-20-14; 10-10-14; 9-25-14; 9-17-14; 9-16-14; 9-15-14; 9-2-14; 8-28-14; 7-18-14; 7-16-14
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	N/A
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	11-5-13
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	12-20-05
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	10-15-14
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	1-9-15
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	None
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) 	Yes
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	1-22-15
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) 	3-6-15
<ul style="list-style-type: none"> Division Director Summary Review (<i>indicate date for each review</i>) 	3-5-15
<ul style="list-style-type: none"> Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) 	2-10-15
<ul style="list-style-type: none"> PMR/PMC Development Templates (<i>indicate total number</i>) 	3
Clinical	
<ul style="list-style-type: none"> ❖ Clinical Reviews 	
<ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	See Cross-Discipline Team Leader Review dated 2-10-15
<ul style="list-style-type: none"> • Clinical review(s) (<i>indicate date for each review</i>) 	12-12-14; 8-12-14
<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	X None
<ul style="list-style-type: none"> ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>) 	Please see page 25 of clinical review dated 12-12-14
<ul style="list-style-type: none"> ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) 	9-29-14

❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	X N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	N/A N/A 12/7/14
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	1-22-15
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	X No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	12-9-14; 8-27-14
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	X No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	X No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	12-8-14; 8-13-14
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	X No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	X No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	12-9-14; 8-7-14
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	X None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	1-29-15
• Supervisory Review(s) (<i>indicate date for each review</i>)	X No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	1-21-15; 8-14-14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	X None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	X No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	X None requested

Product Quality	<input type="checkbox"/> None
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	X No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	X No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	3-4-15; 1-6-15
❖ Microbiology Reviews X NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	8-8-14
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	12-23-14 (Biopharmaceutics)
❖ Environmental Assessment (check one) (original and supplemental applications)	
X Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	Please see page 225 of CMC Review dated 1-6-15.
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	N/A
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: 3-3-15 X Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	X Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ For Breakthrough Therapy(BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	X Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	X Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	X Done
❖ Ensure Pediatric Record is accurate	N/A
❖ Send approval email within one business day to CDER-APPROVALS	X Done

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹		
NDA # 207501 BLA # N/A	NDA Supplement # N/A BLA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: CRESEMBA Established/Proper Name: isavuconazonium Dosage Form: Powder for Injection		Applicant: Astellas Pharma US Inc. Agent for Applicant (if applicable):
RPM: Alison Rodgers		Division: Anti-Infective Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is 03-08-2015 		X AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		X None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): 1P
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments: QIDP designated

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	X Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	X No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	X Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	X Included
Documentation of consent/non-consent by officers/employees	X Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval 3-6-15
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	X Included
• Original applicant-proposed labeling	X Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	<input type="checkbox"/> Included
• Original applicant-proposed labeling	<input type="checkbox"/> Included – Please see Package Insert dated 7-8-14.
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	X Included
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)	3-3-15; 5-12-14
• Review(s) (<i>indicate date(s)</i>)	3-2-15; 8-22-14
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: 9-5-14 DMEPA: 3-4-15; 2-25-15 DMPP/PLT (DRISK): 11-18-14 OPDP: 11-20-14 SEALD: None CSS: None Other: None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	9-5-14
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	X Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	X Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes X No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: Product has orphan designation. 	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	3-9-15 (4); 2-23-15 (3); 2-18-15; 2-17-15; 2-12-14; 12-11-14 (2); 12-9-14; 11-3-14; 10-28-14; 10-20-14; 10-10-14; 9-25-14; 9-17-14; 9-16-14; 9-15-14; 9-2-14; 8-28-14; 7-18-14; 7-16-14
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	
<ul style="list-style-type: none"> ❖ Minutes of Meetings <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	N/A 11-5-13 12-20-05 10-15-14 1-9-15 None
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	Yes 1-22-15
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) 	3-6-15
Division Director Summary Review (<i>indicate date for each review</i>)	3-5-15
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	2-10-15
PMR/PMC Development Templates (<i>indicate total number</i>)	3-5-15
Clinical	
<ul style="list-style-type: none"> ❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	See Cross-Discipline Team Leader Review dated 2-10-15 12-12-14; 8-12-14 X None
<ul style="list-style-type: none"> ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>) 	Please see page 25 of clinical review dated 12-12-14
<ul style="list-style-type: none"> ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) 	9-29-14

❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	X N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	N/A N/A 12/7/14
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	1-22-15
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	X No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	12-9-14; 8-27-14
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	X No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	X No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	12-8-14; 8-13-14
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	X No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	X No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	12-9-14; 8-7-14
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	X None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	1-29-15
• Supervisory Review(s) (<i>indicate date for each review</i>)	X No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	1-21-15; 8-14-14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	X None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	X No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	X None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		X No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		X No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		3-4-15; 12-12-14; 9-5-14
❖ Microbiology Reviews		
X NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		11-21-14
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		
		X None
❖ Environmental Assessment (check one) (original and supplemental applications)		
X Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		Please see page 95 of CMC Review dated 12-12-14.
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		N/A
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		N/A
❖ Facilities Review/Inspection		
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>		Date completed: 3-3-15 X Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		
		X Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
<ul style="list-style-type: none"> ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ For Breakthrough Therapy(BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done <i>(Send email to CDER OND IO)</i>
<ul style="list-style-type: none"> ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Ensure Pediatric Record is accurate 	N/A
<ul style="list-style-type: none"> ❖ Send approval email within one business day to CDER-APPROVALS 	<input checked="" type="checkbox"/> Done

From: [Rodgers, Alison](#)
To: [Reed, Robert \(Robert.Reed@astellas.com\)](#)
Subject: Cresemba Carton & Container Labeling
Date: Monday, March 02, 2015 4:10:00 PM
Importance: High

Hi Robert,

Please note these comments regarding carton and container labeling:

- 1) To be consistent with the wording in the PI, "a (b) (4) vial" needs to be replaced with "a single-dose vial" in the container labels, including both carton and immediate container labels.
- 2) Add "Rx only" statement to the blister label.
- 3) Add the name of the manufacturer or distributor to the blister label.
- 4) Delete the (b) (4) from all the carton labels.

Please submit revised labeling tomorrow if at all possible.

Please confirm receipt of this email.

Thank you,

Alison

*Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882*

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

/s/

ALISON K RODGERS
03/09/2015

From: [Rodgers, Alison](#)
To: [Reed, Robert \(Robert.Reed@astellas.com\)](mailto:Robert.Reed@astellas.com)
Subject: Cresemba - Recommendation for section 2.2
Date: Friday, February 27, 2015 3:57:00 PM
Importance: High

Hi Robert,

This is what we recommend for section 2.2:

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	1 reconstituted vial (372 mg*) intravenously every 8 hours for 6 doses (48 hours)	1 reconstituted vial (372 mg*) intravenously once daily
CRESEMBA Capsules 186 mg** of isavuconazonium sulfate per capsule	2 capsules (372 mg*) orally every 8 hours for 6 doses (48 hours)	2 capsules (372 mg*) orally once daily

*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

Please let me know if you have questions.

Please confirm receipt of this email.

Thank you and have a nice weekend,

Alison

*Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882*

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

/s/

ALISON K RODGERS
03/09/2015

From: [Rodgers, Alison](#)
To: [Reed, Robert \(Robert.Reed@astellas.com\)](#)
Subject: Cresemba Package Insert and Patient Information
Date: Thursday, February 26, 2015 1:41:00 PM
Attachments: [Cresemba Package Insert 022615 to Astellas.docx](#)
Importance: High

Hi Robert,

Please find attached our draft Package Insert and Patient Information for Cresemba.

We would like to schedule a teleconference for 11:00 EST tomorrow morning to discuss the label if that works for your team.

Please let me know. We could schedule the call for 3:00 PM if that would be better for your team.

Please confirm receipt of this email.

Thank you,

Alison

*Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882*

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/s/

ALISON K RODGERS
03/09/2015

From: [Rodgers, Alison](#)
To: [Reed, Robert \(Robert.Reed@astellas.com\)](#)
Subject: Cresemba PMC Language
Date: Monday, March 02, 2015 3:39:00 PM
Importance: High

Hi Robert,

Below is the revised language for the PMC:

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.

Final Protocol Submission:	03/2016
Interim Report:	03/2018
Interim Report:	03/2019
Interim Report:	03/2020
Study Completion:	01/2022
Final Report Submission:	01/2023

Please submit a statement that you agree to conduct the proposed PMRs and PMC as soon as possible. Please list the proposed PMRs and PMC and timetables in your response.

Thank you,

Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882

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/s/

ALISON K RODGERS
03/09/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207500

GAIN Exclusivity

Astellas Pharma US Inc.
Attention: Robert M. Reed
Senior Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Mr. Reed:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cresemba (isavuconazonium sulfate) Capsules, 186 mg for the treatment of invasive aspergillosis and invasive mucormycosis and to the letter dated March 6, 2015, granting approval of this NDA.

We also refer to our correspondences dated November 8, 2013, and February 7, 2014, to your Investigational New Drug (IND) Application #119307 in which we granted Qualified Infectious Disease Product (QIDP) designation for Cresemba (isavuconazonium sulfate) Capsules for the treatment of invasive aspergillosis and invasive mucormycosis, respectively.

This letter is to inform you that your application meets the criteria for the 5-year exclusivity extension under section 505E(a) of the Act. Five years of additional exclusivity will be added to any applicable exclusivity periods described in subsections (c)(3)(E)(ii) and (j)(5)(F)(ii) of section 505 of the Act; clauses (iii) and (iv) of subsection (c)(3)(E) and clauses (iii) and (iv) of subsection (j)(5)(F) of section 505 of the Act; or section 527 of the Act that are otherwise associated with the approval of this NDA.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely yours,

{See appended electronic signature page}

John Farley, MD, MPH
Deputy Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JOHN J FARLEY
03/06/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207501

GAIN Exclusivity

Astellas Pharma US Inc.
Attention: Robert M. Reed
Senior Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Mr. Reed:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cresemba (isavuconazonium sulfate) Powder for Injection, 372 mg for the treatment of invasive aspergillosis and invasive mucormycosis and to the letter dated March 6, 2015, granting approval of this NDA.

We also refer to our correspondences dated November 8, 2013, and February 7, 2014, to your Investigational New Drug (IND) Application #72593 in which we granted Qualified Infectious Disease Product (QIDP) designation for Cresemba (isavuconazonium sulfate) Capsules for the treatment of invasive aspergillosis and invasive mucormycosis, respectively.

This letter is to inform you that your application meets the criteria for the 5-year exclusivity extension under section 505E(a) of the Act. Five years of additional exclusivity will be added to any applicable exclusivity periods described in subsections (c)(3)(E)(ii) and (j)(5)(F)(ii) of section 505 of the Act; clauses (iii) and (iv) of subsection (c)(3)(E) and clauses (iii) and (iv) of subsection (j)(5)(F) of section 505 of the Act; or section 527 of the Act that are otherwise associated with the approval of this NDA.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely yours,

{See appended electronic signature page}

John Farley, MD, MPH
Deputy Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JOHN J FARLEY
03/06/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207500
NDA 207501

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Astellas Pharma US Inc.
1 Astellas Way
Northbrook, IL 60062

ATTENTION: Robert M. Reed
Senior Director, Regulatory Affairs

Dear Mr. Reed:

Please refer to your New Drug Application (NDA) dated and received, July 8, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Isavuconazonium Sulfate Capsules, 186 mg and Isavuconazonium Sulfate for Injection, 372 mg.

We also refer to:

- your correspondence, dated and received, February 9, 2015, requesting re-evaluation of your proposed proprietary name, Cresemba
- your amendments, dated and received, February 20, 2015, updating your dosage information

We have completed our re-evaluation of the proposed proprietary name, Cresemba and have concluded that it is acceptable.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application, contact Alison Rodgers, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
03/03/2015

From: Rodgers, Alison
To: [Reed, Robert \(Robert.Reed@astellas.com\)](mailto:Reed.Robert@astellas.com)
Subject: Statistical Methodology Response
Date: Friday, February 20, 2015 3:12:00 PM
Attachments: [image003.png](#)

Hi Robert,

Following is our response concerning the statistical methodology used to generate confidence intervals:

There is not a transcriptional error in the confidence interval provided in the package insert for Overall Response Success at EOT. The confidence interval calculated by the Agency actually uses a slight modification in the calculation of the variance for each stratum to that which was stated in the Koch reference. The variance for each stratum was calculated as follows:

$$\frac{\hat{p}_{i0}^*(1-\hat{p}_{i0}^*)}{n_{i0}} + \frac{\hat{p}_{i1}^*(1-\hat{p}_{i1}^*)}{n_{i1}} \text{ where } \hat{p}_{ij}^* = \frac{n_{ij1} + 0.5}{n_{ij} + 1}$$

Please note, when we apply the formula provided in the February 18, 2015 email correspondence, we also arrive at the confidence interval stated in the table under "Astellas by Koch Formula".

I hope this is helpful.

Please let me know if you have questions.

Please confirm receipt of this email.

Thank you,

Alison

*Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882*

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/s/

ALISON K RODGERS
02/23/2015

From: Rodgers, Alison
To: ["Reed, Robert"](#)
Subject: RE: PMC Timetable
Date: Friday, February 20, 2015 1:15:00 PM

Thanks, Robert.
Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882

From: Reed, Robert [mailto:Robert.Reed@astellas.com]
Sent: Friday, February 20, 2015 1:06 PM
To: Rodgers, Alison
Subject: RE: PMC Timetable

Thank you Alison, this is fine.

From: Rodgers, Alison [mailto:Alison.Rodgers@fda.hhs.gov]
Sent: Friday, February 20, 2015 11:50 AM
To: Reed, Robert
Subject: PMC Timetable

Hi Robert,

I need to let you know that we added a date for an interim report submission to the PMC timetable:

Final Protocol Submission:	03/2016
Interim Report:	03/2017
Study/Trial Completion:	01/2022
Final Report Submission:	01/2023

Please let me know if this is acceptable.

Thank you,

Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797

Fax: 301-796-9882

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/s/

ALISON K RODGERS
02/23/2015

From: Rodgers, Alison
To: [Reed, Robert \(Robert.Reed@astellas.com\)](mailto:Reed.Robert@astellas.com)
Subject: Cresemba Additional Labeling Comments
Date: Friday, February 20, 2015 6:47:00 AM
Importance: High

Hi Robert,

Please note a few additional comments regarding the label. Please incorporate into your drafts.

Upon review of the section 6 of the CRESEMBA package insert, the following issues were identified.

- 1) There is a typographical error in section 6.1, which should read: "Serious adverse reactions occurred in **223/403 (55%)** of patients..."
- 2) In Table 1, the composite adverse reaction "Elevated liver laboratory tests" contains the following composite preferred terms (from your Clinical Overview, Appendix Table 1.1):

(b) (4) Preferred term	Isavuconazole (N=257)	Voriconazole (N=259)
Elevated LFTs	(b) (4)	(b) (4)
(b) (4)		

Please revise table 1 for this adverse reaction. (b) (4) is not a specific liver function test, especially in a patient population with a high incidence of active malignancy. If (b) (4) are included as component PTs then verify that the values are indeed increased.

Please confirm receipt of this email.

Thank you,

Alison

*Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882*

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ALISON K RODGERS
02/23/2015

From: Rodgers, Alison
To: [Reed, Robert \(Robert.Reed@astellas.com\)](mailto:Reed.Robert@astellas.com)
Subject: Cresemba Nomenclature
Date: Wednesday, February 18, 2015 2:14:00 PM
Importance: High

Hi Robert,

Please see our recommended nomenclature for Cresemba below. We would like to proceed with the teleconference as scheduled for 4:00 PM tomorrow. Please confirm that the time for the teleconference is still acceptable.

CRESEMBA (isavuconazonium sulfate) capsules, 186 ^(b)₍₄₎mg
Equivalent to 100 mg isavuconazole

CRESEMBA (isavuconazonium sulfate) for injection, 372 ^(b)₍₄₎mg
Equivalent to 200 mg isavuconazole

Please let me know if you have questions.

Please confirm receipt of this email.

Thank you!

Alison

*Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882*

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/s/

ALISON K RODGERS
02/18/2015

From: Rodgers, Alison
To: [Reed, Robert \(Robert.Reed@astellas.com\)](mailto:Reed.Robert@astellas.com)
Subject: Labeling - Responses to Request for Clarification
Date: Friday, February 13, 2015 1:39:00 PM
Importance: High

Hi Robert,

In response to your request for clarification of microbiology and statistics issues concerning the label, please note the following:

- 1) The statement [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] The small number of pathogens identified in patients enrolled in the clinical trial were added in Section 14.
- 2) [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
- 3) We calculated the weighted confidence intervals for the differences in the rates using the Mantel-Haenszel estimate of the difference in rates as described by Koch et al in *Statistical Methodology in the Pharmaceutical Sciences*, 1989, pages 414-421.

I hope these responses are helpful. Please let me know if you require additional clarifications.

Please confirm receipt of this email.

Thank you,

Alison

*Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882*

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/s/

ALISON K RODGERS

02/17/2015

From: Rodgers, Alison
To: [Reed, Robert \(Robert.Reed@astellas.com\)](mailto:Robert.Reed@astellas.com)
Subject: Post-Marketing Commitment for Cresemba
Date: Thursday, February 12, 2015 10:08:00 AM
Importance: High

Hi Robert,

Please note the following request for information:

We acknowledge that you have agreed to a (b) (4) registry as a post-marketing commitment for Cresemba-treated Mucormycosis and rare species of Aspergillus. Both the December 2015 date for submission of the final protocol and the annual reporting of interim study results are acceptable. Our concern is whether a (b) (4) period is an adequate amount of time to collect a sufficient number of mucormycosis cases. How many cases do you expect to recruit per year? How much Cresemba use do you project annually within the U.S., and separately within countries participating in the Fungiscope registry over the next (b) (4) ?

*When formulating the protocol we anticipate that the primary endpoint will be (b) (4)
Our concern is that the Fungiscope database (b) (4)*

Please let me know when you expect to respond.

Please confirm receipt of this email.

Thank you,

Alison

*Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882*

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/s/

ALISON K RODGERS
02/12/2015

Rodgers, Alison

From: Rodgers, Alison
Sent: Wednesday, December 31, 2014 11:26 AM
To: Reed, Robert (Robert.Reed@astellas.com)
Subject: CRESEMBA Draft Package Insert and Patient Information
Attachments: isavuconazole-redline-uspi-123114_Final_to_Astellas.docx; isavuconazonium (cresemba) 207500 and 207501 PPI_123114_Final_to_Astellas.docx

Hi Robert,

Please find attached our full draft USPI and PPI for CRESEMBA. We made a few additional edits to the PPI. Please let me know when you expect to respond. Feel free to let me know your response date next week when you are all back to work.

Please confirm receipt of this email.

Thank you,

Alison

*Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882*

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

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ALISON K RODGERS
01/02/2015

From: [Reed, Robert](#)
To: [Rodgers, Alison](#)
Subject: RE: NDAs 207500 and 207501 Name Issue
Date: Friday, December 19, 2014 10:32:37 AM

Thank you Alison !

From: Rodgers, Alison [mailto:Alison.Rodgers@fda.hhs.gov]
Sent: Friday, December 19, 2014 9:14 AM
To: Reed, Robert
Subject: NDAs 207500 and 207501 Name Issue

Hi Robert,

Following is our response regarding the name issue:

We acknowledge your amendment dated November 18, 2014. However, your proposed nomenclature

(b) (4)

[Redacted text block]

[Large redacted text block]

(b) (4)

Please let me know if you have questions.

Please confirm receipt of this email.

Thank you,

Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882

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/s/

ALISON K RODGERS
12/19/2014

From: [Reed, Robert](#)
To: [Rodgers, Alison](#)
Subject: RE: Request for Non-Clinical Information
Date: Thursday, December 11, 2014 12:57:04 PM

Thank you Alison

From: Rodgers, Alison [mailto:Alison.Rodgers@fda.hhs.gov]
Sent: Thursday, December 11, 2014 11:50 AM
To: Reed, Robert
Subject: Request for Non-Clinical Information

Hi Robert,

Please see the following request for non-clinical information (pertinent documents attached):

- (1) There appears to be a discrepancy in the assay % for isavuconazonium in drug batch 17CH03SD.HQ0 0002.02. Purity is listed as 85.2 % in the study report for the 'Thirty Nine-Week Oral Study in Cynomolgus Monkeys', but is listed as 74.1 % on page 16 of the Toxicology Tabulated Summary. Please clarify.
- (2) Patients are being treated for more than 3 months. What are your plans for carcinogenicity testing ?

Please respond by cob tomorrow, 12/12/14, if at all possible.

Please confirm receipt of this email.

Thank you,

Alison

*Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882*

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/s/

ALISON K RODGERS
12/11/2014

Rodgers, Alison

From: Rodgers, Alison
Sent: Wednesday, December 10, 2014 4:09 PM
To: Reed, Robert (Robert.Reed@astellas.com)
Subject: CRESEMBA Draft Labeling and PMR
Attachments: isavuconazole-redline-uspi-07oct2014121014.docx; isavuconazonium (cresemba) 207500 and 207501 DMPP PPI Review Marked NOV-2014.docx

Importance: High

Hi Robert,

Attached please find our draft label and Patient Information for CRESEMBA. Please note that sections 7, 12.2, 12.3, 13, and 14 are not included in the label as we are still working on them.

Also, please note that we are considering the following PMR:

Conduct surveillance studies for five years from the date of marketing CRESEMBA® to determine [REDACTED] (b) (4) in organisms relevant to the indication in the package insert for invasive aspergillosis and mucormycosis.

Please send your response by January 5, 2015.

Please let me know if you have any questions. Please confirm receipt of this email.

Thank you,

Alison

*Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882*

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/s/

ALISON K RODGERS
12/11/2014

Rodgers, Alison

From: Rodgers, Alison
Sent: Tuesday, December 09, 2014 10:28 AM
To: 'Reed, Robert'
Subject: RE: Isavuconazonium Information Request

Hi Robert,
So sorry.. response date is Thursday, 12/11, please.
Thank you!
Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882

From: Reed, Robert [<mailto:Robert.Reed@astellas.com>]
Sent: Tuesday, December 09, 2014 10:26 AM
To: Rodgers, Alison
Subject: RE: Isavuconazonium Information Request

Hi Alison,

I received the request. Will you please confirm the response date? Do you mean Thursday the 11th or Thursday the 18th?

Thank you,

Robert

From: Rodgers, Alison [<mailto:Alison.Rodgers@fda.hhs.gov>]
Sent: Tuesday, December 09, 2014 9:21 AM
To: Reed, Robert
Subject: Isavuconazonium Information Request
Importance: High

Hi Robert,

As promised during yesterday's teleconference, attached is an additional clinical information request. Please respond by cob Thursday, December 4, if at all possible.

Please confirm receipt of this email.

Thank you,
Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager

1) Following an examination of serious, non-fatal convulsive AEs, we have noted within the nervous system disorders SOC at the lowest level term more convulsive events (convulsion, epilepsy, febrile convulsion, and grand mal convulsion) were reported within the isavuconazole treatment arm (7 events in 6 subjects) than within the voriconazole arm (3 events in 3 subjects). Please provide narratives for the following identified patients in regards to the following AEs with a rationale for this observed difference. Convulsions have been described at the case report level for other systemic antifungal azoles, such as fluconazole [Ther Drug Monit. 2000 Oct;22(5):635-6].

For ISV treated patients:

Convulsion: 2004-01, 8603-01, 9114-07

Epilepsy: 0702-02, 3201-07

Febrile Convulsion: 3204-23

For VZC treated patients:

Convulsion 3204-32:

Epilepsy: 4914-01:

Grand Mal: 9104-04:

2) In the phase 1 healthy volunteer population, 7 discontinuations occurred in the group of 39 subjects taking multiple doses of 600 mg isavuconazole. Reasons for discontinuation included AEs of anxiety (3/39), flushing (3/39), headache (3/39), dizziness (2/39) attention disturbances (2/39), nausea (2/39), diarrhea (1/39), and vomiting (1/39). Please further describe the AEs of "attention disturbances" and "flushing", and the rationale for discontinuing the study for these subjects.

3) Within the phase 1 multiple dose groups, the highest incidence of TEAEs occurred in the 600 mg group (34/39, 87.2%). TEAEs in the 600 mg group that occurred at a higher rate than that seen in the other multiple dose groups included flushing (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%), oral hypoesthesia (4/39, 10.3%), disturbance in attention (4/39, 10.3%), palpitations (4/39, 10.3%), vomiting (3/39, 7.7%), and oral paresthesia (2/39, 5.1%). We would like more information about the parasthesias, in particular. Does it occur at lower doses (it was not reported at 200 mg)? Does it happen during infusion? Does it resolve?

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/s/

ALISON K RODGERS
12/09/2014

From: Bhandari, Navi
To: ["Reed, Robert"](#)
Subject: NDA 207500 Information Request Quick Turnaround Requested
Date: Monday, December 08, 2014 1:26:00 PM
Attachments: [NDA 207500 IR 12-8-14 .pdf](#)
Importance: High

Hello Robert,

Please see the attached information request. Please note that the requested turnaround date is December 11, 2014. Please confirm receipt.

Thank you,

Navi Bhandari, Pharm.D
Regulatory Health Project Manager
Office of New Drug Quality Assessment
OPS/CDER/FDA
240-402-3815



NDA 207500

INFORMATION REQUEST

Astellas Pharma US Inc.
c/o Astellas Pharma Global Development, Inc.
Attention: Robert M. Reed, Senior Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Mr. Reed:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

NDA Number	Drug Product
207500	Cresemba (isavuconazonium sulfate) Capsules, (b) (4) mg

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by December 11, 2014, in order to continue our evaluation of your NDA.

We do not agree with the acceptance criterion $Q = \frac{(b)(4)}{(4)}\%$ at 75 minutes you proposed for dissolution method and recommend that you set the dissolution acceptance criterion as $Q = \frac{(b)(4)}{(4)}\%$ at 75 minutes for your proposed product. This recommendation is based on the in vitro performance of the clinical and stability batches. Please submit both an updated Drug Product Specification Table and a Stability Protocol as an amendment to the NDA.

If you have any questions, call Navi Bhandari, Regulatory Health Project Manager, at (240) 402 - 3815.

Sincerely,

Moo-jhong Rhee
Moojhong Rhee -S

Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
cn=Moojhong Rhee -S, 0.9.2342.19200300.100.1.1=1300041261
Date: 2014.12.08 13:22:19 -05'00'

Moo-Jhong Rhee, PhD
Branch Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research



NDA 207500

**METHODS VALIDATION
MATERIALS RECEIVED**

Astellas Pharma US Inc
Attention: Robert M. Reed
1 Astellas Way
Northbrook, IL 60062

Dear Robert M. Reed:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cresemba (isavuconazonium sulfate) Capsules and to our August 25, 2014, letter requesting sample materials for methods validation testing.

We acknowledge receipt on November 26, 2014, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
12/03/2014



NDA 207501

**METHODS VALIDATION
MATERIALS RECEIVED**

Astellas Pharma US Inc
Attention: Robert M. Reed
1 Astellas Way
Northbrook, IL 60062

Dear Robert M. Reed:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cresemba (isavuconazonium sulfate) IV and to our August 25, 2014, letter requesting sample materials for methods validation testing.

We acknowledge receipt on November 26, 2014, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
12/03/2014



NDA 207500
NDA 207501

MID-CYCLE COMMUNICATION

Astellas Pharma US Inc.
Attention: Robert M. Reed
Senior Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Mr. Reed:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cresemba (isavuconazonium sulfate) Capsules (NDA 207500) and Powder for Injection (NDA 207501).

We also refer to the teleconference between representatives of your firm and the FDA on October 15, 2014. The purpose of the teleconference was to provide you with an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

MID-CYCLE COMMUNICATION

Meeting Date and Time: October 15, 2014

Application Number: NDAs 207500 and 207501

Product Name: Cresemba (isavuconazonium sulfate) Capsules (NDA 207500)
Cresemba (isavuconazonium sulfate) Powder for Injection
(NDA 207501)

Indication: Treatment of invasive aspergillosis and mucormycosis

Applicant Name: Astellas Pharma US Inc.

Meeting Chair: John Alexander, MD, MPH

Meeting Recorder: Alison Rodgers

FDA ATTENDEES

Division of Anti-Infective Products

John Alexander, MD, MPH, Clinical Team Leader
Shukal Bala, PhD, Clinical Microbiology Reviewer
Philip Colangelo, PharmD, PhD, Clinical Pharmacology Team Leader
Maureen Dillon-Parker, Chief, Project Management Staff
Cheryl Dixon, PhD, Statistical Reviewer
Karen Higgins, ScD, Statistical Team Leader
Gene Holbert, PhD, Chemistry, Manufacturing, and Controls Reviewer
Katherine Laessig, MD, Deputy Director
Frances LeSane, Chief, Project Management Staff
Dorota Matecka, PhD, Chemistry, Manufacturing, and Controls Lead
Owen McMaster, PhD, Pharmacology and Toxicology Reviewer
Elizabeth O'Shaughnessy, MD, Medical Officer
Sumathi Nambiar, MD, MPH, Director
Kristine Park, PhD, Regulatory Project Manager
Vinyak Pawar, PhD, Product Quality Microbiology Reviewer
Alison Rodgers, Senior Regulatory Project Manager
Yichun Sun, PhD, Chemistry, Manufacturing, and Controls Reviewer
Edward Weinstein, MD, PhD, Medical Officer

Office of Antimicrobial Products

John Farley, MD, MPH, Deputy Director

Office of Clinical Pharmacology

Division of Pharmacometrics

Jeffrey Florian, PhD, Acting Team Leader

Eastern Research Group, Inc.

Christopher Sese, Independent Contractor

APPLICANT ATTENDEES

Astellas Pharma US Inc.

Bernhardt Zeiher, MD, Executive Vice President, Global Development and Therapeutic Area Head, Immunology and Infectious Diseases

Rochelle Maher, MS, Senior Director, Global Development Project Leader

Salim Mujais, MD, Vice President Global Medical Head

Laura Kovanda, Director, Global Development Project Leader/Microbiology

Ahsan Arozullah, MD, MPH, Senior Medical Director, Global Medical Safety

James Keirns, PhD, Vice President, Chief Clinical Pharmacology Scientist

Christopher Lademacher, MD, Senior Medical Director

Marlowe Schneidkraut, Ph.D., DABT, Senior Director, Drug Discovery Science & Management

Robert Townsend, PhD, Associate Director, Clinical Pharmacology and Translational Science

Yili Pritchett, PhD, Senior Director, Biostatistics

Misun Lee, PhD, Associate Director, Biostatistics

Carolyn Sasse, Associate Clinical Program Director

Karen Rodriguez, PhD, Assistant Director, Project and Product Management

Katsutoshi Nakamura, Senior Director, Project and Product Management

Dan Mossman, PhD, Director, Product and Process Technology

Christine Slover, PharmD, Associate Project Director

MaryClare DeLuca, Associate Medical Writing Program Director

Robert Reed, Senior Director, Regulatory Affairs

Basilea Pharmaceutica International Ltd.

Karsten Goedecke, PhD, Regulatory Affairs Manager and Project Manager

INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

1. Significant Review Issues

There are no issues to report at this time.

2. Information Requests

Mid-cycle information requests were sent to Astellas via email on October 8, and 10, 2014. They were communicated to Astellas during the teleconference as follows:

- As communicated in the information request dated October 8, 2014, for the mucormycosis indication, the review team is requesting any additional information that you may have to support a comparison of the results of the isavuconazonium-treated patients to results in a historical control of untreated patients. *(This is a summary of the longer information request sent on October 8, 2014.)*
- Given the two year break in patient enrollment during the conduct of Study 9766-CL-104, we conducted a subgroup analysis by time of enrollment (prior to or after the March 2011 restart) and found numerical differences in the response rates for all-cause mortality at Day 42 and the Data Review Committee (DRC)-assessed overall response at End of Treatment (EOT) by enrollment period. The outcomes are less favorable for those enrolled after the restart of the study and, for all-cause mortality at Day 42, there is a difference in the direction of the treatment effect depending on the enrollment period. We recommend that you investigate this as well and determine if there might be any explanations for these numerical differences.
- A Chemistry, Manufacturing, and Controls Information Request is being prepared and will be sent separately. The CMC IR is related to the drug substance manufacturing process and controls, and the filter use recommendations for the IV drug product.

Astellas commented that they submitted their response to the above requests on October 14, 2014. The FDA will respond once it has reviewed the submission.

Additionally, FDA noted that a request for additional Chemistry, Manufacturing, and Controls, and Product Quality Microbiology information would be sent to Astellas by October 17, 2014.

3. Major Safety Concerns

There are no major safety concerns identified at this time and there is currently no need for a risk evaluation and mitigation strategy.

4. Advisory Committee Meeting Plans

An Advisory Committee Meeting is planned for January 22, 2015.

The briefing book for the Advisory Committee Meeting will be sent to Astellas by December 22, 2014.

Additionally, Astellas asked if the FDA has formulated its thoughts regarding topics and questions for the Advisory Committee Meeting. The FDA explained that it has not as reviews are still ongoing, but that the recent information requests should provide an idea as to the FDA's thoughts regarding the mucormycosis data. The FDA is trying to evaluate whether or not there is sufficient evidence to demonstrate efficacy of Cresemba in mucormycosis.

Astellas noted that while they provided a timely response to the information requests, they are trying to find more information regarding mucormycosis and will provide the information as soon as they find it. The FDA asked to be notified as soon as possible if Astellas will be able to provide this additional information. Astellas agreed, and noted that feedback regarding their responses would be helpful.

The FDA communicated that it will likely send a follow-up information request regarding the mucormycosis data by the end of the week. The Chemistry, Manufacturing, and Controls, Product Quality Microbiology, and Pharmacology and Toxicology information request mentioned above will also be sent by the end of the week.

5. Late-Cycle Meeting/Other Projected Milestones

The Division will convey proposed revisions to the product labeling to Astellas by December 10, 2014.

The Late Cycle Review Meeting is scheduled for January 9, 2015.

6. Conclusions:

- The Division will issue Meeting minutes within 30-days of the meeting.

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/s/

SUMATHI NAMBIAR
11/03/2014

From: Rodgers, Alison
To: [Reed, Robert \(Robert.Reed@astellas.com\)](mailto:Robert.Reed@astellas.com)
Subject: Cresemba NDAs
Date: Tuesday, October 28, 2014 11:58:00 AM

Hi Robert,

Please see below:

Following the USP policy for naming drug products formulated with salts, we recommend that the names and strengths of the proposed drug products be expressed based on isavuconazonium, as follows:

(b) (4)

(b) (4)

Please let me know if you have questions.

Please confirm receipt of this email.

Thank you,

Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882

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/s/

ALISON K RODGERS
10/28/2014

From: [Reed, Robert](#)
To: [Rodgers, Alison](#)
Subject: RE: Cresemba NDAs Request for Information
Date: Monday, October 20, 2014 11:26:10 AM

Thank you Alison! I will pass this information on to the team.

From: Rodgers, Alison [mailto:Alison.Rodgers@fda.hhs.gov]
Sent: Monday, October 20, 2014 10:25 AM
To: Reed, Robert
Subject: Cresemba NDAs Request for Information
Importance: High

Hi Robert,

We have reviewed your response to our information request. A non-inferiority margin for comparison to amphotericin b has not been established. Therefore, our evaluation of the mucormycosis data will focus on defining the benefit of treatment relative to no treatment at all, which in this case would be treatment with Isavuconazole relative to a historical control of no treatment. Compelling, subject-level data may be available within the dataset underlying the publication by Chamilos and colleagues. Communication with Dr. Kontoyiannis revealed that the data were not immediately available. However, we do note that patient mortality appears to approach 100% (Figure 3A) as treatment is delayed. A re-analysis of these data using a later cut-off point may provide a stronger basis of comparison for the effect of Isavuconazole treatment (in the hematologic malignancy sub-group) versus no treatment at all.

Please let me know if you have questions.

Please let me know when you expect to respond.

Please confirm receipt of this email.

Thank you,

Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882

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/s/

ALISON K RODGERS
10/20/2014



NDA 207500 and 207501

INFORMATION REQUEST

Astellas Pharma US Inc.
c/o Astellas Pharma Global Development, Inc.
Attention: Robert M. Reed, Senior Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Mr. Reed:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

NDA #	Drug Product
207500	Cresemba (isavuconazonium sulfate) Capsules, (b) (4)
207501	Cresemba (isavuconazonium sulfate) Powder for Injection, (b) (4)

We are reviewing the CMC section of your submissions and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDAs.

Drug Substance:

- Please submit a list of CAS registry numbers for all materials (other than reagents and solvents) used to manufacture the starting materials as well as for the starting materials themselves. (Section 3.2.S.2.2)*
- There is no description of* (b) (4)
(Section 3.2.S.2.2)
- Critical Process Parameters:* (b) (4)
(Section 3.2.S.2.4)

*For more information, please also refer to the FDA guidance entitled *Guideline for the Submission of Documentation for* (b) (4) *Process Validation in Applications for Human and Veterinary Drug Products.**

Drug Product – Capsules:

- 15. Please include in section 3.2.P.3.4 of the NDA the in-process controls/tests shown in the master batch record, which have established numerical acceptance criteria and are performed during the isavuconazonium sulfate capsules manufacturing process.*

If you have any questions, please contact Navdeep Bhandari, Regulatory Project Manager, at (240) 402-3815.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, PhD
Branch Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

From: [Reed, Robert](#)
To: [Rodgers, Alison](#)
Subject: RE: Cresemba Mid-Cycle Communication
Date: Friday, October 10, 2014 9:44:23 AM

Thank you Alison. Just for clarification, the teleconference is at 11:00 am Eastern, correct?

From: Rodgers, Alison [mailto:Alison.Rodgers@fda.hhs.gov]
Sent: Friday, October 10, 2014 7:38 AM
To: Reed, Robert
Subject: Cresemba Mid-Cycle Communication

Hi Robert,

Please see the following information requests that we plan to communicate during the Mid-Cycle Communication teleconference scheduled for next Wednesday, October 15, at 11:00 AM.

- As communicated in the information request dated 10/08/2014 for the mucormycosis indication, the review team is requesting any additional information that you may have to support a comparison of the results of the isavuconazonium-treated patients to results in a historical control of untreated patients.
- Given the two year break in patient enrollment during the conduct of Study 9766-CL-104, we conducted a subgroup analysis by time of enrollment (prior to or after the March 2011 restart) and found numerical differences in the response rates for all-cause mortality at Day 42 and the Data Review Committee (DRC)-assessed overall response at End of Treatment (EOT) by enrollment period. The outcomes are less favorable for those enrolled after the restart of the study and, for all-cause mortality at Day 42, there is a difference in the direction of the treatment effect depending on the enrollment period. We recommend that you investigate this as well and determine if there might be any explanations for these numerical differences.
- A Chemistry, Manufacturing, and Controls Information Request is being prepared and will be sent separately. The CMC IR is related to the drug substance manufacturing process and controls, and the filter use recommendations for the IV drug product.

Please let me know if you have questions.

Please confirm receipt of this email.

Also, could you please send a call-in number for the teleconference.

Thank you so much,

Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882

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/s/

ALISON K RODGERS
10/10/2014

Rodgers, Alison

From: Reed, Robert <Robert.Reed@astellas.com>
Sent: Wednesday, October 08, 2014 1:37 PM
To: Rodgers, Alison
Subject: RE: Cresemba NDAs - Clinical Information Request

Thank you Alison!

From: Rodgers, Alison [<mailto:Alison.Rodgers@fda.hhs.gov>]
Sent: Wednesday, October 08, 2014 12:36 PM
To: Reed, Robert
Subject: Cresemba NDAs - Clinical Information Request
Importance: High

Hi Robert,

Please see the attached request for clinical information regarding the Cresemba NDAs.

Please respond by Wed., 10/15/14.

Please confirm receipt of this email.

Thank you,

Alison

*Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882*

Clinical Review Comments:

For the mucormycosis indication, the Fungiscope matched case analysis provides limited evidence of isavuconazole efficacy relative to amphotericin B because of the wide confidence margins and the absence of an agreed upon non-inferiority margin. We have therefore concentrated on the benefit of isavuconazole relative to no treatment at all. We do note your literature review provided in Module 5, which was carefully reviewed.

The paper by Roden and colleagues¹ indicated an overall mortality rate of 97% for cases that were not treated, but many of the cases were identified post-mortem. We contacted the authors to ascertain the number of patients who were diagnosed with mucormycosis prior to death. There were 241 patients who received no treatment. Of these, 8 survived. Of the 233 patients that died, 18 were diagnosed pre mortem and 215 were diagnosed post mortem. Moreover, details regarding the underlying medical condition of these specific patients are not discernable from the available information.

The closest publication that we could identify that approximates a natural history study was from Dimitrios Kontoyiannis' group², who looked at the effect of delaying antifungal therapy in a population with hematologic malignancy. We recognize that this represents a delay of treatment of at least 6 days, and not the absence of treatment.

We next reviewed the study by Skiada and colleagues³, which reported mortality in 21 of 22 (95%) patients who did not receive treatment. Later within this paper, it is stated that a total of 24 patients received no treatment: 10 were diagnosed post-mortem and 14 were diagnosed during the last 24 hours prior to death. This study therefore offers limited evidence for an estimate of mortality in the absence of treatment.

Combined with nonclinical data, these data will likely be a subject of discussion at the advisory committee. We would like your analysis and commentary on these studies, as well as any additional studies, case reports, or other data that you believe would demonstrate a clinical benefit of isavuconazole in comparison to no treatment at all.

¹ Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, et al. "Epidemiology and outcome of zygomycosis: a review of 929 reported cases." *Clin Infect Dis*. 2005;41:634-53.

² Chamilos G, Lewis RE, Kontoyiannis DP. "Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis." *Clin Infect Dis*. 2008 Aug 15;47(4):503-9.

³ Skiada A, Pagano L, Groll A, Zimmerli S, Dupont B, Lagrou K, Lass-Flörl C, Bouza E, Klimko N, Gaustad P, Richardson M, Hamal P, Akova M, Meis JF, Rodriguez-Tudela JL, Roilides E, Mitrousia-Ziouva A, Petrikos G; European Confederation of Medical Mycology Working Group on Zygomycosis. "Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007." *Clin Microbiol Infect*. 2011 Dec;17(12):1859-67.

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/s/

ALISON K RODGERS
10/09/2014

From: [Reed, Robert](#)
To: [Rodgers, Alison](#)
Subject: RE: Cresemba NDAs Information Request
Date: Thursday, September 25, 2014 3:25:41 PM

Thank you Alison.

From: Rodgers, Alison [mailto:Alison.Rodgers@fda.hhs.gov]
Sent: Thursday, September 25, 2014 2:18 PM
To: Reed, Robert
Subject: Cresemba NDAs Information Request
Importance: High

Hi Robert,

Please see the question below:

Two columns in Tables 6 and 7 (pages 76-77) of the clinical pharmacology summary report include either PD Target EI90 or PD Target EI50. Please clarify what EI represents.

Please respond as soon as possible.

Please confirm receipt of this email.

Thank you,

Alison

*Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882*

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/s/

ALISON K RODGERS
09/25/2014

From: [Reed, Robert](#)
To: [Rodgers, Alison](#)
Subject: RE: Cresemba NDAs - Request for Information
Date: Thursday, September 25, 2014 3:47:13 PM

Thank you Alison!

From: Rodgers, Alison [mailto:Alison.Rodgers@fda.hhs.gov]
Sent: Thursday, September 25, 2014 2:46 PM
To: Reed, Robert
Subject: Cresemba NDAs - Request for Information

Hi Robert,

Here is another request for information. Sorry I did not send the two together.

With reference to the submitted NDA material, please provide the following:
Please submit the relevant PK simulation/analysis codes and model input and output datasets so that the reviewer can reproduce the results in Tables 6 and 7 (pages 76-77) of the clinical pharmacology summary report.
We request this information to be submitted by September 30, 2014. "

Please confirm receipt of this email.

Thank you,

Alison

*Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882*

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/s/

ALISON K RODGERS

09/25/2014

From: [Reed, Robert](#)
To: [Rodgers, Alison](#)
Subject: Re: Cresemba NDAs - Filing Letters
Date: Wednesday, September 17, 2014 9:05:15 AM

Thank you Alison!

On Sep 17, 2014, at 7:50 AM, "Rodgers, Alison"
<Alison.Rodgers@fda.hhs.gov<<mailto:Alison.Rodgers@fda.hhs.gov>>> wrote:

Hi Robert,

Please find attached courtesy copies of our "No Filing Review Issues Identified" letters for the Cresemba NDAs. You should receive hard copies in the mail soon.

Please let me know if you have questions.

Please confirm receipt of this email.

Thank you,

Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882

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/s/

ALISON K RODGERS
09/17/2014



NDA 207500

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Astellas Pharma US Inc.
Attention: Robert M. Reed
Senior Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Mr. Reed:

Please refer to your New Drug Application (NDA) dated July 8, 2014, received July 8, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Cresemba (isavuconazonium sulfate) Capsules, ^{(b) (4)} mg.

This application is subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V, refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>. Therefore, the user fee goal date is March 8, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 10, 2014. In addition, the planned date for our internal mid-cycle review meeting is October 3, 2014. We are currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you respond to the following requests for information by September 26, 2014:

Biopharmaceutics

1. We could not locate in your NDA submission the complete dissolution profile data for the clinical and registration batches of your drug product. Please provide the data collected at

15, 20, 30, 45, 60, 75 and 90 minutes for the clinical and registration batches (i.e., individual, mean, SD, profiles; n=12); or if submitted, indicate where these data are located.

2. To support the bridging between the clinical and commercial drug products, provide the dissolution profile comparison data (n=12) with the statistical testing comparing the profiles for the clinical and commercial batches using the proposed dissolution method.

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

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. All headings in Highlights must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column). 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.

2. White space should be present before each major heading in Highlights.

Comment: White space is missing before “Dosage Forms and Strengths,” “Contraindications,” and “Drug Interactions.”

3. Each summarized statement or topic in Highlights 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.

4. Initial U.S. Approval in Highlights 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 included as a place holder.

5. The Patient Counseling Information statement should include the following verbatim statement: “*See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.*”

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug has orphan drug designation for the proposed indications, you are exempt from this requirement.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUMATHI NAMBIAR
09/16/2014



NDA 207501

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Astellas Pharma US Inc.
Attention: Robert M. Reed
Senior Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Mr. Reed:

Please refer to your New Drug Application (NDA) dated July 8, 2014, received July 8, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Cresemba (isavuconazonium sulfate) Powder for Injection.

This application is subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V, refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>. Therefore, the user fee goal date is March 8, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 10, 2014. In addition, the planned date for our internal mid-cycle review meeting is October 3, 2014. We are currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you respond to the following requests for information by September 26, 2014:

Clinical

1. The patient profiles for study 9766-CL-0103 were noted in section 5.3.5.2, and selected narratives were provided as an appendix in the main study report. Please provide narratives for all 37 patients in the zygomycosis sub-group.

Division of Medication Error Prevention and Analysis

2. We note that your product will form visible particulates after dilution, and you propose administering the product through an infusion set with an in-line filter. Given the complexity of the use of your product along with the uncommon use of a product for infusion with visible particulates, we request that you submit your use-related risk analysis which includes comprehensive evaluation of the steps involved in preparing and administering your product (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform (e.g., do not use an in-line filter or use the wrong size filter), the potential negative clinical consequences of use errors and task failures, and the risk-mitigation strategies you plan to employ to reduce any moderate or high risks to acceptable levels (e.g., communication/education plan, label and labeling interventions, etc.). We need this information to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable (i.e., not easily reduced further and outweighed by the benefits of the product).

Chemistry, Manufacturing, and Controls

3. Provide samples of lyophilized (b) (4) WFI diluent, syringe, and IV infusion bag (either saline or D5W) with in-line filters with different pore sizes.
4. In the proposed labeling, you proposed that: “(b) (4) *must be administered*
(b) (4) *an infusion set with an in-line filter* (b) (4) *pore size of 0.2*
µm to 1.2 µm. (b) (4)

Do not administer as an IV bolus injection.” However, we note that all studies were performed using a filter pore size of 1.2 µm only. Thus, conduct a study using a filter with pore size of 0.2 µm (the worst case) to assess if an infusion flow rate comparable to that seen with a filter with pore size of 1.2 µm is maintained prior to and post filtration.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review

resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. All headings in Highlights must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column). 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.

2. White space should be present before each major heading in Highlights.

Comment: White space is missing before “Dosage Forms and Strengths,” “Contraindications,” and “Drug Interactions.”

3. Each summarized statement or topic in Highlights 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.

4. Initial U.S. Approval in Highlights 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 included as a place holder.

5. The Patient Counseling Information statement should include the following verbatim statement: “*See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.*”

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug has orphan drug designation for the proposed indications, you are exempt from this requirement.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUMATHI NAMBIAR
09/16/2014

Rodgers, Alison

From: Rodgers, Alison
Sent: Friday, September 12, 2014 3:52 PM
To: Reed, Robert (Robert.Reed@astellas.com)
Subject: Cresemba NDAs - Microbiology Information Request
Attachments: Isavuconazole Summary Table template.docx

Hi Robert,

Please see the attached request for Microbiology information regarding the Cresemba NDAs. Please respond by Monday, September 22, 2014 if at all possible.

Please let me know if you have questions.

Please confirm receipt of this email.

Thank you,

Alison

*Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882*

1. Please provide a Table summarizing MICs data for different antifungal drugs by fungal species for all baseline pathogens tested as shown in Table 1.

Table 1: MIC₉₀ (Range) of baseline clinical isolates from patients enrolled in Study 9766-CL-0104 and Study 9766-CL-0103 by the CLSI and EUCAST method

Organism	MIC ₉₀ (Range) of baseline clinical isolates (µg/mL)				
	Isavuconazole	Voriconazole	Posaconazole	Caspofungin	Amphotericin B
CLSI method					
<i>Aspergillus</i> species					
<i>A. fumigatus</i>					
<i>A. flavus</i>					
<i>A. niger</i>					
EUCAST method					
<i>Aspergillus</i> species					
<i>A. fumigatus</i>					
<i>A. flavus</i>					
<i>A. niger</i>					

Comment [SB1]: List all species

Comment [SB2]: List all species

2. Please provide tables summarizing clinical and mycological response by fungal species at different visits as shown in Tables 2 and 3; a separate Table should be created for each of the study.
3. Please provide a table summarizing clinical and mycological response by isavuconazole MIC against different *Aspergillus* and *Mucor* species as shown in Table 4; a separate Table should be created for each of the study.

Table 2: Study ISN 9766-CL-0104 – clinical and mycological response by baseline pathogen

Baseline Pathogen (N)*	Day 42						Day 84					
	Isavuconazole			Voriconazole			Isavuconazole			Voriconazole		
	All cause mortality [% (n)]	Clinical Response [% (n)]	Mycological Response [% (n)]	All cause mortality [% (n)]	Clinical Response [% (n)]	Mycological Response [% (n)]	All cause mortality [% (n)]	Clinical Response [% (n)]	Mycological Response [% (n)]	All cause mortality [% (n)]	Clinical Response [% (n)]	Mycological Response [% (n)]
mITT-FDA												
<i>A. fumigatus</i> (N)												
<i>A. flavus</i> (N)												
<i>A. terreus</i> (N)												
<i>A. niger</i> (N)												
<i>A. nidulans</i> (N)												
<i>A. ustus</i> (N)												
<i>A. westerdijkiae</i> (N)												
<i>Rhizopus oryzae</i> (N)												
Mixed infections												
<i>A. fumigatus</i> + <i>A. flavus</i> (N)												
PPS-FDA												
<i>A. fumigatus</i> (N)												
<i>A. flavus</i> (N)												
<i>A. terreus</i> (N)												
<i>A. niger</i> (N)												
<i>A. ustus</i> (N)												
<i>A. nidulans</i> (N)												
<i>A. ustus</i> (N)												
<i>A. westerdijkiae</i> (N)												
<i>Rhizopus oryzae</i> (N)												
Mixed infections												
<i>A. fumigatus</i> + <i>A. flavus</i> (N)												

Comment [SB3]: List all the species
Patients with mixed infections should be shown separately

Comment [SB4]: List all the species
Patients with mixed infections should be shown separately

*Number of patients

Table 3: Study ISN 9766-CL-0103 – clinical and mycological response by baseline pathogen

Baseline Pathogen (N)*	All cause mortality [% (n)]	Day 42		All cause mortality [% (n)]	Clinical Response [% (n)]	Day 84 Mycological Response [% (n)]
		Clinical Response [% (n)]	Mycological Response [% (n)]			
mITT-FDA						
<i>A. fumigatus</i> (N)						
<i>A. flavus</i> (N)						
<i>A. terreus</i> (N)						
<i>A. niger</i> (N)						
<i>A. nidulans</i> (N)						
<i>A. ustus</i> (N)						
<i>A. westerdijkiae</i> (N)						
<i>Rhizopus oryzae</i> (N)						
Mixed infections						
<i>A. fumigatus</i> + <i>A. flavus</i> (N)						
PPS-FDA						
<i>A. fumigatus</i> (N)						
<i>A. flavus</i> (N)						
<i>A. terreus</i> (N)						
<i>A. niger</i> (N)						
<i>A. ustus</i> (N)						
<i>A. nidulans</i> (N)						
<i>A. ustus</i> (N)						
<i>A. westerdijkiae</i> (N)						
<i>Rhizopus oryzae</i> (N)						
Mixed infections						
<i>A. fumigatus</i> + <i>A. flavus</i> (N)						

Comment [SB5]: List all the species
Patients with mixed infections should be shown separately

Comment [SB6]: List all the species
Patients with mixed infections should be shown separately

* Number of patients

Table 4: All-cause mortality, clinical and mycological response by isavuconazole MICs for *Aspergillus* and *Mucor* species

Pathogen	MIC ≤1 µg/mL			MIC 2 µg/mL			MIC ≥4 µg/mL		
	All-cause mortality n/N (%)	Clinical success n/N (%)	Mycological eradication n/N (%)	All-cause mortality n/N (%)	Clinical success n/N (%)	Mycological eradication n/N (%)	All-cause mortality n/N (%)	Clinical success n/N (%)	Mycological eradication n/N (%)
<i>A. flavus</i>									
<i>A. fumigatus</i>									
<i>A. nidulans</i>									
<i>A. niger</i>									
<i>A. westerdijkiae</i>									
<i>Aspergillus</i> species									

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/s/

ALISON K RODGERS
09/15/2014



NDA 207500

PRIORITY REVIEW DESIGNATION

Astellas Pharma US Inc.
c/o Astellas Pharma Global Development, Inc.
Attention: Robert M. Reed
Senior Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Mr. Reed:

Please refer to your New Drug Application (NDA) dated July 8, 2014, received July 8, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Cresemba (isavuconazonium sulfate) Capsules.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is March 8, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 10, 2014.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before September 20, 2014.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUMATHI NAMBIAR
09/02/2014



NDA 207501

PRIORITY REVIEW DESIGNATION

Astellas Pharma US Inc.
c/o Astellas Pharma Global Development, Inc.
Attention: Robert M. Reed
Senior Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Mr. Reed:

Please refer to your New Drug Application (NDA) dated July 8, 2014, received July 8, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Cresemba (isavuconazonium sulfate) Powder for Injection.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is March 8, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 10, 2014.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before September 20, 2014.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUMATHI NAMBIAR
09/02/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207501
NDA 207500

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Astellas Pharma Global Development, Inc.
1 Astellas Way
Northbrook, IL 60062

ATTENTION: Robert M. Reed
Senior Director, Regulatory Affairs

Dear Mr. Reed:

Please refer to your New Drug Application (NDA) dated and received, July 8, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Isavuconazonium Sulfate Capsules, (b) (4) mg, and Isavuconazonium Sulfate for Injection, (b) (4) mg per vial.

We also refer to your correspondence, dated and received, July 29, 2014, requesting review of your proposed proprietary name, Cresemba. We have completed our review of the proposed proprietary name, Cresemba, and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your July 29, 2014 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application, contact Alison Rodgers, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
08/28/2014

From: Rodgers, Alison
To: [Reed, Robert \(Robert.Reed@astellas.com\)](mailto:Robert.Reed@astellas.com)
Cc: [Jarzabek, Jeanne \(Jeanne.Jarzabek@astellas.com\)](mailto:Jeanne.Jarzabek@astellas.com)
Subject: FW: NDAs 207500 and 207501 - Request for Information
Date: Wednesday, July 16, 2014 4:33:00 PM
Importance: High

Hi Robert,

Regarding the question below, please note that the question is specific to BIMO clinsite.xpt dataset for Study WSACS003.

Sorry I did not send that clarification earlier.

Thank you,

Alison

*Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882*

From: Rodgers, Alison
Sent: Wednesday, July 16, 2014 3:17 PM
To: Reed, Robert (Robert.Reed@astellas.com)
Cc: Jarzabek, Jeanne (Jeanne.Jarzabek@astellas.com)
Subject: NDAs 207500 and 207501 - Request for Information
Importance: High

Hi Robert,

Please see the following IR regarding the data submitted for the isavuconazole NDAs:

“Please confirm whether TRTEFFE is reported as % subjects that survived or died.”

Please respond by tomorrow if at all possible.

Please confirm receipt of this email.

Thank you,

Alison

*Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882*

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/s/

ALISON K RODGERS
07/18/2014



NDA 207500

NDA ACKNOWLEDGMENT

Astellas Pharma US Inc.
c/o Astellas Pharma Global Development, Inc.
Attention: Robert M. Reed
Senior Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Mr. Reed:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Cresemba (isavuconazonium sulfate) Capsules, (b) (4) mg

Date of Application: July 8, 2014

Date of Receipt: July 8, 2014

Our Reference Number: NDA 207500

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 6, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Alison Rodgers, Senior Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Maureen P. Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAUREEN P DILLON PARKER
07/16/2014



NDA 207501

NDA ACKNOWLEDGMENT

Astellas Pharma US Inc.
c/o Astellas Pharma Global Development, Inc.
Attention: Robert M. Reed
Senior Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Mr. Reed:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Cresemba (isavuconazonium sulfate) Powder for Injection, (b) (4) mg

Date of Application: July 8, 2014

Date of Receipt: July 8, 2014

Our Reference Number: NDA 207501

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 6, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to NDA 207501 submitted on July 8, 2014, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Alison Rodgers, Senior Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Maureen P. Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAUREEN P DILLON PARKER
07/16/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 072593
IND 119307

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Astellas Pharma Global Development, Inc.
1 Astellas Way
Northbrook, IL 60062

ATTENTION: Robert M. Reed
Senior Director, Regulatory Affairs

Dear Mr. Reed:

Please refer to your Investigational New Drug Applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Isavuconazonium Sulfate Capsules, (b) (4) mg, and Isavuconazonium Sulfate for Injection, (b) (4) mg per vial.

We also refer to your December 11, 2013, correspondence, received December 12, 2013, requesting review of your proposed proprietary name, Cresemba.

We have completed our review of the proposed proprietary name, Cresemba, and have concluded that it is acceptable.

A request for proprietary name review for Cresemba should be submitted once the NDA is submitted.

If any of the proposed product characteristics as stated in your December 11, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application, contact Alison Rodgers, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0797.

Sincerely,
{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
05/12/2014



IND 72593
IND 119307

MEETING MINUTES

Astellas Pharma Global Development, Inc.
Attention: Robert Reed
Senior Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Mr. Reed:

Please refer to your Investigational New Drug Applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Isavuconazonium Sulfate (BAL8557) I.V. (IND 72,593) and Oral Capsules (IND 119,307).

We also refer to the meeting between representatives of your firm and the FDA on November 5, 2013. The purpose of the meeting was to discuss the details of the NDA submissions for isavuconazonium I.V. and Oral Capsules for the treatment of patients with invasive aspergillosis or invasive mucormycosis.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Katherine A. Laessig, MD
Deputy Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: November 5, 2013, 4:00 – 5:00 PM
Meeting Location: 20903 New Hampshire Avenue, Silver Spring, MD 20903, Building 22, Room 1415

Application Numbers: IND 72593 and 119307
Product Name: Isavuconazonium Sulfate Intravenous (IND 72593)
Isavuconazonium Sulfate Oral Capsules (IND 119307)
Indication: Treatment of invasive aspergillosis and mucormycosis
Sponsor/Applicant Name: Astellas Pharma Global Development, Inc.

Meeting Chair: Sumathi Nambiar, MD, MPH
Meeting Recorder: Alison Rodgers

FDA ATTENDEES

Division of Anti-Infective Products

Sumathi Nambiar, MD, MPH, Acting Director
Katherine Laessig, MD, Deputy Director
John Alexander, MD, MPH, Clinical Team Leader
Shukal Bala, PhD, Clinical Microbiology Reviewer
Dakshina Chilukuri, PhD, Clinical Pharmacology Reviewer
Philip Colangelo, PharmD, PhD, Clinical Pharmacology Team Leader (by phone)
Mara Deitrick, PhD, Clinical Microbiologist
Maureen Dillon-Parker, Chief, Project Management Staff
Karen Higgins, ScD, Statistical Team Leader
Owen McMaster, PhD, Pharmacology and Toxicology Reviewer
Elizabeth O'Shaughnessy, MD, Medical Officer
Alison Rodgers, Regulatory Project Manager
Kerry Snow, MS, Clinical Microbiology Team Leader
Edward Weinstein, MD, PhD, Medical Officer

Office of Antimicrobial Products

Dave Roeder, MS, Associate Director for Regulatory Affairs

Office of Surveillance and Epidemiology

Mihaela Jason, Safety Evaluator, DPV

EASTERN RESEARCH GROUP ATTENDEES

Christopher Sese, Independent Assessor

SPONSOR ATTENDEES

Astellas Pharma Global Development, Inc. (Astellas)

Bernhardt Zeiher, MD, Senior Vice President, Therapeutic Area Head, Immunology and Infectious Diseases

Rochelle Maher, MS, Senior Director, Global Development Project Leader, Infectious Diseases

Christopher Lademacher, MD, PhD Senior Medical Director, Medical Science

Misun Lee, PhD, Associate Director, Biostatistics

Wenmei Huang, PhD, Senior Manager, Biostatistics

Robert Townsend, PhD, Associate Director, Clinical Pharmacology and Translational Science

Jeanne Jarzabek, BSN, MBA, Global Regulatory Leader

Robert Reed, Senior Director, Regulatory Affairs

Melinee Wilson, Associate Regulatory Submission Manager, Regulatory Affairs

Karsten Goedecke, PhD, Regulatory Affairs Manager and Project Manager, Basilea Pharmaceutical International, Ltd.

BACKGROUND

The IND for Isavuconazonium Sulfate Intravenous (IND 72593) was submitted on June 9, 2005 and 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.

On August 20, 2013, Astellas submitted a request for a Pre-NDA meeting. A briefing package was submitted on September 25, 2013. The Division provided responses to the briefing package questions on October 25, 2013 via email [copy appended for reference]. The meeting served to clarify the responses.

Astellas presented slides to aid the discussion [copy appended].

A Chemistry, Manufacturing, and Controls Pre-NDA meeting was held on October 29, 2013.

DISCUSSION

Astellas agreed to submit the Nonclinical Pharmacology/Toxicology sections to the IND prior to submission of the NDA.

Regarding Question 2, Astellas agreed with the Division's responses and stated that *in vitro* susceptibility data as well as the results of the quality control testing conducted at different laboratories using both the CLSI and EUCAST methods will be presented separately. Astellas also agreed to present galactomannan and culture results for clinical studies in the datasets.

Astellas discussed their plan for submission of microbiology datasets; the datasets will be submitted in two components, PK/PD and MIC. The PK/PD dataset will have a clinical outcome

correlation. Astellas also agreed to provide information on the correlation between MIC and clinical response and to provide a sample of the planned analysis datasets for review.

With regards to the galactomannan data, the Division stated that the analysis should be based on testing of two aliquots of one bronchoalveolar lavage sample with galactomannan index of ≥ 1.0 OR two consecutive serum samples with galactomannan index of ≥ 0.5 . The Division would also like to see galactomannan indices included in the datasets. Astellas noted that they will analyze the galactomannan data based on the cut-off proposed by the Division in addition to those cut-off values stated in the slides.

Questions 3 and 4: Astellas acknowledged the Division's responses to questions 3 and 4 and had no need for further discussion.

With regards to Question 5, Astellas does not agree that a formal drug interaction study of isavuconazonium with sensitive substrates of CYP2C8 is required as recommended by the Division. Astellas maintains that while they would expect some interaction with CYP2C8, it would be mild, so no dose adjustment would be required. Astellas will provide a justification for their position in the NDA submission.

The Division noted that Astellas had evaluated other CYP enzymes that were lower than CYP2C8 in the Drug-Drug Interaction potency list. Astellas explained that the probe substrates of CYP2C8 are oncology drugs (e.g., paclitaxel) and isavuconazonium is not used with oncology drugs since it is an antifungal. The Division noted that it is not uncommon that oncology patients are immunocompromised and are at risk of developing fungal infections while on anti-cancer drug therapy and may need anti-fungal drugs. The Division requested Astellas submit their justification for not conducting the drug interaction study with isavuconazonium and CYP2C8 prior to NDA submission. The Division also noted that a drug interaction study could become a required postmarketing study and suggested that Astellas has time to conduct the study prior to NDA submission. Astellas agreed to submit the justification prior to NDA submission.

The Division inquired about data for the *in vitro* testosterone and bupropion interaction studies. Astellas will provide *in vitro* study reports regarding the testosterone interaction and they will provide justification regarding bupropion prior to NDA submission. The Division may have questions regarding the data once received and reviewed.

Astellas acknowledged the Division's responses to questions 6, 7, and 8 and had no further questions.

To address Question 9, Astellas described their plan for patient narratives (slide 9) and asked if this addressed the Division's request for CRFs. The Division agreed that the proposed patient narratives would be acceptable. The Division asked if the start and end dates for concomitant medications were included in the datasets because this information is important in the assessment of safety. Astellas responded that start and end dates for concomitant medications were included in the datasets. Astellas asked for a follow-up clinical meeting to discuss individual mucormycosis cases due to the complexity of these cases. The Division agreed.

The Division stated that the request for a random sample of CRFs would not be necessary.

Regarding Question 10, Astellas stated that they were granted orphan designation for the mucormycosis indication, therefore, PREA will not apply to either indication in the proposed NDA.

Astellas agreed to provide supporting information on the natural history of mucormycosis from the scientific literature or other sources as per the Division's request in its response to question #11.

Astellas acknowledged the responses to questions 12, 13, and 14, and there was no need for further discussion.

Astellas presented its proposal for submitting two NDAs (see last slide). The Division will ask the Chemistry, Manufacturing, and Controls review team for confirmation that the plan for submission of module 3 is acceptable. Otherwise, the planned submission of the two NDAs is acceptable.

The Division discussed the need for a food effect study and for exploring the effect of altering the pH on the absorption of the oral capsule. Astellas commented that they have conducted a food effect study; however, they do not have information regarding the effect of altering the pH on the oral capsule. Astellas has not studied the effect of antacids on absorption of the capsule. The Division would prefer to see data from a clinical study, but Astellas could provide a justification for some other approach to evaluating these issues. Astellas agreed to submit a justification along with the CYP2C8 DDI information.

The Division noted that Astellas could submit their non-clinical microbiology studies prior to NDA submission if they are available.

Astellas will notify the Division regarding their timelines for submission of all of the items.

Astellas expects to submit the NDA in the first half of 2014. The exact timeline for submission cannot be confirmed until topline results of the mucormycosis study are available.

Per the October 29, 2013, CMC Pre-NDA meeting, Astellas has several issues to address, including providing a justification for the IV formulation and the particulate issue, and details regarding dissolution.

Astellas presented an overview of their topline results (see attached slides)

Astellas confirmed that the NDA submission will include the clinical sites inspection list as requested by the Division of Scientific Investigations.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The content of a complete application was discussed. FDA explained that it expected Astellas to submit a complete application on Day 1. If there are going to be any minor components that

would not be included with the initial submission, then an agreement needs to be reached on those during the meeting.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

A preliminary discussion on the need for a REMS was held and it was concluded that a REMS was not anticipated at the time of the meeting. The need for a REMS would be determined during review of the application.

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. Astellas stated that they intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product has orphan drug designation for these indications, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements of Prescribing Information website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents, and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues for further discussion.

ACTION ITEMS

Astellas will:

- submit the Nonclinical Pharmacology/Toxicology sections to the IND prior to submission of the NDA.
- provide sample datasets.
- submit a justification for not conducting a drug interaction study with isavuconazonium and CYP2C8.
- provide justification prior to NDA submission for potential testosterone and bupropion interactions.
- provide end dates for concurrent medications in the patient narratives.

- provide supporting information on the natural history of mucormycosis from the scientific literature or other sources as per the Division's request in its response to question #11.
- provide an analysis of the risk of alterations in gastric pH.
- notify the Division regarding their timelines for submission of all of the items.

Division will:

- Confirm with the Chemistry, Manufacturing, and Controls review team that the plan for submission of module 3 is acceptable.

ATTACHMENTS

-Slides

-Division responses to the briefing package questions, communication October 25, 2013

SPONSOR'S ORIGINAL QUESTIONS AND DIVISION'S RESPONSES

2.1 Quality (Chemistry, Manufacturing and Controls)

This briefing document does not include information regarding Quality/Chemistry, Manufacturing and Controls (CMC) for isavuconazonium.

2.2 Nonclinical Pharmacology, Pharmacokinetics and Toxicology

Question 1: Nonclinical Development Program

Astellas believes that the results of the nonclinical studies conducted to date with isavuconazonium, isavuconazole (BAL8415), and the inactive cleavage product (BAL8728) as outlined in the briefing document [Section 6], are adequate to support the submission of an NDA for isavuconazonium.

Does the Agency agree that the nonclinical data are sufficient to support the proposed NDA?

Response: Yes, the nonclinical data are adequate to support the submission of an NDA for isavuconazonium.

Does the Agency have any comments on the proposed nonclinical data presentation in the NDA?

Response: Please submit the available Nonclinical Pharmacology/Toxicology sections all together in electronic format to the IND as soon as possible.

2.3 Clinical Microbiology

Question 2: Clinical Microbiology: Microbiology Report and Datasets

A list and description of the microbiology studies conducted with isavuconazonium and the active moiety, isavuconazole, is provided in [Attachment 1] including both in vitro studies and in vivo studies.

A summary of microbiology information for isavuconazonium will be provided in a Microbiology Report in Module 5 of the proposed NDA and will include the following: in vivo efficacy, in vitro spectrum of antifungal activity, mode of action, mechanism of resistance, cross-

resistance within and among antifungal classes, in vitro interaction studies with other antifungal classes, the potential for the development of drug resistance, the PK/PD relationship and the results of antifungal susceptibility testing of fungal isolates from Studies WSA-CS-003/9766-CL-0103 and WSA-CS-004/9766-CL-0104. The table of contents of the Microbiology Report is provided in [Attachment 3]. A brief overview of the microbiology report for isavuconazonium is provided in [Section 7].

In addition to the data summaries in the Microbiology Report, 2 datasets will be provided in accordance with FDA Draft Guidance for Industry, Microbiological Data for Systemic Antibacterial Drug Products

Development, An

2009). The first microbiology dataset will include all of the available in vitro susceptibility testing results from various nonclinical studies conducted over the course of isavuconazonium development. The second microbiology dataset will include the clinical fungal isolate susceptibility data from Studies WSA-CS-003/9766-CL-0103 and WSA-CS-004/9766-CL-0104 and will house the pharmacokinetic/pharmacodynamic (PK/PD) data and the corresponding clinical outcome data by patient. This dataset will be the same dataset used for the PK/PD analysis.

Astellas is of the opinion that the microbiological activity of isavuconazole as described in Sections 6.1.3 (in vitro) and 6.1.4 (in vivo) has been assessed in sufficient detail and that the presentation of the microbiological data is according to ICH and FDA guidelines. Does the Agency have any comments regarding the presentation of the microbiology data?

Response: Your overall proposal for presentation of microbiology data is appropriate. The following information should be included in the NDA submission:

- *The results of in vitro susceptibility testing as well as the quality control testing in different laboratories by the CLSI and EUCAST methods should be presented separately.*
- *We encourage you to share the sham analyses datasets especially for Studies WSA-CS-003/9766-CL-0103 and WSA-CS-004/9766-CL-0104 that will allow analysis by MIC and clinical response for individual patients.*
- *The galactomannan testing (qualitative and quantitative findings in serum and/or bronchoalveolar lavage fluid) as well as culture results (such specimen source and species identified), for patients enrolled in Studies WSA-CS-003/9766-CL-0103 and WSA-CS-004/9766-CL-0104 should be included in the datasets.*

Question 3: Clinical Microbiology: Interpretive Breakpoints

Astellas plans to propose interpretive breakpoints for *Aspergillus* spp. in the NDA submission. The interpretive breakpoints will be estimated based on an assessment of the following data:

- Epidemiologic Cut-off values (ECOFFs) for *Aspergillus* spp.
- Pharmacodynamic targets from two in vivo PK/PD studies and one ex vivo dynamic model
 - Disseminated IA, non-neutropenic murine model
 - Invasive pulmonary aspergillosis (IPA), neutropenic murine model
 - Dynamic model of IPA
- Utilizing pharmacodynamic targets from in vivo models, Monte Carlo simulations will be conducted to assess the probability of target attainment at a range of the minimum inhibitory concentration (MIC) values

- An exposure-response analysis will be completed with efficacy and trough concentration data from the phase 3 study in IA. Additionally, using the population pharmacokinetic model, predicted AUCs will be calculated by patient and exposure-response analysis will be conducted with these values.

Does the Agency agree with or have any comments regarding the proposed method for clinical interpretive breakpoint determination?

Response: It appears that you propose to establish interpretive criteria/breakpoints for Aspergillus species based on epidemiologic cut-off values, PK/PD studies in animals including Monte Carlo simulations, and exposure-response analysis based on the results of the two clinical trials (Studies WSA-CS-003/9766-CL-0103 and WSA-CS-004/9766-CL-0104). We agree that these are important parameters to evaluate for determining interpretive criteria/breakpoints. The acceptability of the breakpoints will be determined at the time of the NDA review. However, we think that analysis of MIC data by clinical response data collected from the two clinical trials will also be an important consideration in establishing interpretive criteria/breakpoints.

2.4 Clinical Pharmacology and Pharmacokinetics

Question 4: Bioavailability and Food Effect Studies

Astellas believes that the oral bioavailability of 98% (as isavuconazole) and no evidence of a food effect with orally administered isavuconazonium allows patients to use the intravenous and oral formulations interchangeably. Tabular summaries of these studies are provided in [Attachment 8, Module 2.7.2, Appendix Tables 2.1 and 2.3].

Does the Agency agree that the 98% oral bioavailability and lack of food effect support the interchangeability of dosing as proposed in the isavuconazonium label?

Response: The interchangeability of the oral and IV formulations will be determined at the time of the NDA review.

Question 5: Clinical Pharmacology

The clinical pharmacology summary of isavuconazonium includes 16 in vitro and ex vivo studies that were conducted with human biomaterials relevant to pharmacokinetic processes, and clinical pharmacokinetic studies of absorption, distribution, metabolism and excretion of isavuconazonium, the active moiety isavuconazole (BAL4815) and the inactive cleavage product (BAL8728) in healthy volunteers and special populations.

The isavuconazonium phase 1 clinical program also includes 32 completed and 6 ongoing biopharmaceutic and pharmacokinetic studies. These studies evaluated isavuconazole bioavailability, food-effect, single- and multiple-dose pharmacokinetics, pharmacokinetics in subjects with hepatic impairment, pharmacokinetics in subjects with renal impairment, pharmacokinetics in Chinese subjects, age/gender, thorough QT, mass balance (both isavuconazole and the inactive cleavage product, BAL8728), and the potential for drug interactions following administration of isavuconazonium.

A summary of Clinical Pharmacology Highlights was submitted to the Agency on September 15, 2011. Following communications with the Agency, Astellas has conducted a thorough QT study (9766-CL-0017).

Astellas believes that the results of the clinical biopharmaceutic and pharmacokinetic studies conducted to date, as outlined in [Sections 8.1.1 (biopharmaceutics), 8.1.2 (pharmacokinetics), 8.1.3 (hepatic impairment), and 8.1.4 (drug-drug interaction [DDI])], in addition to the ongoing studies described in Section 8.2.3, are sufficient for labeling purposes and adequate to support the submission of an NDA for isavuconazonium.

A list of clinical studies with isavuconazonium including key design features is provided in [Attachment 9, Module 5.2]. Tabular summaries of the results of phase 1 studies are provided in [Attachment 8, Module 2.7.1 Appendix Table 2 (bioavailability [BA] and food effect [FE]) and Module 2.7.2 Appendix Tables 1 (human biomaterials), 2 (single ascending dose [SAD], multiple ascending dose [MAD] and QT), 3 (intrinsic factors), 4 (DDI), 5 (PD) and 6 (safety results)].

The effect of age, gender, race (Chinese and Western subjects), and hepatic impairment on the pharmacokinetics of isavuconazonium will be assessed in population pharmacokinetic analyses.

Does the Agency agree that the clinical pharmacology program is sufficient to support the proposed NDA?

Does the Agency have any comments on the proposed data presentation?

Response: The clinical pharmacology program appears to be adequate to support the proposed NDA. However, the acceptability of the data generated in the NDA will be determined at the time of the review. Also, we note that your pre-NDA package indicates that isavuconazonium is an inhibitor of CYP2C8. Please clarify your plans to characterize the in vivo drug interaction potential of isavuconazonium with sensitive substrates of CYP2C8. Given the complex nature of potential drug interactions for isavuconazonium, we recommend that you consult the FDA Guidance for Industry entitled “Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations” to determine the need to conduct in vivo DDI studies.

2.5 Clinical Development

Question 6: Proposed Package Insert

Astellas proposes to submit an NDA for the following indications:

- Treatment of adult patients with IA
- Treatment of adult patients with invasive mucormycosis

Astellas intends to propose dosing recommendations based on the clinical dosing regimen in the phase 3 studies. Dosing of isavuconazonium is expressed as (b) (4)

(b) (4)

Switching between the oral and intravenous formulations is acceptable as bioequivalence has been demonstrated.

Further details of the draft labeling language regarding the indication(s), dosage forms and strengths, product description, instructions for use, and packaging of isavuconazonium are provided in [Attachment 6].

Does the Agency have any comments on the proposed labeling?

Response: The proposed labeling appears to follow the Physician Labeling Rule (PLR) format. The intended indications for the treatment of invasive aspergillosis and invasive mucormycosis are noted. Specific comments regarding labeling will be provided during review of the new drug application.

Question 7: Integrated Summary of Efficacy

Astellas proposes to provide a Summary of Clinical Efficacy for each of the proposed indications (IA and invasive mucormycosis). Primary support for these indications will be provided based on the results of 2 phase 3 studies: a randomized, double-blind, active controlled (i.e., voriconazole) study of adult patients with IA (WSA-CS-004/9766-CL-0104) and an open-label, noncomparative study of isavuconazonium in adult patients with IA and renal impairment or in patients with IFD caused by rare fungi (WSA-CS-003/9766-CL-0103).

Astellas believes that the Summaries of Clinical Efficacy (i.e., Module 2.7.3 IA and Module 2.7.3 Invasive Mucormycosis) are adequate to support efficacy in these indications. Presentation of efficacy data will be based on data from each individual study.

Does the Agency agree to submission of a separate Summary of Clinical Efficacy for each indication (i.e., IA and invasive mucormycosis)?

Response: Yes, this is acceptable.

Does the Agency have any comments regarding the presentation of efficacy data from each individual study?

Response: The proposed SDTM and ADaM dataset formats are acceptable.

Question 8: Integrated Summary of Safety

Astellas is considering providing a single Summary of Clinical Safety with tables presenting additional supporting analyses in Module 5. A summary of the safety of isavuconazonium will be provided for the safety analysis set (SAF) defined as all subjects who received at least one dose of isavuconazonium or comparator by the following study groupings. A detailed description of the safety population groupings is provided in [Attachment 4, SAP Table 2].

- Phase 3 controlled study (Study WSA-CS-004/9766-CL-0104 only)
- Phase 2/3 studies
- Phase 1 studies

Safety will be evaluated in the safety population groupings described above at the 3 levels recommended by ICH E3, M4 and 21CFR§314.50 and associated guidance and guidelines:

- Extent of exposure
- Summary of adverse events
- Summary of changes in laboratory tests and ECG parameters

Listings will be provided for all deaths, treatment-emergent adverse events (TEAEs) leading to permanent discontinuation of study drug, and subjects with hepatotoxicity and nephrotoxicity. Astellas will provide all integrated adverse event tables in MedDRA version 12.1. The subgroup analysis will also be performed for the following factors, such as age, race, ethnicity, sex, BMI, geographical region, allogeneic bone marrow transplant status, uncontrolled malignancy status,

hematologic malignancy status, baseline neutropenic status, baseline renal status and treatment duration) for studies where this information was collected.

The assessment of hepatotoxicity will be evaluated based on laboratory parameters. The assessment of nephrotoxicity will be evaluated based on serum creatinine.

Study WSA-CS-008/9766-CL-0105 is currently ongoing and will not be completed by the time of the NDA submission. A listing of blinded serious adverse events (SAEs) from the Astellas Safety Database from Study WSA-CS-008 and from subjects enrolled in Study WSA-CS-003/9766-CL-0103 after January 25, 2013 will be provided in the NDA submission (SAE data cut-off September 1, 2013).

A list of the clinical studies to be provided in the NDA is available in [Attachment 9, Module 5.2]. Safety results from phase 1 clinical studies are summarized in [Attachment 8, Module 2.7.2, Appendix Table 6]. Safety results from the phase 2 clinical studies are summarized in [Section 8.2.2.6].

A draft SAP for the Summary of Clinical Safety (SCS) is provided in [Attachment 4]. A Data Plan describing the clinical datasets is available in [Attachment 2].

Is the approach described above acceptable to the Agency?

Response: The proposed approach is acceptable.

Does the Agency have any comments on the SCS SAP?

Response: The SCS SAP is acceptable.

Question 9: Patient Narratives

Given the morbidity of patients with IA and invasive mucormycosis in the clinical patient studies, it is expected that 65% to 90% of patients will experience an adverse event at some time during the study and the majority of patients will experience a serious adverse event.

[REDACTED] (b) (4)

Patient profiles will be provided in lieu of CRFs for all patients.

Does the Agency have any comments regarding the approach described above?

Response: [REDACTED] (b) (4) *if*
questions arise you should be prepared to provide specific CRFs upon request. [REDACTED] (b) (4)
[REDACTED] *submission of CRFs would expedite an efficient review.*
Please clarify what data will be presented [REDACTED] (b) (4)
forms. For the mucormycosis patient population, CRFs of all patients in addition to narratives are preferable due to the complexities of treatment in this patient population. Additionally, we are requesting submission of a sample of CRFs of patients from the controlled invasive aspergillosis study, Study WSA-CS-004 (9766-CL-0104). Please submit a listing of patient IDs and randomized treatment for Study WSA-CS-004 (9766-CL-0104) so that we can generate a

10% random sample and then provide you with the list of patients to provide CRFs for in the submission.

Question 10: Pediatric Labeling

The phase 2 and phase 3 studies of isavuconazonium were conducted in adult patients. Astellas has received ODD for isavuconazonium for the treatment of IA and, therefore, a pediatric study plan is not required. Astellas intends to submit a formal Request for Waiver of Pediatric Studies according to the FDA draft Guidance for Industry How to Comply with the Pediatric Research Equity Act (September 2005) for both indications.

Does the Agency have any comments?

Response: The ODD applies to the invasive aspergillosis indication. Consequently, the Pediatric Research Equity Act (PREA) applies only to the mucormycosis indication. For mucormycosis, if you wish to request a waiver from the requirements under PREA, then please submit a justification.

2.6 NDA Structure and Format/General Submission Issues

Question 11: Clinical Studies to be Provided in the NDA

Data from 38 phase 1 biopharmaceutic/pharmacokinetic studies (32 of which are now completed), 16 studies of human biomaterials, 2 phase 2 studies and 2 phase 3 studies will be provided in a single NDA submitted for isavuconazonium for the treatment of adult patients with IA and for the treatment of adult patients with invasive mucormycosis. A list of clinical studies and key study design features is provided in [Attachment 9, Module 5.2]. A draft table of contents for the eCTD is provided in [Attachment 5].

Isavuconazonium has been administered to 952 subjects in 32 completed phase 1 clinical studies. Twelve studies in healthy subjects have used the phase 3 dose of an initial isavuconazole loading dose of 600 mg per day (i.e., 200 mg q8h) for 2 days followed by 200 mg/day for at least 9 days (DDI studies: WSA-CP-011/9766-CL-0011, WSA-CP-012/9766-CL-0012, 9766-CL-0020, 9766-CL-0021, 9766-CL-0023, 9766-CL-0025, 9766-CL-0027, 9766-CL-0033, 9766-CL-0035, and 9766-CL-0044; QT study 9766-CL-0017; and an ongoing pharmacokinetic study in Chinese subjects 9766-CL-0038).

In the 2 completed phase 2 studies, 144 patients were administered isavuconazonium equivalent to isavuconazole doses ranging from 50 mg/day for 14 to 21 days to 400 mg/day for up to 28 days.

In phase 3 Study WSA-CS-004/9766-CL-0104, 527 patients were randomized in a 1:1 ratio to receive voriconazole or isavuconazonium for up to 84 days.

Isavuconazonium administration:

- Day 1 and 2: isavuconazole 200 mg tid (iv)
- Day 3 to EOT (up to 84 days): isavuconazole 200 mg/day (iv or po)

Voriconazole administration:

- Day 1: 6 mg/kg bid (iv)
- Day 2: 4 mg/kg bid (iv)
- Day 3 to EOT (up to 84 days): either 4 mg/kg bid (iv) or 200 mg bid (po)

Phase 3 Study WSA-CS-003/9766-CL-0103 is ongoing. Patient data planned for inclusion in the NDA from this study is based on a data freeze that coincided with the last patient out (March 2013) for Study WSA-CS-004/9766-CL-0104. Therefore, a data cut-off was set as March 2013

for Study WSA-CS-003 with data available from 133 patients, the last of whom had data up to the day 42 visit. Study WSA-CS-003 allowed variable treatment duration dependent on clinical conditions, therefore, data including all visits that occurred by March 8, 2013, will be presented in an interim study report in the NDA. Fourteen patients were allowed to receive extended therapy (> 180 days of isavuconazonium) in Country Specific Amendment 4 of the protocol, 7 of these 14 remain on treatment as of May 2013.

Astellas' intention is to provide adequate data from Study WSA-CS-003/9766-CL-0103 to support the indication for the treatment of invasive mucormycosis. Although the isolated pathogens are still being confirmed at the central laboratory, there are approximately 20 patients in this dataset who received isavuconazonium for primary treatment of mucormycosis. Since WSA-CS-003 is an open-label study, study outcomes for mucormycosis patients receiving primary therapy will be assessed in the context of an evaluation of the historical literature and also via case-matching from the [Fungiscope Global Rare Fungal Infection Registry database]. An additional approximately 20 patients received isavuconazonium for mucormycosis and were either refractory or intolerant to other therapies. This dataset also includes approximately 40 patients with IFD who had baseline renal impairment, defined as creatinine clearance < 50 mL/min, approximately half of which had IA or mucormycosis.

Safety data from the two phase 3 studies evaluating isavuconazonium for the treatment of IA and invasive mucormycosis will be provided in the NDA from approximately 667 patients who received at least one dose of study medication. Among these 667 patients, approximately 488 patients received at least 2 weeks of study medication and approximately 359 patients received at least 6 weeks of study medication.

Data from these studies will form the basis of the safety assessment of isavuconazonium for the NDA. Astellas believes that there is sufficient data and an adequate number of patients have been exposed to isavuconazonium to support review of an NDA for the treatment of IA and for the treatment of invasive mucormycosis.

Does the Agency agree that the clinical data are sufficient to support the proposed indications?

Does the Agency have any comments on the proposed data presentation?

Response: The data from the two phase 3 studies and the two phase 2 studies are sufficient to meet the requirements for filing a new drug application for both indications. The proposed data presentation is acceptable. Given the open label, single arm design of your WSA-CS-003 trial, please provide supporting information on the natural history of mucormycosis from the scientific literature or other sources. Please indicate whether you have pursued an orphan drug designation for mucormycosis.

Question 12: Datasets and Files for each Pivotal Study and for the Integrated Summary Database

For the Summary of Clinical Safety, the phase 2 and phase 3 studies will be integrated separately from the phase 1 studies. A list with key design features of the clinical phase 1, phase 2 and phase 3 studies to be included in the NDA is provided in [Attachment 9, Module 5.2]. Astellas plans to submit the integrated database used to generate the safety data presented in the NDA.

The datasets that will support the safety analyses for the phase 2 and phase 3 studies are listed in [Table 1]. Additional safety datasets may be provided if new information is obtained for a safety event.

Table 1 Datasets to Support the Safety Analyses for the Phase 2/3 Studies

Dataset	Dataset Description	Population†
ADSL	Subject level data	Phase 2/3 studies
ADAE	Adverse events	Phase 2/3 studies
ADEG	ECG tests	Phase 2/3 studies (possibly only phase 3 studies)
ADEG2	ECG abnormalities	Phase 2/3 studies (only phase 3 studies)
ADLBCH	Chemistry laboratory tests	Phase 2/3 studies

†Studies include WSA-CS-001/9766-CL-0101 and WSA-CS-002/9766-CL-0102 (phase 2), and WSA-CS-003/9766-CL-0103 and WSA-CS-004/9766-CL-0104 (phase 3).

The datasets that will support the safety analyses for the phase 1 studies are listed in [Table 2]. Additional safety datasets may be provided if new information is obtained for a safety event.

Table 2 Datasets to Support the Safety Analyses for Phase 1 Studies

Dataset	Dataset Description	Population
ADSL_P1	Subject level data	Phase 1 studies
ADAE_P1	Adverse events	Phase 1 studies
ADLBCH_P1	Chemistry laboratory tests	Phase 1 studies (hepatotoxicity, nephrotoxicity and thrombocytopenia only)

In addition, individual study data will be submitted. Individual study datasets will be provided following Clinical Data Interchange Standards Consortium (CDISC) standard, see [Attachment 2, Clinical Data Plan, Table 3] for details of standard version number. An overview of the Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets to be submitted in the NDA is provided in [Table 3].

Table 3 SDTM and ADaM Datasets

Study Number	Submission Datasets	Comments
Phase 3 studies:	9766-CL-0103, 9766-CL-0104	
Phase 1 studies:	9766-CL-0016, 9766-CL-0017, 9766-CL-0018, 9766-CL-0020, 9766-CL-0021, 9766-CL-0022, 9766-CL-0023, 9766-CL-0024, 9766-CL-0025, 9766-CL-0027, 9766-CL-0030, 9766-CL-0031, 9766-CL-0033, 9766-CL-0035, 9766-CL-0038, 9766-CL-0040, 9766-CL-0041, 9766-CL-0042, 9766-CL-0043, 9766-CL-0044, 9766-CL-0050, 9766-CL-0051, 9766-CL-0052	
	SDTM and ADaM	SDTM and ADaM datasets were used to produce TLFs

Phase 2 studies: 9766-CL-0101, 9766-CL-0102
Phase 1 studies: 9766-CL-0001, 9766-CL-0002, 9766-CL-0003, 9766-CL-0004, 9766-CL-0005, 9766-CL-0006, 9766-CL-0007, 9766-CL-0008, 9766-CL-0009, 9766-CL-0010, 9766-CL-0011, 9766-CL-0012, 9766-CL-0013, 9766-CL-0014, 9766-CL-0015
SDTM and ADaM SDTM and ADaM datasets were a legacy conversion. Analysis datasets and/or ADaM datasets were used to produce TLFs. Astellas also conducted a complete revalidation of TLFs using the ADaM datasets. Major discrepancies between Basilea TLFs and revalidation have been addressed in each individual CSR.

For details please refer to each individual study in the reviewer's guide.

ADaM: Analysis Data Model; SDTM: Study Data Tabulation Model; TLFs: Tables, listings and figures.

An overview of the individual study datasets to be provided for the NDA submission can be found in [Attachment 2, Clinical Data Plan, Table 1]. A comprehensive list of the SDTM

domains created within the submission can be found in [Attachment 2, Clinical Data Plan, Table 2]. Domains for each individual study were created only if data for the domain was collected for that study.

OpenCDISC will be used to check CDISC compliance for all SDTM and ADaM datasets and any unresolved errors will be documented in the Study Data Reviewer's Guide and Analysis Data Reviewer's Guide, respectively.

Data definition files will be provided in the form of define.xml and define.pdf for STDM datasets, ADaM datasets, and safety datasets.

Does the Agency have any comments regarding the approach described above?

Response: Yes, we agree with the approach.

Question 13: Electronic Submission

Astellas intends to provide a review guide with the NDA to orient the reviewer to the electronic submission. The review guide will be included as a separate leaf document in section 1.2 (cover letter).

Question A: Does the Agency agree with the use of a review guide and the proposed location?

Response: Yes, we agree.

There are approximately 6 reports that are referenced in multiple sections of Module 4 (ADME) and/or also included in Module 5. The eCTD specification recommends not including a file more than once within a sequence. Therefore, Astellas intends to provide a single page PDF reference for these reports so that they are only included once in the sequence. The single page PDF document will include all modules where the report is referenced and will be hyperlinked to direct the reviewer to the report.

Question B: Does the Agency agree with this approach?

Response: Yes, we agree.

Astellas is aware of requests from the Agency for file types not supported by the ICH eCTD standard (e.g., Pharmacokinetic modeling file types such as .ssc, .prn, .txt) (b) (4)

Question C: Should a request for file types not supported by ICH eCTD standard be made, is the above approach acceptable or does the Agency have another preference for how these files are to be provided to the reviewer(s)?

Response: (b) (4) *To submit these files, create a new subfolder under M5, and name it something easily identifiable, such as "SimCYP" and place the files there. All files should be referenced in the eCTD backbone. Even though the file*

types are not allowed by the eCTD validation rules, the errors will not result in rejection of the submission.

Astellas intends to provide ECG tracings for the QT study (9766-CL-0017) that will be stored at the Mortara Warehouse.

Question D: Which members of the FDA review team will need access to the Mortara Warehouse to conduct the review?

Response: The QT-Interdisciplinary Review Team (QT-IRT) already has access to the Mortara Warehouse. If you are required to provide a contact, please add: Alison Rodgers, Project Manager, DAIP/OAP/OND, Alison.Rodgers@fda.hhs.gov; Tel. (301) 796-0797.

Question 14: Summary Level Clinical Site Data

CLINSITE datasets will be prepared using the document Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions, which states that sponsors should provide electronic datasets to the FDA by clinical site and treatment arm for the population used in the primary analysis for each study used to support efficacy. The structure and content of the CLINSITE dataset will be prepared using the CLINSITE dataset specifications referenced in the guidance and last revised on 7 Nov 2012. For isavuconazonium, the pivotal studies to support efficacy are WSA-CS-004/9766-CL-0104 for IA and WSA-CS-003/9766-CL-0103 for mucormycosis and Astellas intends to provide the requested electronic datasets for these 2 studies.

Question A: Does the Division agree with Astellas providing datasets by clinical site and treatment arm for the population used to assess the primary efficacy endpoint for the 2 pivotal studies (WSA-CS-004 for IA and WSA-CS-003 for mucormycosis)?

Response: Your proposal to provide the Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning as recommended in the guidance appears acceptable. The information should include site-specific individual data listings for the pivotal studies.

In addition, a separate Bioresearch Monitoring Program (BIMO) Reviewer's Guide will be included in the NDA submission to detail the location of the site listings, Office of Scientific Investigations datasets and define files, relevant clinical trial materials, sample CRFs and the original protocol and amendments. The BIMO Reviewer's Guide will also detail information (e.g., name, address and contact information) for CROs used in the conduct of the clinical trial.

Question B: Does the Agency have any comments regarding the BIMO Reviewer's Guide?

Response: BIMO Reviewers' Guide should be included in the BIMO STF, in m5.3.5.4 (see instructions below for submitting BIMO documents).

Also, data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module

5.3.5.4, *Other Study reports and related information.* The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

<i>DSI Pre- NDA Request Item</i>	<i>STF File Tag</i>	<i>Used For</i>	<i>Allowable File Formats</i>
<i>I</i>	<i>data-listing-dataset</i>	<i>Data listings, by study</i>	<i>.pdf</i>
<i>I</i>	<i>annotated-crf</i>	<i>Sample annotated case report form, by study</i>	<i>.pdf</i>
<i>II</i>	<i>data-listing-dataset</i>	<i>Data listings, by study</i>	<i>.pdf</i>
<i>III</i>	<i>data-listing-dataset</i>	<i>Site-level datasets, across studies</i>	<i>.xpt</i>
<i>III</i>	<i>data-listing-data-definition</i>	<i>Define file</i>	<i>.pdf</i>

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

From a technical standpoint (not content related) yes, the proposed format for the planned NDA is acceptable. However, please see additional comments below.

- For archival purposes, you should also submit a pdf file of any labeling document submitted in word. Also, when you submit word documents, make sure the leaf title includes "word", so reviewers could quickly identify the word version of the document.*
- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in tabular format and linked to the referenced studies in m5.*
- Do not provide placeholders for sections that will not be submitted (e.g. 4.2.1.4 Pharmacodynamic drug interactions, “No studies”). Placeholders are only required when submitting ANDAs.*
- Study Tagging Files (STF) are required for submissions to the FDA when providing study information in modules 4 and 5, with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be tagged and placed under the study’s STF including case report forms (crfs). Please refer to the eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008), located at:
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>*
- To submit PADER descriptive portion (only) in eCTD format, it should be provided as a single pdf file with bookmarks, table of contents and hyperlinks in the eCTD section, m5.3.6. Please ensure that the leaf title of the report includes the reporting period, since each report is for a specific time period and it also helps when the leaf title follows a standard format, so reviewers can quickly differentiate one report from another.*

- *The descriptive portion of the Periodic ADE Report in module 5.3.6 should not contain the 3500a forms, but instead, at the end of the summary, it should specify how the 3500a forms were submitted. For example, you would reference the 3500A forms were submitted in Paper to AERS or the 3500A forms were sent in E2B XML format via the Electronic Submissions Gateway. For Steps to Submitting ICSRs Electronically in the XML Format, please visit: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115914.htm>*

- *If you submit the 3500A forms in paper, it's recommended that you provide the date of the submission, address shipped to, as well as any other pertinent information.*

Below is the address for the 3500A paper submissions:

*FDA/Central Document Room
Attn: AERS 3500A Reports Production
5901-B Amundale Rd.
Beltsville, MD. 20705-1266*

Subject level data listings will be provided in the Clinical Study Report of each pivotal trial. Separate listings for screening failures, randomization, discontinuation reasons, reasons for subjects considered non-evaluable for a specific analysis population, inclusion/exclusion criteria, all adverse events, all SAEs, all deaths, protocol deviations, primary and secondary efficacy parameters, concomitant medications, and laboratory test results will be included in the Study Tagging File (STF) for each study. Each listing will be sorted by site and subject number.

Question C: Does the Agency have any comments regarding the CSR listings?

Response: The proposed listings for the CSRs appear appropriate.

Additional Comments:

1) *The IV and oral capsule formulations will require two NDA submissions. Please see the Guidance for Industry, "Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees" available via the web address below for further information. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079320.pdf>*

2) *At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.*

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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.

/s/

KATHERINE A LAESSIG
12/03/2013



IND 72593

MEETING MINUTES

Astellas Pharma Global Development, Inc.
Attention: Robert M. Reed
Senior Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Mr. Reed:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Isavuconazonium sulfate (BAL8557).

We also refer to the meeting between representatives of your firm and the FDA on October 29, 2013. The purpose of the meeting was to discuss CMC development activities including drug substance impurities, drug substance and drug product specifications, justification for specifications for potentially genotoxic impurities BAL19714 and 2-butenal, oral drug product dissolution test method, and IV drug product infusion solution.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have questions, call me, at 240-402-3815.

Sincerely,

{See appended electronic signature page}

Navi Bhandari, Pharm.D
Regulatory Health Project Manager
Office of Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: October 29, 2013 10:00 - 11:00 am, EST
Meeting Location: CDER WO Building 22 Room 1421

Application Number: IND 72593 with cross reference to IND 119307
Product Name: Isavuconazonium sulfate (BAL8557)
Indication: Treatment of patients with invasive aspergillosis,
[REDACTED] (b) (4)

Sponsor/Applicant Name: Astellas Pharma Global Development, Inc.
Meeting Chair: Rapti Madurawe, Ph.D.
Meeting Recorder: Navdeep Bhandari, Pharm.D.

FDA ATTENDEES

Rapti D. Madurawe, Ph.D.	Branch Chief
Dorota M. Matecka, Ph.D.	CMC Lead
Houda Mahayni, Ph.D.	Biopharmaceutics Reviewer
Maotang Zhou, Ph.D.	CMC Reviewer
Owen McMaster, Ph.D.	Pharmacologist
Wendy Schmidt, Ph.D.	Clinical Team Leader
Elizabeth O'Shaughnessy, M.D.	Clinical Reviewer (by phone)
Alison Rodgers	Regulatory Health Project Manager
Sandra Suarez, Ph.D.	Biopharmaceutics Acting Team Leader
John Alexander, M.D., M.P.H.	Medical Team Leader
Edward Weinstein, M.D.	Medical Officer (by phone)
Dakshina Chilukuri, Ph.D.	Pharmacologist (by phone)
Philip Colangelo, Pharm.D, Ph. D.	Clinical Pharmacy Team Leader
Navdeep Bhandari, Pharm.D	Regulatory Health Project Manager

SPONSOR ATTENDEES

Rochelle Maher, MS	Global Development Project Leader
Katsutoshi Nakamura, Ph.D.	Senior Director, Project and Product Management
Karen Rodriguez, Ph.D.,	Assistant Director, Project and Product Management
Marlowe Schneidkraut, Ph.D.	Senior Director, Translational & Development Toxicology
Robert Reed	Senior Director Regulatory Affairs

[REDACTED] (b) (4)

[REDACTED] (b) (4)

Meeting Minutes
Type B Meeting

(b) (4)

Karsten Goedecke, Ph.D.

(b) (4)

Regulatory Affairs Manager and Project Manager

Meeting Minutes
Type B Meeting

1.0 BACKGROUND

Isavuconazomium sulfate (BAL8557) is a water-soluble prodrug that is currently being developed for oral and intravenous administration for the treatment of invasive fungal disease (IFD). Isavuconazonium sulfate is currently being investigated in three Phase 3 studies, for the treatment of patients with invasive aspergillosis (IA) and treatment of invasive mucormycosis.

A pre-NDA meeting was requested by Astellas as follow-up to the Type C meeting held January 2012 in order to provide the reviewers with more detailed information on several CMC topics and to solicit feedback on these topics.

2.0 DISCUSSION

The Agency sent preliminary responses on October 25, 2013 to the Sponsor. The Sponsor provided slide deck on October 28, 2013 which is attached.

3.0 QUESTIONS

Drug Substance Impurities:

1. Does the agency have any comments on the approach that has been used to identify/characterize the impurities and/or the proposed control strategy?

Agency Response:

It seems that your decision [REDACTED] (b) (4)

The Agency recommends the NDA include information on c [REDACTED] (b) (4)

[REDACTED] Additionally, the Agency recommends submission of data from scale-up batches (pilot or commercial scale) to demonstrate impurities are adequately eliminated. The adequacy of the control strategies for all related substances and the need for specification will be assessed during NDA review based on the overall data submitted to the NDA.

Discussion: The Sponsor was in general agreement with the Agency but some clarification was provided. The Sponsor discussed Table 23 in section S.4.5 of the brief document which showed data regarding genotoxic impurities from four commercial scale batches. The Sponsor believes that the data demonstrate that these impurities are

adequately eliminated and proposes to eliminate further testing of these impurities. The Agency indicated that, in order to agree the Sponsor's proposal, the Sponsor should conduct a risk assessment on the robustness of the process in lowering impurity levels and provide data to demonstrate the magnitude of reduction that each step is capable of achieving. The Agency asked if the Sponsor had fate and tolerance data for the impurities, and the Sponsor responded that these data are not available currently and indicated that such data might be not possible to generate for some impurities due to their instability. The Agency clarified that the Sponsor should indicate which impurities are not stable and which impurities are considered to be the most difficult to eliminate through the process. Justification with supporting data should be provided if fate and tolerance data are not possible for certain impurities. The Sponsor agreed to include the requested information in the NDA.

Drug Substance Specifications:

2. a. Does the agency have any comments regarding the approach for setting the proposed specifications?

Agency Response:

We note that tests for drug substance (DS) solid state form and particle size are not included in the proposed drug substance specifications. Adequate data should be provided to demonstrate solid state form and particle size are not relevant attributes for drug product manufacture and/or stability. In the absence of such data, we recommend you include tests for these attributes in the drug substance specification. Note that the adequacy of the DS specification (tests, analytical procedures and acceptance criteria) will be assessed based on the overall data submitted to the NDA.

Discussion: The Sponsor addressed the two items separately. For the solid state form, the Sponsor stated that (b) (4) are not included in the briefing document, but the data are available and will be submitted in the NDA. The Sponsor proposed to eliminate this testing based the data. The Agency requested data that demonstrate that the amorphous state will remain constant over time (e.g. on stability). For example, the Agency would like to understand if there are conditions under which the solid states form changes. If there is evidence that the solid state form changes over time or under certain conditions, the Sponsor should provide information to support that the conversion is not clinically relevant.

For particle size, (b) (4)

(b) (4) (b) (4)

The Agency indicated that the results should be presented in the NDA along with a rationale as to which manufacturing process parameters control the particle size. If a relationship cannot be established, the particle size should be measured.

2. b. Does the agency have any comments regarding the approach for setting the proposed specifications (drug substance) – BAL19714?

Agency Response:

The Sponsor should continue to attempt to reduce levels of this genotoxic impurity to as low as reasonably practicable. Proposed level may be acceptable because of favorable pharmacokinetics and indication for life threatening diseases. Please note that carcinogenicity studies may be needed if duration of administration exceeds 6 months.

Discussion: The Sponsor stated that they had no specific comments regarding this question. The Sponsor indicated that they have carcinogenicity studies. In the pivotal Phase 3 study, the mean treatment duration was 45 days. The Sponsor indicated that there should be no risk of treatment exceeding 6 months. The longest treatment that the Sponsor observed was 102 days for aspergillus. The Agency asked about repeat dosing and how often a 2nd or 3rd course of treatment was needed. The Sponsor responded that usually one course is sufficient and that if a second course was needed that the patients survival rate is low at that point. The Sponsor has limited data on repeat dosing. The Agency indicated that the Sponsor should consider long term studies if long term treatment for mucormycosis is planned. The Agency may allow Sponsor to provide this information as a Phase 4 commitment. The Sponsor indicated that Page 5 shows an estimate lifetime treatment of 98 days and they do not know the extremes yet. The Agency indicated that completed carcinogenicity studies would support longer periods of treatment in the future.

IV Drug Product Specifications

3. a. Does the agency have any comments regarding the approach for setting the proposed specifications?

Agency Response:

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The approach for setting the drug product (DP) specifications appears reasonable. We recommend including specification for reconstitution time. Note that the adequacy of the DP specifications (tests, analytical procedures and acceptance criteria) will be assessed based on the overall data submitted to the NDA.

Discussion: The Sponsor indicated that they did not include reconstitution time in their briefing document; but reconstitution time has been reported for all clinical and registration batches. Since reconstitution time was (b) (4) for all batches tested, the Sponsor proposed (b) (4). The Agency asked the Sponsor to provide a detailed justification in the NDA and requested that the justification include data at the end of the proposed shelf life (i.e., stability results at end of stability study). The Sponsor agreed to include the requested information in the NDA.

3. b. Does the agency have any comments regarding specification or the adequacy of the proposed justification (IV drug product) – 2-Butenal?

Agency Response:

The Sponsor should continue to attempt to reduce levels of this genotoxic impurity to as low as reasonably practicable. However, proposed level may be acceptable because the risk from exposure to 2-butenal at these levels (b) (4) µg/day) would be no greater than the risk from eating fruits, vegetables, fish and meats (which may contain up to 200 µg/day of 2-butenal).

Discussion: The Sponsor acknowledged the Agency's comments and had no further comments.

Oral Drug Product Specifications:

4. a. Does the agency have any comments regarding the approach for setting the proposed specifications?

Agency Response:

Since your product is (b) (4) (using the proposed testing conditions); a two-point specification option would be more adequate to your product. With respect to dissolution, the following are additional points to consider for setting the dissolution acceptance criterion (a) for your product:

- a. The dissolution profile data (i.e., 15, 20, 30, 45, & 60 minutes) from the clinical batches and primary (registration) stability batches should be used for the setting of

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- the dissolution acceptance criterion of your proposed drug product [i.e., specification-sampling time point and specification value].
- b. The in vitro dissolution profile should encompass the timeframe over which at least (b) (4) % of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.
 - c. The selection of the specification time point should be where $Q = (b) (4) \%$ dissolution occurs. However, if you have a (b) (4) product or includes a BCS-Class 2, poor-soluble drug, a two-point specifications option may be adequate for your product. The first time point should be during the initial dissolution phase (i.e., 15-20 minutes) and the second time point should be where $Q = (b) (4) \%$ dissolution occurs.
 - d. The dissolution acceptance criterion should be based on average in vitro dissolution data (n=12).

Note that the adequacy of the DP specifications (tests, analytical procedures and acceptance criteria) will be assessed based on the overall data submitted to the NDA.

Discussion: Refer to discussion of Question 5 (below).

4. b. Does the agency have any comments regarding the specification or the adequacy of the proposed justification (oral drug product) – 2-Butenal?

Agency Response:

See response to 3b.

Discussion: There was no specific discussion on this question.

Dissolution Testing Conditions:

5. Does the agency have any comments regarding the proposed changes for this dissolution method?

Agency Response:

On face, the selected method does not appear to be optimal for your product. The provided dissolution information shows that dissolution (b) (4)

We would like to inform you that (b) (4) is accepted by FDA for the dissolution testing of immediate release oral dosage forms. The limited information provided in your meeting's document shows that the dissolution (b) (4)

(b) (4)

The following is information to be included in the dissolution method report to be included in the NDA submission:

- a. Solubility data for the drug substance covering the pH range;
- b. Detailed description of the dissolution test being proposed for the evaluation of the proposed drug product and the developmental parameters used to select the proposed dissolution method as the optimal test for the proposed product (i.e., selection of the equipment/ apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.). If a surfactant was used, the data supporting the selection of the type and amount of surfactant should be included. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete (i.e., 15, 20, 30, 45, 60, 75, and 90 minutes) and cover at least ^{(b) (4)} % of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend that at least twelve samples be used per testing variable;
- c. Provide the complete dissolution profile data (individual, mean, SD, profiles) for the proposed drug product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim); and

Include the complete dissolution data for the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.). In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant critical manufacturing variables (e.g. drug substance particle size, ratio of amorphous/crystalline content, tablet hardness, water content, etc.).

Discussion: The Sponsor provided a slide presentation to discuss the dissolution method and acceptance criteria.

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The Sponsor clarified that Apparatus 2 ^{(b) (4)} as Guidance from the Agency states that Apparatus 2 is ^{(b) (4)} standard/conventional for quality control ^{(b) (4)}

The Agency asked where in the gastrointestinal tract the drug is expected to be absorbed, the stomach or the small intestine. The Sponsor responded the small intestine because the ^{(b) (4)} The Agency asked why the Sponsor chose a dissolution media of pH 6. The Sponsor responded that the dissolution methods validation showed the compound to be stable in the media that they chose. ^{(b) (4)}

^{(b) (4)}

^{(b) (4)}

^{(b) (4)}

^{(b) (4)}

Infusion Solution:**6. Does the agency have any comments regarding this planned approach?****Agency Response:**

We are concerned with the quality of the infusion solution. Particulate matter in an injection drug product is a safety concern. Loss of potency due to hydrolysis/precipitation of the prodrug could result in loss of efficacy. The Agency generally discourages the use of inline filters. The Agency recommends developing a robust formulation that complies with USP <788> after reconstitution and dilution prior to patient administration.

Discussion: The Sponsor responded to the Agency's comments via prepared slides. The Agency reiterated that the infusion solution should comply with USP <788> criteria. The Agency indicated that they would like to avoid the use of an inline filter due to the possibility of non-compliance in commercial use as well as the difficulty in assessing compatibility of various types of available filters. The Agency emphasized their recommendation for a particulate free formulation. The Agency agreed to evaluate prior to submission of the NDA a summary of available information to support the Sponsor's claim that the infusion solution is safe and efficacious.

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/s/

DOROTA M MATECKA
11/29/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 72,593

Astellas Pharma Global Development, Inc.
Attention: Mr. Robert Reed
Director, Regulatory Affairs
Three Parkway North
Deerfield, Illinois, 60015

Dear Mr. Reed:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for isavuconazole (BAL8557).

We also refer to the meeting between representatives of your firm and the FDA on October 6, 2010. The purpose of the meeting was to further discuss the primary endpoint for your aspergillosis study, WSA-CS-004.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jacquelyn Smith, M.A., Regulatory Project Manager at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

IND 72,593

MEMORANDUM OF TELECONFERENCE MINUTES

Meeting Type: C
Meeting Category: IND
Meeting Date October 6, 2010
Application Number: IND 72,593
Product Name: Isavuconazole (BAL8557)
Indication: Invasive Fungal Disease
Sponsor Name: Astellas Pharma Global Development, Inc.
Meeting Chair: Eileen Navarro Almario, M.D.
Meeting Recorder: Jacquelyn Smith, M.A.

FDA ATTENDEES

Division of Special Pathogen and Transplant Products (DSPTP)

Renata Albrecht, M.D.	Director
Eileen Navarro Almario, M.D.	Acting Deputy Director
Joette Meyer, Pharm.D.	Clinical Team Leader
Elizabeth O'Shaughnessy, M.D.	Medical Officer
Karen Higgins, Sc.D.	Statistics Team Leader
Cheryl Dixon, Ph.D.	Statistics Reviewer
Philip M. Colangelo, Pharm.D., Ph.D	Clinical Pharmacology Team Leader
Dakshina Chilukuri, Ph.D.	Clinical Pharmacology Reviewer
Shukal Bala, Ph.D.	Microbiology Team Leader
Anne Purfield, Ph.D.	Microbiology Reviewer
Jacquelyn Smith, M.A.	Regulatory Health Project Manager

SPONSOR ATTENDEES

Astellas Pharma Global Development, Inc. - US

Bernhardt Zeiher, M.D.	Global Therapeutic Area Head
Mr. Robert Reed	Director, Regulatory Affairs
Neddie Zadeikis, M.D., MBA	Medical Director, Medical Sciences

Chunzhang Wu, Ph.D.
Shobha Dhadda, Ph.D.
Ms. Laura Kovanda
Rochelle Maher, M.S.

Ms. Leah Arnold
Dr. Eisuke Nozawa

Senior Manager, Biostatistics
Associate Director, Biostatistics
Associate Director, Drug Development
Sr. Director, Global Development
Project Manager
Sr. Manager, Clinical Studies
Visiting Senior Director Regulatory Affairs

Astellas Pharma, Inc. – Tokyo Japan

Dr. Masahito Kaneko

Global Project Management Leader

Basilea Pharmaceutica International, Ltd.

Mark Jones, Ph.D.

Medical Microbiology and Isavuconazole
Project Manager

Karsten Goedecke, Ph.D.

Regulatory Affairs Specialist
Chief Medical Officer

BACKGROUND

The purpose of the October 6, 2010, Type C, meeting was to discuss the aspergillosis Protocol WSA-CS-004.

DISCUSSION

FDA's preliminary responses to Astellas' questions (in **bold**) are listed below in *italicized* font, and the meeting discussion minutes are listed in normal font:

Question 1:

The Sponsor provided information regarding the interim analysis and confirmation that this analysis was conducted in a manner that was blinded to the Sponsors (Basilea and Astellas).

Does this information adequately address the Division's request?

FDA Response:

The information provided adequately addresses our concern as to whether the Sponsors remain blinded to the interim analysis for futility.

Meeting Discussion:

This was acknowledged by both FDA and Astellas.

Question 2:

The Sponsor proposes to change the primary endpoint of the invasive aspergillosis protocol (WSA-CS-004) to all cause mortality through day 42 in the all treated (i.e., intent-to-treat [ITT]) population using a 10% non-inferiority margin.

Does the Division concur?

FDA Response:

We agree with the use of the endpoint of all cause mortality through day 42 in Study 004. However, the choice of endpoint and the choice of analysis population for a non-inferiority study are highly dependent on the data available to justify the non-inferiority margin and the ability of the study to have assay sensitivity.

Please note that we will follow closely the draft Guidance for Industry on Non-inferiority Clinical Trials:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf>

In this guidance there is discussion of the need for a non-inferiority study to have assay sensitivity. This includes evidence of the historical evidence of drug effect and the constancy assumption, as well as the need for the non-inferiority study to have high study quality.

Based on the voriconazole study, we believe that a conservative non-inferiority margin of 10% for an endpoint of overall outcome (based on clinical, mycological, and radiological response) at 12 weeks is justified for an intent-to-treat (ITT) population and that a conservative non-inferiority margin of 5% for all cause mortality at 6 weeks is justified for an ITT population. We realize that these are conservative estimates since they are not based on the effect of voriconazole over placebo, but instead are based on the benefit that voriconazole showed over amphotericin B plus other therapy, which is believed to have some efficacy.

To increase these conservative margins, evidence of the efficacy of amphotericin B (over no treatment) should be provided. As the voriconazole data is strong and from a randomized trial, we believe that use of that data along with supportive information will lead to the strongest justification of the non-inferiority margin. The Denning review (Clinical Infectious Diseases 1996;23:608-15) attempted to determine the efficacy of amphotericin B by comparing duration of treatment (< 14 days to ≥ 14 days). The patients treated for < 14 days could be considered to have received inadequate treatment, representing a conservative estimate of placebo. However, we have some concerns regarding whether or not the populations described in the Denning paper are similar enough to the current study in order to be comparable and why particular patients were not treated or treated for < 14 days should be addressed. Both of these issues should be addressed in order address the issue of assay sensitivity.

We understand that it is difficult to gather the needed information to support the efficacy of amphotericin B since placebo-controlled studies have not been conducted for this indication. We will also attempt to find additional supportive information for a non-inferiority margin justification.

Finally, please note that while we believe it may be possible to justify a non-inferiority margin for an ITT population in Study 004, if the study is found to enroll many patients who are later determined to not have invasive aspergillosis infection, we will have concerns regarding the reliable interpretation of the study.

Meeting Discussion

FDA acknowledged the challenges in defining a noninferiority margin that is specific to the population under study and encouraged Astellas to clarify the different patient populations that would be in study 004 (i.e. HIV patients) and further examine the patient population in the *Denning review (Clinical Infectious Diseases 1996;23:608-15)* to determine if the population is similar enough to the voriconazole study and Astellas' current trial to be comparable,. FDA also encouraged Astellas to more closely review the details of the historical literature as to the endpoint and timing of assessment such that it supports their proposed non-inferiority margin. FDA referred Astellas to the Community Acquired Pneumonia and Acute Bacterial Skin and Skin Structure Infections Advisory Committee transcripts for some guidance regarding the approaches taken for defining a noninferiority margin.

Additional Comments:

1. *In Section 8.2.2.3 Mycological Assessment of protocol WSA-CS-004 (Amendment 3.1), you incorporated some of the changes, discussed at the meeting held on April 14, 2010. These changes include*
 - *testing of consecutive serum samples and two aliquots of the same BAL sample by Bio-Rad Platelia® galactomannan enzyme assay, and*
 - *exclusion of patients receiving Plasma-Lyte™ or concomitant medication with piperacilin-tazobactam.*

However, the remaining recommendations were not addressed. We highly recommend the following:

- *We agree with your justification for use of galactomannan (GM) as an inclusion criterion. However, we highly recommend that as is the standard practice, continued efforts should be made to obtain specimens for fungal smear, culture or histological confirmation according to EORTC/MSG criteria; all positive and negative results should be documented on case reports form and in the datasets. All patients with pathogens which cross react such as Penicillium, Paecilomyces, Geotrichum and Histoplasma with the Platelia Aspergillus EIA (for details see Platelia Aspergillus EIA test brochure) should be excluded from analysis in conjunction with documentation of negative culture. The Platelia Aspergillus EIA test brochure also specifies that the results of the galactomannan test should be*

- interpreted in conjunction with mycological assessments, including culture, histological findings or cytology.*
- *Please document the actual galactomannan index for each patient; the basis of characterizing galactomannan positive findings on a single value of ≥ 0.7 or two consecutive values each of ≥ 0.5 to < 0.7 , for serum samples, will be a review issue.*

Meeting Discussion

Astellas agreed.

- *We strongly recommend excluding patients receiving amoxicillin/clavulanate.*

Meeting Discussion

Astellas agreed.

- *It is unclear whether galactomannan testing will be measured at the site laboratory or a central laboratory. We recommend that all efforts be made to maintain consistency in different laboratories or testing be done at a central laboratory. If testing is done at site laboratories then validation of a subset of samples should be done at a central laboratory.*

Meeting Discussion

Astellas stated that patient samples will be submitted to a central laboratory for galactomannan testing.

2. *We acknowledge your efforts to have as many study centers as possible use the GM assay.*

Meeting Discussion

This was acknowledged by Astellas.

3. *The justification for your use of the EORTC/MSG 2008 diagnostic criteria with exclusion of patients with rheumatologic diseases is acceptable.*

Meeting Discussion

This was acknowledged by Astellas.

Action Items:

- Astellas will attempt to find additional supportive information for a non-inferiority margin justification and address whether or not the populations described in the Denning review (Clinical Infectious Diseases 1996;23:608-15) are similar enough to the current study in order to be comparable.
- The FDA will also attempt to find additional supportive information for a non-inferiority margin justification.

- Astellas will submit a protocol amendment with an updated non-inferiority justification.

Minutes Preparer: Jacquelyn Smith, MA, Regulatory Project Manager, DSPTP
Concurrence: Eileen Navarro Almario, M.D., Deputy Director, DSPTP

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/s/

EILEEN E NAVARRO ALMARIO
11/02/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 72593

Astellas Pharma Global Development, Inc.
Attention: Mr. Robert Reed
Director, Regulatory Affairs
Three Parkway North
Deerfield, Illinois, 60015

Dear Mr. Reed:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for isavuconazole (BAL8557).

We also refer to the meeting between representatives of your firm and the FDA on April 13, 2010. The purpose of the meeting was to discuss your aspergillosis study, WSA-CS-004 and potential changes for the candidemia study, WSA-CS-008.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jacquelyn Smith, M.A., Regulatory Project Manager at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes
Presentation

IND 72593

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: IND
Meeting Date April 13, 2010
Application Number: 72593
Product Name: Isavuconazole (BAL8557)
Indication: Invasive Fungal Disease
Sponsor Name: Astellas Pharma Global Development, Inc.
Meeting Chair: Eileen Navarro Almario, M.D.
Meeting Recorder: Jacquelyn Smith, M.A.

FDA ATTENDEES

Division of Special Pathogen and Transplant Products (DSPTP)

Renata Albrecht, M.D.	Director
Eileen Navarro Almario, M.D.	Acting Deputy Director
Rapti Madurawe, Ph.D.	Chemistry Pharmaceutical Assessment Leader
Joette Meyer, Pharm.D.	Clinical Team Leader
Tafadzwa Vargas-Kasambira, M.D.	Medical Officer
Elizabeth O'Shaughnessy, M.D.	Medical Officer
Karen Higgins, Sc.D.	Statistics Team Leader
Cheryl Dixon, Ph.D.	Statistics Reviewer
Philip M. Colangelo, Pharm.D., Ph.D	Clinical Pharmacology Team Leader
Dakshina Chilukuri, Ph.D.	Clinical Pharmacology Reviewer
Owen McMaster, Ph.D.	Pharmacology and Toxicology Reviewer
Shukal Bala, Ph.D.	Microbiology Team Leader
Anne Purfield, Ph.D.	Microbiology Reviewer
Jacquelyn Smith, M.A.	Regulatory Health Project Manager

SPONSOR ATTENDEES

Astellas Pharma Global Development, Inc.

Mr. Robert Reed	Director, Regulatory Affairs
Neddie Zadeikis, M.D., MBA	Medical Director, Medical Sciences

Chunzhang Wu, Ph.D.	Senior Manager, Biostatistics
Shobha Dhadda, Ph.D.	Associate Director, Biostatistics
Ms. Laura Kovanda	Associate Director, Drug Development
Rochelle Maher, M.S.	Sr. Director, Global Development Project Manager
Ms. Leah Arnold, Sr.	Manager, Clinical Studies
William Fitzsimmons, Pharm.D.	Sr. Vice President, Research and Development

Basilea Pharmaceutica International, Ltd.

Mark Jones, Ph.D.	Medical Microbiology and Isavuconazole Project Manager
Karsten Goedecke, Ph.D.	Regulatory Affairs Specialist
C. Douglas Webb, M.D.	Clinical Scientist Consultant
Achim Kaufhold, M.D.	Chief Medical Officer

BACKGROUND

The purpose of the April 13, 2010, Type B, meeting was to discuss the aspergillosis Protocol WSA-CS-004. There were also three questions in the briefing package (BP) relevant to the candidiasis Protocol WSA-CS-008.

DISCUSSION

FDA's preliminary responses to Astellas' questions (in **bold**) are listed below in *italicized* font, and the meeting discussion minutes are listed in normal font:

Question 1: Protocol WSA-CS-004, All Cause Mortality

As described in section 3.1.1 of the briefing document, section 10.2.2 of the protocol [Appendix B], and in the brief justification of non-inferiority margin [Appendix C], Astellas proposes to change the primary endpoint of the invasive aspergillosis protocol (WSA-CS-004) to all cause mortality through day 42 in the all treated (i.e., intent-to-treat [ITT]) population using a 10% non-inferiority margin.

Does the Division have any comments on these proposed changes?

FDA Response:

The aspergillosis study, Protocol WSA-CS-004, is currently ongoing and has enrolled 311 patients out of a projected 360. An interim analysis has already been conducted on the first 180 subjects who reached 42 days. You propose to change the primary endpoint from overall response at Day 42 to all cause mortality at Day 42 and based on this change increase the sample size to 510 subjects. In general, we agree that an endpoint of mortality is a preferred endpoint, given the possible subjectiveness of overall response. However, we are concerned with changing the primary endpoint at this late point in the trial, especially given the fact that an interim analysis has already conducted.

Prior to our being able to agree to this substantial change in the trial, we would like more information regarding the study conduct, including how this trial is being monitored, how the interim analysis was conducted, who prepared the interim analysis report, who participated in the discussion of the interim analysis data and outcome, and who within the independent drug safety and monitoring board (IDSMB) and outside the board has access to this information. We would also be interested in the level of detail of information the IDSMB and others have regarding the interim analysis. Also, please submit the IDSMB charter for our review.

The reason for our request is to understand whether any unblinded information, including information using codes such as “Treatment A” and “Treatment B,” was available to anyone outside the IDSMB and whether this information in any way influenced the proposal to change the primary endpoint. Please see the guidance document “Establishment and Operation of Clinical Trial Data Monitoring Committees” located at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf>, specifically page 21, section 4.4.1.4

“Sponsors who wish to have the ability to request interim protocol changes without raising concerns about biasing the study should establish procedures to minimize bias, such as ensuring that they are completely unaware of unblinded comparative data”

If we are able to determine that a change of primary endpoint is acceptable, we would recommend that the primary analysis population for this endpoint also be the mITT population, i.e., patients with proven and probable infection.

We appreciate your submission of the brief non-inferiority margin justification. Please complete your justification, include all references cited, and submit it for further review. In your justification please include a discussion of the constancy of the effect, by discussing the similarities of the patient populations, concomitant treatment, etc. At that time we will conduct a complete review of the justification.

Meeting Discussion

Astellas stated that the trial is being monitored by (b) (4). One team monitors patient records (blinded) and the other monitors pharmacy records (unblinded). Unblinded monitors who review pharmacy records have no access to patient Case Report Forms.

The interim analysis reviewed by the IDSMB was a futility analysis with treatment groups coded A and B. (b) (4) prepared the data analyses with fake randomization codes. IDDI, an independent statistical group, prepared data analyses with actual randomization codes. The individuals involved in the discussion of the interim analysis were not involved in the decision to modify the primary endpoint.

The sponsors (Baseilea and Astellas) remain completely unaware of any summary data by treatment arm either unblinded or data labeled “group A” and “group B”.

Astellas agreed to officially submit the information regarding the monitoring of the trial.

Astellas stated that they believe that the most appropriate analysis population is the all-treated (ITT) versus Modified intent-to-treat (MITT) and they provided some examples to support their assertion. According to Astellas, the ITT population includes all patients who received at least one dose of the study drug, it avoids potential selection bias, and more accurately reflects the patients that will be treated in a real-world setting.

The Division stated that the MITT population is the usual population of interest and that use of the MITT population would make it easier to match up the trials for the non-inferiority justification.

Astellas stated that use of the MITT population would require a further increase in the sample size to approximately 700 patients. They anticipate losing approximately one-third of the patients when moving from an ITT to an MITT population for analysis. Astellas asked, if the MITT population is to be used as the primary analysis population, if they could they use a larger M2 for the non-inferiority margin. The Division responded that they would need to consider this proposal and that Astellas should provide a discussion of this matter when they submit the complete justification of the non-inferiority margin.

The Division asked about the data available from the trial thus far, and Astellas stated that of 131 patients enrolled to date, 52 had probably invasive aspergillosis, 15 had proven disease, and 64 had possible disease, based on 2002 European Organization for Research and Treatment of Cancer (EORTC) criteria. Astellas stated that future enrollment criteria would be guided by the 2008 EORTC criteria.

Question 2: Protocol WSA-CS-004, Inclusion Criteria

Astellas proposes to allow patients with applicable host factors who develop new evidence of invasive fungal disease while on prophylactic therapy for at least 14 days with itraconazole, fluconazole, amphotericin B (any formulation), or an echinocandin will be eligible for enrollment in Study WSA-CS-004.

Does the Division agree?

FDA Response:

The Infectious Diseases Society of America (IDSA) guidelines on treatment of aspergillosis state that the management of breakthrough invasive aspergillosis in the context of mold-active azole prophylaxis or suppressive therapy is not defined by clinical trial data but would suggest a switch to another drug class.¹ You have stated that your preclinical studies on isavuconazole appear to show that there is no cross-resistance with fluconazole, and that the drug is at least as active as established comparators in aspergillosis animal models. Please provide information on cross-resistance between

¹ Walsh TJ, Anaissie EJ, Denning DW et al. Treatment of Aspergillosis : Clinical Practice Guidelines of the Infectious Diseases Society of America. CID 2008;46:327-60

itraconazole, isavuconazole, and voriconazole. The IDSA guidelines do not specify how long the duration of prophylaxis should be before alternative therapy is used, but two weeks appears to be an appropriate period of time after which failure of prophylaxis can be assumed in the context of breakthrough infection.

Meeting Discussion

Astellas stated that they will provide the data on cross-resistance as per the Division's request, and will remove itraconazole as a permitted prophylactic agent. They requested confirmation that an echinocandin and amphotericin derivative (for at least 14 days) or fluconazole (any treatment duration) were permitted prophylactic agents. The Division questioned the use of fluconazole as a prophylactic agent in patients with evidence of invasive aspergillosis, and Astellas stated that because fluconazole has no *in vitro* activity against *Aspergillus*, this will essentially be akin to using a placebo and would have no treatment effect.

Question 3: Protocol WSA-CS-004, Classification of Probable IFD
Considering changing clinical practice, recently published scientific data supporting the utility of serum and bronchoalveolar lavage (BAL) galactomannan testing in clinical trials, as well as the 2008 EORTC/MSG revised guidelines [see section 3.1.2]. Astellas proposes to amend inclusion criterion #6c of the invasive aspergillosis infection protocol (WSA-CS-004) to add BAL galactomannan testing: a single value of OD \geq 1.0.

3a. Does the Division agree to allow a positive BAL galactomannan Platelia® EIA test with a single OD value of \geq 1.0 as adequate mycological evidence to enable classification as “probable” IFD?

FDA Response:

As mentioned previously in communications dated June 5, 2006, August 8, 2006 and meeting minutes dated August 16, 2006; the performance characteristics of the Biorad Platelia Aspergillus EIA, for detection of galactomannan in specimens other than serum will be a review issue. We suggest that performance characteristics of the assay in the laboratory where testing is done should be provided for our review at the time of NDA submission.

3b. Does the Division have any other comments on the utility of serum and BAL galactomannan testing?

FDA Response:

You have proposed to use detection of galactomannan antigen in serum [REDACTED] (b) (4) [REDACTED] as a stand alone microbiologic criteria for inclusion of patients with aspergillosis into the study. We assume that galactomannan will be detected by the Bio-RAD Platelia® enzyme immunoassay. Since the use of the assay will be different from that recommended in the test brochure for the specific purpose of study inclusion, we recommend that the data supporting these cut-offs

as a stand alone microbiologic criterion for diagnosis of probable invasive aspergillosis should be provided for our review at the time of NDA submission.

We recommend the following for testing of both serum and BAL samples:

- Documentation of the actual galactomannan index on case report forms and in the datasets.
- Exclusion of patients concomitantly receiving antibiotics known to result in a false positive GM (piperacillin/tazobactam, amoxicillin/ clavulanate). Use of Plasma-Lyte should be excluded for bronchoscopies in patients being considered for enrollment in clinical trials for the treatment of invasive aspergillosis.
- As is the standard practice, continued efforts should be made to obtain specimens for fungal smear, culture or histologic confirmation according to EORTC/MSG criteria; all positive and negative results should be documented on case report forms and in the datasets. Presence of bacterial infections should be reported. All patients with pathogens which cross react such as *Penicillium*, *Paecilomyces*, *Geotrichum* and *Histoplasma* with the *Platelia Aspergillus* EIA (for details see *Platelia Aspergillus* EIA test brochure) should be excluded from analysis.
- It is unclear whether galactomannan testing will be measured at the site laboratory or a central laboratory. We recommend that all efforts be made to maintain consistency in different laboratories or testing be done at a central laboratory. If testing is done at site laboratories then validation of a subset of samples should be done at a central laboratory.
- The primary efficacy analysis should be performed on all patients in the MITT populations. A subset analysis should be done for patients that are diagnosed based on standard microbiologic criteria (culture, histopathology, etc.) excluding those whose microbiological diagnosis is based only on a GM positive result.

Meeting Discussion

Astellas acknowledged the Division's comments and agreed to the recommendations. They also confirmed that the Bio-RAD *Platelia*® enzyme assay will be used.

Question 4: Protocol WSA-CS-004 Response Definitions

Astellas would like to clarify the protocol definitions of Clinical, Mycological and Radiological response [see section 3.1.3 of the briefing document] in the invasive aspergillosis protocol (WSA-CS-004). In addition, the overall response criteria have been harmonized for both lower respiratory tract disease (LRTD) and non lower respiratory tract disease (NLRTD) in a single table "Definition of Overall Response". Overall response will be assessed by the Data Review Committee as a secondary endpoint.

Does the Division agree with the proposed clarifications of the outcome assessment definitions?

FDA Response:

Your clarifications of the protocol definitions of Clinical, Mycological and Radiological response are acceptable. The harmonization of LRTD and NLRTD response criteria into a single table is also acceptable. The acceptability of overall response as a secondary endpoint, however, will depend upon whether or not we can agree with your proposal to change the primary endpoint to all-cause mortality at day 42, as noted in our response to Question #1.

Meeting Discussion

Astellas acknowledged the Division's comments.

Question 5: Protocol WSA-CS-004,

(b) (4)

[Redacted]

[Appendix B].

[Redacted]

(b) (4)

FDA Response:

[Redacted]

(b) (4)

Meeting Discussion

[Redacted]

(b) (4)

Question 6: Protocol WSA-CS-008, Proposed Endpoint

The primary efficacy analysis of overall response [see section 3.2 of the briefing document] at follow-up visit 1 (2 weeks after the end of all antifungal therapy) will be performed using the modified intent-to-treat (mITT) population for study WSA-CS-008. Additional evaluations of efficacy will be assessed at other defined time points as secondary endpoints.

Does the Division have any comments on the proposed endpoint?

FDA Response:

The primary efficacy analysis of overall response in the mITT population was previously agreed to and is still considered to be acceptable. We have no further comments.

Meeting Discussion

Astellas acknowledged the Division's comments.

Question 7: Protocol WSA-CS-008, Duration of Therapy

In order to be consistent with standard of care and to facilitate enrollment in the invasive candidiasis/candidemia study (WSA-CS-008), Astellas proposes to shorten the duration of minimum initial iv therapy from at least 10 days to 7 days [see section 3.2 of the briefing document].

Does the Division have any comments on the proposed changes to the minimum duration of iv therapy?

FDA Response:

*The IDSA guidelines for treatment of candidiasis state that one option for treating hemodynamically stable patients who have candidiasis is a short course of parenteral echinocandin therapy (3-5 days), followed by a transition to oral fluconazole or voriconazole (for *Candida krusei* infection).² It is noted, however, that this approach is not supported by a significant amount of clinical data, and may apply only for non-neutropenic patients. In addition, the original studies that formed the basis for approval of caspofungin for treatment of candidiasis used a minimum duration of IV therapy of 10 days before allowing a switch to oral therapy. Therefore, to justify the non-inferiority margin for your study, caspofungin should be used in the duration for which it was used in the studies that supported approval of the drug. In addition, it is expected that subjects will have a confirmed negative blood culture for *Candida* prior to the switch to oral therapy.*

² Pappas PG, Kauffman CA, Andes D et al. Clinical Practice Guidelines for the Management of Candidiasis : 2009 Update by the Infectious Diseases Society of America. CID 2009;48:503-35

However, we are concerned that for neutropenic patients this shortened duration of therapy is not adequate. Please indicate whether neutropenic patients have been, and will continue to be, enrolled in this trial. If so, provide literature data to support a shortening of the duration of minimum initial therapy. In addition, please provide a rationale for treatment duration shortening given the aforementioned duration used in the caspofungin trials which supported approval.

Meeting Discussion

Astellas acknowledged the Division's comments. Astellas confirmed that they will retain a minimum of 10 days IV therapy as originally planned. They also confirmed that neutropenic patients will be allowed in the study, and that they will have to have recovered their absolute neutrophil counts (ANC) before a switch to oral therapy can be considered.

Astellas also asked the Division if there was any shift in thinking on the (b) (4) for a candidiasis indication and the Division responded not at this time.

Question 8: Protocol WSA-CS-008, Noninferiority Margin

The invasive candidiasis/candidemia (WSA-CS-008) analysis is based on a noninferiority margin of 15% for the primary endpoint [see Appendix D].

Does the Division have any comments or suggestions on the proposed noninferiority margin?

FDA Response:

We appreciate the brief justification of the non-inferiority margin provided for Protocol WSA-CS-008. We acknowledge the difficulties in calculating an actual estimate of placebo response based on the endpoint of treatment success. Note that we will have difficulty relying on an imputed rate as you have used for the Almirante et al. study. Currently the estimate of the control effect is based solely on the historical data from trials of caspofungin which was followed by oral fluconazole after at least 10 days of caspofungin therapy. The control in the current trial, however, is a minimum of 10 days of caspofungin followed by oral voriconazole. The impact of using oral voriconazole instead of oral fluconazole should be addressed when providing an estimate of the control effect. As was stated in our response to Question 1, we would request that when your justification is complete that you submit it for our review and include all references cited. In your justification please include a discussion of the constancy of the effect, by discussing the similarities of the patient populations, concomitant treatment, etc.. At that time we will conduct a complete review of the justification.

Meeting Discussion

Astellas acknowledged the Division's comments.

Additional Comments:

Microbiology

1. *You state that a central laboratory manual will be provided to study sites and will contain guidelines for obtaining, culturing and shipping fungal isolates. Please include the central laboratory manual for review.*
2. *We recommend that speciation should be done for all clinical isolates. We also suggest in vitro susceptibility testing on all isolates using standardized methods, such as those recommended by Clinical Laboratory Standards Institute.*

Clinical Pharmacology

3. *You have proposed to evaluate the influence of covariates (e.g., gender, body weight) on trough concentrations during dosing and at EOT. In addition to this, we strongly recommend that you evaluate the association between trough concentrations and efficacy and safety outcomes in the study.*
4. *In the PK sub study, we recommend that you evaluate the association between AUC and trough concentrations (C_{trough}) to see whether C_{trough} can be used as a surrogate for systemic exposure.*

Meeting Discussion

Astellas acknowledged the Division's comments and agreed with the recommendations.

Action Items:

- Astellas to provide the interim analysis information from Study 004 and the DSMB charter
- Astellas to provide a justification for the proposed non-inferiority margins for Study 004 (invasive aspergillosis) and Study 008 (invasive candidiasis)
- Astellas to provide the following for Study 004
 - A proposal for use of the ITT population as the primary analysis population as opposed to an MITT population
 - A proposal and rationale for a larger M2 if the MITT population is used
 - Data on use of galactomannan as inclusion criteria and assay sensitivity of dropped patients in relation to ITT and MITT populations when examined in context of the data from the voriconazole invasive aspergillosis study
 - Preliminary report of their food effect study
 - How changing entry criteria from 2002 EORTC to 2008 EORTC will change the definition of proven, probably, and possible disease and the implication on study results

Minutes Preparer: Jacquelyn Smith, MA, Regulatory Project Manager, DSPTP

Concurrence: Renata Albrecht, M.D., Director, DSPTP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-72593	GI-1	ASTELLAS PHARMA GLOBAL DEVELOPMENT INC	BAL 8557 (WATER SOLUBLE AZOLE)

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/s/

RENATA ALBRECHT
05/13/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 72,593

Basilea Pharmaceutica Ltd.
c/o Kleinfeld, Kaplan and Becker
Attention: Mr. Dan Dwyer
1140 Nineteenth Street, N.W.
Washington, D.C. 20036

Dear Mr. Dwyer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BAL 8557 (Water Soluble Azole).

We also refer to the meeting between representatives of your firm and the FDA on December 20, 2005. The purpose of the meeting was to discuss your meeting package submitted November 17, 2005. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

The official minutes of that meeting are enclosed.

If you have any questions, call Jacquelyn Smith, M.A., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Steven Gitterman, M.D., Ph.D.
Deputy Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES



Meeting Date: December 20, 2005

Time: 1:00 PM

Location: U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and Transplant Products (DSPTP)
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

IND: 72,593

Drug: BAL 8557 (Water Soluble Azole)

Sponsor: Basilea Pharmaceutica Ltd.

Type of Meeting: End-of-Phase 2 Meeting

Meeting Chair: Steven Gitterman, M.D., Ph.D., Deputy Director, DSPTP

Meeting Recorder: Jacquelyn Smith, M.A., Regulatory Project Manager, DSPTP

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Steven Gitterman, M.D., Ph.D.	Deputy Director, DSPTP
Leonard Sacks, M.D.	Medical Team Leader, DSPTP
Regina Alivisatos, M.D.	Medical Reviewer, DSPTP
William Taylor, Ph.D.	Pharmacology/Toxicology Team Leader, DSPTP
John Powers, M.D.	Lead Medical Officer, DSPTP
Owen McMaster, Ph.D.	Pharmacologist, DSPTP
Karen Higgins, Sc.D.	Statistics Team Leader, DSPTP
Cheryl Dixon, Ph.D.	Statistician, DSPTP
Philip Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology/Biopharmaceutics Team Leader, DSPTP
Dakshina Chilukuri, Ph.D.	Clinical Pharmacology/Biopharmaceutics Reviewer, DSPTP
Jacquelyn Smith, M.A.	Regulatory Project Manager, DSPTP

BASILEA PHARMACEUTICA LTD. ATTENDEES AND TITLES:

Marcus Heep, M.D.	Medical Microbiology
Jeff Hardenberg, Ph.D.	Project Management
Rienk Pypstra, M.D.	Clinical Development

Anne Schmitt-Hoffman, Ph.D.
Lutz Wevelsiep, Ph.D.

Non-Clinical & Clinical Pharmacology
Regulatory Affairs

Background: Basilea Pharmaceuticals requested an End of Phase II (EOPII) meeting with the Agency on October 18, 2005. A Phase II study of BAL8557 comparing three dosing regimens of BAL8557 to fluconazole in patients with esophageal candidiasis was recently completed. Per the information submitted, all three BAL8557 dosing regimens were as effective as the fluconazole comparator for the primary endpoint of endoscopically confirmed complete clinical cure.

Preliminary responses to the questions in the briefing package were sent to Basilea in an E-mail dated December 19, 2005. The contents of the briefing package and the Agency's comments were discussed as follows:

1. Does the Agency agree that the proposed microbiology plan would be adequate for NDA submission?

The Division agreed that the proposed microbiology plan seemed appropriate; however additional information might be needed in the course of the review, such as the criteria used for defining isolates to be fluconazole and amphotericin B resistant, and the methodology for determining ED50 values in the animal studies indicating whether these were based on survival or reduction in fungal burden.

2. Does the Agency agree that the available and proposed toxicology and pre-clinical studies would be adequate for NDA submission?

The division stated that the Toxicology Package of completed and proposed studies provided a good examination of the toxic effects of BAL8557. However, the adequacy of the Toxicology Package for an NDA submission would depend on the indications sought and the relevant dosing/duration parameters. For example, in determining the safety of extended treatment, the Division would take into account that the longest intravenous toxicology studies conducted were the six week studies in rats and monkey.

Also, since toxicity is affected by the infusion rate as well as by the dose, the most useful toxicology studies would be those in which the test drug was infused at rates and doses similar to those used clinically.

The sponsor agreed with the above.

3. Does the Agency agree that because of the long half-life of the product a human mass balance study would not be feasible and is therefore not required for NDA submission?

The Division wished to discuss this issue further with the sponsor and requested an explanation as to why this study was not feasible. The sponsor was asked to provide an

alternate proposal to adequately characterize the ADME of BAL 4815, in particular, the metabolism and excretion/elimination pathways of the drug.

As an alternative to a traditional mass-balance study, the Sponsor proposed to conduct a pharmacokinetic (PK) “excretion” study in healthy volunteers. The proposed study would involve collection of urine and feces, in addition to plasma, for a period of 1 month following administration of BAL 8557 (pro-drug).

The Agency accepted this proposal on condition that the protocol for such a study would be submitted for Agency review and comment prior to initiation. The Agency also commented that the Sponsor should not only determine concentrations of BAL 4815 (active species), but also any other major metabolites in urine, feces, and plasma so that the “fate” of BAL 8557 in the body could be adequately characterized.

4. Does the Agency agree that the available and proposed clinical pharmacology studies would be adequate to support NDA submission of the initial indications?

- a. The Division requested a comprehensive summary of the in vitro metabolism data obtained to date on BAL 8557 and BAL4815 characterizing the potential to act as a substrate, inhibitor, or inducer of the human CYP450 enzymes. In the November 8, 2004, Investigator’s Brochure, the in vitro information regarding the potential of BAL 4815 to act as a substrate for CYP450 may not have been adequately characterized in the 2-hours incubation experiments.*
- b. In view of the results of the in vitro metabolism studies which demonstrated the potential inhibitory activity against CYP2C9 and CYP2C19 in addition to CYP3A4, the Division felt it necessary for the sponsor to conduct an additional in vivo drug interaction study with substrates of CYP2C19 such as omeprazole or esoprazole.*
- c. In protocol WSA-CS-002 for the prophylaxis of patients undergoing chemotherapy for acute myeloid leukemia, a single loading doses of 400 or 800 mg of BAL8557/4815 was to be administered. It would be necessary to characterize the PK, safety and tolerability of the single 800 mg dose of BAL 8557 in healthy subjects prior to administration of that dose in patients. On review of the background package, it did not appear that the single dose PK, safety and tolerability of BAL 4815 had been characterized using the 800 mg single dose of BAL8557.*

This point was discussed with the sponsor and it was agreed that this data could be collected in patients. If performed in patients, information on concurrent medications would be needed.

- d. The background package did not indicate that a food effect study had been performed for BAL8557. The Division recommended conducting a food-effect study and referred the sponsor to the FDA Guidance titled “Food-Effect Bioavailability and Fed Bioequivalence Studies” (<http://www.fda.gov/cder/guidance/index.htm>).*

- e. *The sponsor indicated that study BAP00400 to determine if BAL8557 affects cardiac repolarization (QT Study) was complete. However, the bioanalytic measurements of BAL 8557 blood samples were ongoing and would be submitted to the FDA as soon as available. The Division responded that a review of all the data from this QT study would be needed to determine if additional studies were required to characterize the QT prolongation effect of BAL8557.*

During the discussion of this question, the clinical review team indicated that the proposed dose escalation study in the background package could proceed from a safety standpoint. However, if the Sponsor intended to give the drug with meals in the Phase 3 clinical studies, then a Food-Effect PK study would be needed prior to initiation of these studies so that the effects of a meal on the PK of BAL 8557/4815 were understood.

The Agency also requested a PK assessment study be done in the elderly (~20 (both sexes)). This could be nested in a phase 3 study.

- 5. Does the Agency agree that the available data provide adequate information to initiate the proposed Phase 3 study in [REDACTED] (b) (4) and the proposed dose escalation study?**

The Division agreed that there appeared to be adequate safety and efficacy data from the Phase I and Phase II trials to support the initiation of a Phase III trial for the [REDACTED] (b) (4)

The Sponsor indicated that they planned to initiate the study.

- 6. Does the Agency agree that the completed dose-ranging study in [REDACTED] (b) (4) and the proposed Phase 3 study [REDACTED] (b) (4)**

[REDACTED] (b) (4)

- 7. Does the Agency agree that the proposed [REDACTED] (b) (4)**

[REDACTED] (b) (4)

[REDACTED] (b) (4)

It was noted that numerous issues in [REDACTED] (b) (4) trials complicated the evaluation of efficacy including:

[REDACTED] (b) (4)

An adequate and well-controlled study demonstrating efficacy in the primary treatment of invasive aspergillosis could be supportive of efficacy [REDACTED] (b) (4)

The Sponsor acknowledged the Division's position regarding [REDACTED] (b) (4)

[REDACTED]

The sponsor agreed to pursue a primary indication for the treatment of invasive aspergillosis in a randomized controlled study. The division expressed its preference for blinding of treatment in such as study if this was possible. The division agreed that a single study of invasive aspergillosis might be sufficient for this indication.

The division agreed that a prophylaxis study could be performed, possibly with fluconazole as the comparator. However this should be viewed as a secondary goal following the demonstration of efficacy in a treatment indication. The division agreed that both such studies could be submitted simultaneously.

8. Based upon previous applications are there any primary endpoints which would not be acceptable to the Agency?

Clarification of this question was requested by the Division. There was no further discussion.

10. What does the Agency require in terms of pre-clinical/PK data in order to initiate a combination study with BAL8557 and an echinocandin?

The Division needs to see preclinical combination studies of BA 8557 since it is a new molecular entity before clinical studies are undertaken. The potential that this new drug could act synergistically with an echinocandin to produce severe toxic effects in patients needs to be addressed.

Based on the known PK characteristics of approved echinocandins, the Division felt that from a PK perspective, no dedicated PK drug-interaction studies would be needed. However, it was noted that it might be helpful to obtain the systemic concentrations of BAL 8557/4815 and the echinocandin used in combination as part of the Phase III study to assess the relationship between systemic concentrations and the occurrence of any adverse events when the two drugs are given together.

Also, in view of the potential risk of liver injury to patients on combined therapy with BAL8557 and echinocandins, the Division felt it necessary for the sponsor to monitor the hepatic safety of the patients receiving the combined therapies of BAL8557 and echinocandins.

The Division agreed that animal models would be helpful to evaluate the efficacy of a drug combination.

Possible human study designs included a three arm study looking at each individual drug and the combination, or a factorial design using voriconazole with or without an echinocandin as a comparator.

The division discouraged initial human efficacy studies of BAL8557 in combination with an echinocandin. This would require the demonstration of superiority to the comparator. The division felt it would be easier to demonstrate the efficacy of BAL-8557 when used as mono-therapy.

11. We would like to obtain the Agency's perspective on the medical need of these supplementary indications. Based on this, would the agency recommend to prioritize the assessment of efficacy/safety of BAL8557 in any of these indications.

The Division agreed that

(b) (4)

12. Does the Agency agree that the proposed safety database of approximately 500 patients would be adequate for initial NDA submission?

(b) (4)

The sponsor was referred to the ICH E1A Guidance Document from March, 1995. Most ADEs would be expected to occur within the first few months of drug treatment. The Division felt that the cohort of exposed subjects should be large enough to observe whether more frequently occurring events increase or decrease over time. The study should also be designed to observe delayed events of reasonable frequency (e.g., in the general range of 0.5%-5%). The Division felt that 300-600 patients might be adequate to address these objectives. As some uncommon ADEs may increase in frequency or severity with time or after 6 months, some patients (about 100) should be treated with the drug for 12 months. Generally higher doses would support the lower doses but not the opposite. A safety database of a minimum of 300 - 600 subjects with at the proposed dose and duration of treatment or greater might be adequate to support an approval provided no signals of toxicity emerged.

This was acknowledged by the Sponsor.

The Sponsor also discussed the utility of pursuing fast track designation and priority review status. The Agency referred the sponsor to the FDA document "Guidance for Industry on Fast Track Drug Development Programs: Designation, Development, and Application Review." This document is also available on the internet at <http://www.fda.gov/cder/guidance/index.htm>. The Sponsor was informed that fast track designation does not guarantee a priority review and that determination is made at the time of NDA submission and depends on the merits of the final NDA application.

Minutes Preparer: Jacquelyn Smith, M.A., Regulatory Project Manager, DSPTP
Chair Concurrence: Steven Gitterman, M.D., Ph.D., Deputy Director, DSPTP

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this page is the manifestation of the electronic signature.**

/s/

Steven Gitterman
1/19/2006 11:41:12 AM

LATE-CYCLE COMMUNICATION
DOCUMENTS

Rodgers, Alison

From: Rodgers, Alison
Sent: Friday, December 19, 2014 4:37 PM
To: Reed, Robert (Robert.Reed@astellas.com)
Subject: NDAs 207500 and 207501 Late Cycle Meeting Agenda
Attachments: Late Cycle Meeting Agenda template.pdf

Importance: High

Hi Robert,

As promised, please see the attached Late Cycle Meeting Agenda for the Cresemba NDAs.

Also, we will not be sending our final label today. It should be ready week after next.

Please confirm receipt of this email.

Take care and have a wonderful holiday,

Alison

*Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882*



NDA 207500
NDA 207501

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Astellas Pharma US Inc.
Attention: Robert M. Reed
Senior Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Mr. Reed:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cresemba (b) (4) Capsules (NDA 207500) and Powder for Injection (NDA 207501).

We also refer to the Late-Cycle Meeting (LCM) scheduled for January 9, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date: January 9, 2015
Meeting Location: 10903 New Hampshire Avenue, Silver Spring, MD 20993
Building #22 Room 1415
Application Numbers: NDAs 207500 and 207501
Product Name: CRESEMBA (b) (4) Capsules (NDA 207500)
CRESEMBA (b) (4) Powder for Injection
(NDA 207501)
Indications: Treatment of invasive aspergillosis and mucormycosis
Sponsor/Applicant Name: Astellas Pharma US Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans, and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to the LCM or the AC meeting, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

There are no substantive review issues to discuss.

ADVISORY COMMITTEE MEETING

Date of AC meeting: January 22, 2015

Date AC briefing package will be received under separate cover from the Division of Advisory Committee and Consultant Management: December 23, 2014

Potential discussion topics for AC meeting are as follows:

1. Has the applicant provided substantial evidence of the safety and effectiveness of isavuconazonium for the treatment of invasive aspergillosis?
 - If yes, please provide any recommendations concerning labeling.
 - If no, what additional studies/analyses are needed?

2. Has the applicant provided substantial evidence of the safety and effectiveness of isavuconazonium for the treatment of invasive mucormycosis?
 - If yes, please provide any recommendations concerning labeling.
 - If no, what additional studies/analyses are needed?

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:

<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

REMS OR OTHER RISK MANAGEMENT ACTIONS

As conveyed during the Mid-Cycle Communication on October 15, 2014, the Agency does not anticipate the need for a Risk Evaluation and Mitigation Strategy (REMS).

LATE CYCLE MEETING AGENDA

1. Introductory Comments –

Welcome, Introductions, Ground rules, and Objectives of the meeting

2. Discussion of Minor Review Issues – 5 minutes

- Some discrepancies regarding specifications for impurities are still under review (see information request).

3. Information Requests – 5 minutes

We expect that there will be further information requests regarding specifications for impurities.

4. Discussion of Upcoming Advisory Committee Meeting – 10 minutes

There is a planned Advisory Committee Meeting on January 22, 2015.

5. Postmarketing Requirements/Postmarketing Commitments –10 minutes

Postmarketing Requirements:

- Conduct surveillance studies for five years from the date of marketing CRESEMBA to determine if there [REDACTED] (b) (4) in organisms relevant to the indication in the package insert for invasive aspergillosis and mucormycosis.
- Discuss the possibility of conducting a carcinogenicity study.
- We acknowledge that PREA does not apply to an orphan drug product, but wish to discuss any additional plans for pediatric studies in these indications.

Postmarketing Commitments:

- Discuss the potential for a postmarketing commitment to develop a registry of isavuconazonium-treated patients with *Aspergillus* or Mucorales infections.

6. Major labeling issues – 10 minutes

We have provided you with our initial recommendations at this time and we still need to come to agreement on the changes recommended by the Division. We expect a response from you by January 5, 2015.

In our communication of December 19, 2014, our recommendation on the name and strength of the drug product has been conveyed.

At this time, the labeling that has been provided does not include [REDACTED] (b) (4) [REDACTED] for *Aspergillus*.

7. Review Plans – 5 minutes

- Discipline reviews are expected to be completed within pre-specified timelines.
- Continue with labeling review and discussions

8. Wrap-up and Action Items – 5 minutes

January 22, 2015 AIDAC Meeting.

Complete labeling discussions.

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/s/

SUMATHI NAMBIAR
12/19/2014



NDA 207500
NDA 207501

LATE-CYCLE MEETING MINUTES

Astellas Pharma US Inc.
Attention: Robert M. Reed
Senior Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Mr. Reed:

Please refer to your New Drug Applications (NDAs) dated July 8, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for CRESEMBA (isavuconazonium) Capsules (NDA 207500) and Powder for Injection (NDA 207501).

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA held on January 9, 2015.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

John J. Alexander, MD, MPH
Clinical Team Leader
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: January 9, 2015, 11:00 AM – 12:00 PM

Meeting Location: Teleconference

Application Numbers: NDA 207500 and 207501

Product Names: CRESEMBA (b) (4) Capsules (NDA 207500)
CRESEMBA (b) (4) Powder for Injection
(NDA 207501)

Applicant Name: Astellas Pharma US Inc.

Meeting Chair: John J. Alexander, MD, MPH

Meeting Recorder: Alison Rodgers

Applicant: Astellas Pharma US Inc.

FDA ATTENDEES

Division of Anti-Infective Products

John J. Alexander, MD, MPH, Clinical Team Leader
Shukal Bala, PhD, Clinical Microbiology Reviewer
Dakshina Chilukuri, PhD, Clinical Pharmacology Reviewer
Cheryl Dixon, PhD, Statistics Reviewer
Philip Colangelo, PharmD, PhD, Clinical Pharmacology Team Leader
Karen Higgins, ScD, Statistics Team Leader
Gene Holbert, PhD, Chemistry, Manufacturing, and Controls Reviewer
Katherine Laessig, MD, Deputy Director
Owen McMaster, PhD, Pharmacology and Toxicology Reviewer
Sumathi Nambiar, MD, MPH, Director
Nina Ni, PhD, Chemistry, Manufacturing, and Controls Reviewer
Elizabeth O'Shaughnessy, MD, Medical Officer
Wendelyn Schmidt, PhD, Pharmacology and Toxicology Team Leader
Yichun Sun, PhD, Chemistry, Manufacturing, and Controls Reviewer
Edward Weinstein, MD, PhD, Medical Officer
Banu Zolnik, PhD, Biopharmaceutics Reviewer

Office of Antimicrobial Products

John Farley, MD, MPH, Deputy Director

Office of Clinical Pharmacology

Division of Pharmacometrics

Dhananjay Marathe, PhD, Pharmacometrics Reviewer

2.0 DISCUSSION

1. Introductory Comments

2. Discussion of Minor Review Issues

- Some discrepancies regarding specifications for impurities are still under review (see information request).

3. Information Requests

- We expect that there will be further information requests regarding specifications for impurities.

Discussion: FDA thanked Astellas for sending the corrected information regarding the impurity levels in the CRESEMBA batches and indicated that we did not anticipate requesting additional information.

4. Discussion of Upcoming Advisory Committee Meeting

- There is a planned Advisory Committee Meeting on January 22, 2015.

Discussion: The Advisory Committee Meeting is scheduled for January 22, 2015, and will be held in White Oak Building 31, Great Room, Sections B and C.

FDA acknowledged receipt of Astellas' submission concerning discrepancies between FDA's Advisory Committee Briefing Book and theirs. FDA will address issues as needed during the Advisory Committee Meeting. Astellas agreed.

Astellas asked if the FDA had identified any new issues since Astellas submitted their briefing book. FDA responded that we had not identified any new issues, but that final questions would not be publicly available until just before the meeting.

Based on FDA's briefing book and draft label, Astellas asked if an Advisory Committee Meeting was necessary as there appears to be general agreement on the key issues. FDA agreed that there is concordance but explained that it is important to have input from the Advisory Committee, particularly regarding the mucormycosis indication.

FDA described the agenda for the Advisory Committee.

5. Postmarketing Requirements/Postmarketing Commitments

Postmarketing Requirements (PMR):

- Conduct surveillance studies for five years from the date of marketing CRESEMBA to determine if there is a (b) (4) in organisms relevant to the indication in the package insert for invasive aspergillosis and mucormycosis.

Discussion: Astellas noted that this PMR is already underway and they have provided written agreement to conduct the microbiology surveillance studies. Astellas will submit interim standalone reports to the NDA. FDA acknowledged receipt of Astellas' agreement to conduct the study.

- Discuss the possibility of conducting a carcinogenicity study.

Discussion: FDA referenced the ICH document "Guideline on the need for carcinogenicity studies of pharmaceuticals, S1A" which states that carcinogenicity studies should be performed for any pharmaceutical whose expected clinical use is continuous for at least six months and also states that a drug that is given for three months would also likely be used for six months. FDA acknowledged the applicant's assertion that CRESEMBA is indicated for serious diseases which are often fatal and that other azoles have been shown to be carcinogenic, (b) (4) FDA recommended a two year carcinogenicity study in rats and a second (b) (4) transgenic mouse study. Astellas should submit their plan to evaluate carcinogenicity and FDA will request review by the Executive Carcinogenicity Assessment Committee for approval.

Astellas agreed with the recommendation and requested clarification of the timeline for submitting a protocol. FDA asked that Astellas include their proposal for a carcinogenicity study when they respond to the PMR. Astellas should provide a plan for assessing carcinogenicity and include a proposed timeline in their official submission to FDA.

- We acknowledge that PREA does not apply to an orphan drug product, but wish to discuss any additional plans for pediatric studies in these indications.

Discussion: (b) (4)

(b) (4)

(b) (4)

Astellas noted that they have orphan designation for invasive candidiasis (b) (4)

(b) (4)

Postmarketing Commitments (PMC):

- Discuss the potential for a postmarketing commitment to develop a registry of isavuconazonium-treated patients with *Aspergillus* or Mucorales infections.

Discussion: FDA expressed that it might be useful to have a registry of patients being treated for these indications. Astellas asked if the purpose of the registry would be to collect efficacy and safety data for both aspergillosis and mucormycosis. The FDA requires further internal discussion before responding to this question, but suggested that additional data on infections due to less common *Aspergillus* species may be useful. Astellas asked if the registry would be United States (US) only or global. FDA is open to either. There is currently a registry in Europe for patients with mucormycosis (Fungiscope), but the FDA is open to a US branch of that registry or just collecting data on US patients.

Astellas noted that the data in the European registry is primarily mortality data. FDA acknowledged that we would be interested in data besides mortality for mucormycosis.

Astellas asked the FDA to comment regarding the size and duration of the registry it envisions. The FDA cannot respond to this question at this time as it does not know how long it will take to collect a number of Mucorales infections. The FDA asked if Astellas had any thoughts as to the time it would take to have a

number of patients with Mucorales infections. Astellas needs more internal discussion and asked when a response is required. The FDA responded that a response should be submitted by mid-February. A statement of agreement from Astellas along with a timeline for a protocol for the registry and a timeline for an interim submission(s) are required.

6. Major labeling issues

We have provided you with our initial recommendations at this time and we still need to come to agreement on the changes recommended by the Division. We expect a response from you by January 5, 2015.

In our communication of December 19, 2014, our recommendation on the name and strength of the drug product has been conveyed.

At this time, the labeling that has been provided does not include [REDACTED] (b) (4) for *Aspergillus*.

Discussion: *In response to some comments made during the discussion of the PMC for a registry, Astellas asked [REDACTED] (b) (4) [REDACTED] Astellas acknowledged the response.*

The FDA acknowledged receipt of Astellas' response to labeling on January 8, 2015. FDA will review the label and respond to Astellas after the Advisory Committee Meeting, including a teleconference to discuss disagreements, if necessary.

Astellas expressed concern that [REDACTED] (b) (4) of the drug could lead to medication errors and requested further discussion with the appropriate individuals. FDA will address the topic during labeling discussions.

With regard to the Patient Package Insert (PPI), Astellas noted that some of the directions regarding how to open the blister pack had been removed by the FDA. Astellas deems these instructions to be important so they added them back in. FDA will address the issue with the team that reviews the PPI.

7. Review Plans

- Discipline reviews are expected to be completed within pre-specified timelines.
- Continue with labeling review and discussions

Discussion: *FDA indicated that the review process was proceeding as expected, and*

FDA expected to provide a response regarding Astellas' labeling response after the AIDAC meeting.

8. Wrap-up and Action Items

- January 22, 2015 AIDAC Meeting
- Complete labeling and PMR/PMC discussions

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

JOHN J ALEXANDER
02/04/2015