IND 072593
IND 119307
NDA 207500
NDA 207501

WRITTEN REQUEST – AMENDMENT 1

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

Dear Mr. Reed:

Please refer to your correspondence dated July 29, 2022, requesting changes to FDA's October 24, 2017, Written Request for pediatric studies for Cresemba (isavuconazonium sulfate).

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on October 24, 2017, remain the same. (Text added is underlined. Text deleted is strikethrough.)

Reference is made to your February 23, 2017, Proposed Pediatric Study Request for Cresemba (isavuconazonium sulfate) Capsules (NDA 207500) and Powder for Injection (NDA 207501).

BACKGROUND:

Cresemba (isavuconazonium sulfate) was approved in patients 18 years of age and older for the treatment of invasive aspergillosis (IA) and invasive mucormycosis (IM) on March 6, 2015; Cresemba received orphan drug designation for both indications. These are rare life-threatening fungal infections found in both adult and pediatric patients. It is estimated that patients less than 18 years of age comprise 4.7% of IA patients in the United States, producing an incidence rate of roughly one case per 77,000 hospital discharges.[1] Invasive mucormycosis is less common than IA, and likewise occurs less frequently in pediatric patients than in adults. A report based on European registry data identified a total of 63 cases from 15 countries over a 10 year period. [2] Neonates and

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[2] Pana, ZD; Seidel, D; Skiada, A; Groll, AH; Petrikkos, G; Cornely, OA; Roilides, E; Collaborators of Zygomyco net and/or FungiScope™ Registries. Invasive mucormycosis in children: an epidemiologic study in European and non-European countries based on two registries. BMC Infect Dis. 2016 Nov 10;16(1):667.

infants comprise less than 8% of children diagnosed with IA and IM. [2,3]These diseases result in significant mortality in the pediatric population with 31% and 35% case-fatality rates for IA and IM, respectively, in treated patients ≤18 years of age. [4] Importantly, there are no mold-active azoles approved for treatment of children less than 12 years of age.

The pathophysiology of both IA and IM in pediatric patients is similar to that of adults, with similar patient risk factors, causative species, signs, symptoms, and clinical outcomes, allowing for extrapolation of the adult efficacy data to pediatric patients once adequate pharmacokinetic (PK) and safety data have been collected. Due to the rarity of the infections as described above, studies in pediatric patients under the age of 1 year including neonates are not considered feasible and are not requested.

Cresemba is available as an intravenous (IV) formulation and an oral capsule. Thus far, the physicochemical properties of the active moiety have impeded the development of an age appropriate oral formulation for children under the age of 12 years.

To obtain needed pediatric information on isavuconazonium for the treatment of IA and IM, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical studies*:
  Based on review of the available nonclinical toxicology, including nonclinical juvenile toxicity studies, no additional animal studies are required at this time to support the clinical studies described in the written request.

- *Clinical Studies*:

  Study 1:
  A Phase 1, open-label study to evaluate the pharmacokinetics (PK) and safety of IV Cresemba in children and adolescents ages 1 to less than 18 years of age who may, in the judgment of the investigator, benefit from systemic anti-mold prophylaxis.

  Study 2:

[3] Burgos A1, Zaoutis TE, Dvorak CC, Hoffman JA, Knapp KM, Nania JJ, Prasad P, Steinbach WJ. Pediatric invasive aspergillosis: a multicenter retrospective analysis of 139 contemporary cases. Pediatrics. 2008 May;121(5):e1286-94.
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A Phase 2, interventional, non-comparative, open-label, multi-center study to evaluate the pharmacokinetics, safety, and efficacy of IV and/or oral Cresemba in children and adolescents ages 1 to less than 18 years of age.

Efficacy of Cresemba for IA and IM in children 1 to less than 18 years of age can be extrapolated from adequate and well-controlled adult studies because the course of the disease and the effects of therapy are sufficiently similar between adults and pediatric patients. The pharmacokinetic results from Study 1 will identify the dose regimen of Cresemba that will achieve systemic PK exposure similar to that attained in adults. Additional supportive efficacy, safety, and pharmacokinetic data will be provided by the results from Study 2.

Study 1 must be completed before Study 2 to inform dosing. The results of Study 1 must be reported to the Agency prior to the initiation of Study 2 in order to gain agreement on the dosing in Study 2.

- *Objective of each study:*

Study 1:
To evaluate the pharmacokinetics and safety of IV Cresemba with loading and after repeated daily maintenance dosing in children (1 to 5 years and 6 to 11 years of age) and in adolescents (12 to less than 18 years of age) who may, in the judgment of the investigator, benefit from systemic anti-mold prophylaxis.

Study 2:
To describe the safety and efficacy of IV and/or oral Cresemba for the treatment of IA or IM in pediatric patients aged 1 to less than 18 years.

- *Patients to be Studied:*

Study 1:

Pediatric patients aged 1 to less than 18 years who may, in the judgment of the investigator, benefit from systemic anti-mold prophylaxis.
Three age cohorts will be enrolled as follows:

Cohort 1: 12 to < 18 years of age

Cohort 2: 6 to < 12 years of age

Cohort 3: 1 to < 6 years of age

Study 2:
Pediatric patients aged 1 to less than 18 years of age diagnosed with IA or IM. A positive diagnosis is defined as proven, probable, or possible invasive fungal infection per the European Organisation for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) 2008 criteria (specific glactomannan cut off values to be agreed upon with FDA at the time of protocol development).[5]

- *Number of patients to be studied:*

Study 1:
A minimum of 24 subjects will be enrolled into 3 age cohorts to yield at least 8 PK-evaluable subjects in each cohort. Within each cohort (i.e., 1 year to less than 6 years; 6 years to less than 12 years; 12 years to less than 18 years) an approximately equal age distribution of patients should be enrolled.

Study 2:
A minimum of 30 subjects treated with isavuconazonium will be enrolled.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*
Study 1:
Pharmacokinetic endpoints:
The PK endpoints for Study 1 must include; clearance (CL), AUC at steady state (AUC_{ss}), maximum concentration at steady state (C_{max}), time to C_{max} (T_{max}) and volume of distribution at steady state (V_{ss}).

The 24-hour PK profile must include blood samples collected on day 3 (through 24 hours post dose), and/or day 7 (through 24 hours post dose) and/or at the end-of-treatment (EOT) visits.

[5] De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/ Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008; 46:1813–21

If the subject is available for PK sampling beyond day 9, trough sampling should be performed weekly.

Safety Endpoints:
Safety outcomes must include: adverse events, tolerability, vital signs, electrocardiograms (ECGs) and laboratory parameters.

The following adverse events must be actively monitored: hepatic adverse events and abnormal liver tests (enzymes, bilirubin, albumin, coagulation). Monitoring should include liver tests performed at baseline, study day 3, study day 7, then weekly thereafter while subjects are receiving test drug.

All adverse events must be monitored until symptom resolution or until the condition stabilizes.

Study 2:
Efficacy Endpoints:
The primary efficacy endpoint will be all-cause mortality at Day 42, and a key secondary endpoint will be all-cause mortality at Day 84.

Safety Endpoints:
Safety outcomes must includeadverse events, tolerability, vital signs, electrocardiograms (ECGs) and laboratory parameters.

The following adverse events must be actively monitored: hepatic adverse events and abnormal liver tests (enzymes, bilirubin, albumin, coagulation). Monitoring should include liver tests performed at baseline, study day 3, study day 7, then weekly thereafter while subjects are receiving test drug.

All adverse events must be monitored until symptom resolution or until the condition stabilizes.

Pharmacokinetic Endpoints:

Sparse PK samples must be collected from all enrolled patients.

- *Known drug safety concerns and monitoring:*
  Adverse events, including laboratory parameters and survival, should be assessed for all subjects who receive at least one dose of study drug. Specific adverse events, such as abnormal liver tests, and isolated instances of serious

hypersensitivity reactions (anaphylaxis and anaphylactoid) have been reported with the use of Cresemba and should be monitored throughout the study.

- *Extraordinary results:* In the course of conducting these studies you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

  Study 1:

  - *dosage form:* intravenous injection
  - *route of administration:* intravenous infusion
  - *regimen:* loading regimen every 8 hours for 6 doses followed by once daily maintenance dose

  Study 2:

  - *dosage form:* intravenous injection and/or oral capsules
  - *route of administration:* intravenous infusion and/or oral
  - *regimen:* loading regimen every 8 hours for 6 doses followed by once daily maintenance dose as guided by the results from Study 1. Intravenous and oral formulations may be dosed interchangeably, as equivalence has been established in adults.

  Use an age-appropriate oral formulation in Study 2 described above. If an age-appropriate oral formulation is not currently available, you must develop and test an age-appropriate oral formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate oral formulation.

  In accordance with section 505A(e)(2), if

  1) you develop an age-appropriate oral formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);

2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

The pharmacokinetics of any age appropriate oral formulation used in Study 2 must be characterized in pediatric patients, and as needed, a relative bioavailability study comparing the approved oral capsule formulation to the age appropriate oral formulation may be conducted in adults.

- *Statistical information, including power of study(ies) and statistical assessments:*

  Study 1:
  The PK profile of intravenous Cresemba must be characterized. Plasma concentration data and PK parameters must be summarized by descriptive statistics and by each individual subject by treatment day. The incidence of treatment emergent adverse events must be summarized by relationship to study drug and overall. In addition, laboratory values and vital signs (if applicable) must be summarized.

  Study 2:
  The incidence of treatment emergent adverse events must be summarized by relationship to study drug and in general. The PK of IV and/or oral Cresemba

must be characterized based on a Population PK model. In addition, laboratory values and vital signs (if applicable) must be summarized. A descriptive summary of the efficacy outcomes must be provided.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that Cresemba is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document “Study Data Specifications,” which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in

the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before ~~December 15, 2022~~ December 15, 2023. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated October 24, 2017, as amended by this letter must be submitted to the Agency on or before December 15, 2023, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION**

REQUESTED" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[6]

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

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

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Director
Office of Infectious Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Complete Copy of Written Request as Amended

[6] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

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WRITTEN REQUEST – AMENDMENT 1

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Attention: Robert M. Reed
Executive Director, Regulatory Affairs
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Dear Mr. Reed:

Please refer to your correspondence dated July 29, 2022, requesting changes to FDA's October 24, 2017, Written Request for pediatric studies for Cresemba (isavuconazonium sulfate).

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on October 24, 2017, remain the same. (Text added is underlined. Text deleted is strikethrough.)

Reference is made to your February 23, 2017, Proposed Pediatric Study Request for Cresemba (isavuconazonium sulfate) Capsules (NDA 207500) and Powder for Injection (NDA 207501).

BACKGROUND:

Cresemba (isavuconazonium sulfate) was approved in patients 18 years of age and older for the treatment of invasive aspergillosis (IA) and invasive mucormycosis (IM) on March 6, 2015; Cresemba received orphan drug designation for both indications. These are rare life-threatening fungal infections found in both adult and pediatric patients. It is estimated that patients less than 18 years of age comprise 4.7% of IA patients in the United States, producing an incidence rate of roughly one case per 77,000 hospital discharges.[1] Invasive mucormycosis is less common than IA, and likewise occurs less frequently in pediatric patients than in adults. A report based on European registry data identified a total of 63 cases from 15 countries over a 10 year period. [2] Neonates and

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infants comprise less than 8% of children diagnosed with IA and IM. [2,3]These diseases result in significant mortality in the pediatric population with 31% and 35% case-fatality rates for IA and IM, respectively, in treated patients ≤18 years of age. [4] Importantly, there are no mold-active azoles approved for treatment of children less than 12 years of age.

The pathophysiology of both IA and IM in pediatric patients is similar to that of adults, with similar patient risk factors, causative species, signs, symptoms, and clinical outcomes, allowing for extrapolation of the adult efficacy data to pediatric patients once adequate pharmacokinetic (PK) and safety data have been collected. Due to the rarity of the infections as described above, studies in pediatric patients under the age of 1 year including neonates are not considered feasible and are not requested.

Cresemba is available as an intravenous (IV) formulation and an oral capsule. Thus far, the physicochemical properties of the active moiety have impeded the development of an age appropriate oral formulation for children under the age of 12 years.

To obtain needed pediatric information on isavuconazonium for the treatment of IA and IM, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical studies*:
  Based on review of the available nonclinical toxicology, including nonclinical juvenile toxicity studies, no additional animal studies are required at this time to support the clinical studies described in the written request.

- *Clinical Studies*:

  Study 1:
  A Phase 1, open-label study to evaluate the pharmacokinetics (PK) and safety of IV Cresemba in children and adolescents ages 1 to less than 18 years of age who may, in the judgment of the investigator, benefit from systemic anti-mold prophylaxis.

  Study 2:

[3] Burgos A1, Zaoutis TE, Dvorak CC, Hoffman JA, Knapp KM, Nania JJ, Prasad P, Steinbach WJ. Pediatric invasive aspergillosis: a multicenter retrospective analysis of 139 contemporary cases. Pediatrics. 2008 May;121(5):e1286-94.
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A Phase 2, interventional, non-comparative, open-label, multi-center study to evaluate the pharmacokinetics, safety, and efficacy of IV and/or oral Cresemba in children and adolescents ages 1 to less than 18 years of age.

Efficacy of Cresemba for IA and IM in children 1 to less than 18 years of age can be extrapolated from adequate and well-controlled adult studies because the course of the disease and the effects of therapy are sufficiently similar between adults and pediatric patients. The pharmacokinetic results from Study 1 will identify the dose regimen of Cresemba that will achieve systemic PK exposure similar to that attained in adults. Additional supportive efficacy, safety, and pharmacokinetic data will be provided by the results from Study 2.

Study 1 must be completed before Study 2 to inform dosing. The results of Study 1 must be reported to the Agency prior to the initiation of Study 2 in order to gain agreement on the dosing in Study 2.

- *Objective of each study:*

Study 1:
To evaluate the pharmacokinetics and safety of IV Cresemba with loading and after repeated daily maintenance dosing in children (1 to 5 years and 6 to 11 years of age) and in adolescents (12 to less than 18 years of age) who may, in the judgment of the investigator, benefit from systemic anti-mold prophylaxis.

Study 2:
To describe the safety and efficacy of IV and/or oral Cresemba for the treatment of IA or IM in pediatric patients aged 1 to less than 18 years.

- *Patients to be Studied:*

Study 1:

Pediatric patients aged 1 to less than 18 years who may, in the judgment of the investigator, benefit from systemic anti-mold prophylaxis.
Three age cohorts will be enrolled as follows:

Cohort 1: 12 to < 18 years of age

Cohort 2: 6 to < 12 years of age

Cohort 3: 1 to < 6 years of age

Study 2:
Pediatric patients aged 1 to less than 18 years of age diagnosed with IA or IM. A positive diagnosis is defined as proven, probable, or possible invasive fungal infection per the European Organisation for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) 2008 criteria (specific glactomannan cut off values to be agreed upon with FDA at the time of protocol development).[5]

- *Number of patients to be studied:*

Study 1:
A minimum of 24 subjects will be enrolled into 3 age cohorts to yield at least 8 PK-evaluable subjects in each cohort. Within each cohort (i.e., 1 year to less than 6 years; 6 years to less than 12 years; 12 years to less than 18 years) an approximately equal age distribution of patients should be enrolled.

Study 2:
A minimum of 30 subjects treated with isavuconazonium will be enrolled.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*
Study 1:
Pharmacokinetic endpoints:
The PK endpoints for Study 1 must include; clearance (CL), AUC at steady state (AUC_{ss}), maximum concentration at steady state (C_{max}), time to C_{max} (T_{max}) and volume of distribution at steady state (V_{ss}).

The 24-hour PK profile must include blood samples collected on day 3 (through 24 hours post dose), and/or day 7 (through 24 hours post dose) and/or at the end-of-treatment (EOT) visits.

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If the subject is available for PK sampling beyond day 9, trough sampling should be performed weekly.

Safety Endpoints:
Safety outcomes must include: adverse events, tolerability, vital signs, electrocardiograms (ECGs) and laboratory parameters.

The following adverse events must be actively monitored: hepatic adverse events and abnormal liver tests (enzymes, bilirubin, albumin, coagulation). Monitoring should include liver tests performed at baseline, study day 3, study day 7, then weekly thereafter while subjects are receiving test drug.

All adverse events must be monitored until symptom resolution or until the condition stabilizes.

Study 2:
Efficacy Endpoints:
The primary efficacy endpoint will be all-cause mortality at Day 42, and a key secondary endpoint will be all-cause mortality at Day 84.

Safety Endpoints:
Safety outcomes must includeadverse events, tolerability, vital signs, electrocardiograms (ECGs) and laboratory parameters.

The following adverse events must be actively monitored: hepatic adverse events and abnormal liver tests (enzymes, bilirubin, albumin, coagulation). Monitoring should include liver tests performed at baseline, study day 3, study day 7, then weekly thereafter while subjects are receiving test drug.

All adverse events must be monitored until symptom resolution or until the condition stabilizes.

Pharmacokinetic Endpoints:

Sparse PK samples must be collected from all enrolled patients.

- *Known drug safety concerns and monitoring:*
  Adverse events, including laboratory parameters and survival, should be assessed for all subjects who receive at least one dose of study drug. Specific adverse events, such as abnormal liver tests, and isolated instances of serious

hypersensitivity reactions (anaphylaxis and anaphylactoid) have been reported with the use of Cresemba and should be monitored throughout the study.

- *Extraordinary results:* In the course of conducting these studies you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

  Study 1:

  - *dosage form:* intravenous injection
  - *route of administration:* intravenous infusion
  - *regimen:* loading regimen every 8 hours for 6 doses followed by once daily maintenance dose

  Study 2:

  - *dosage form:* intravenous injection and/or oral capsules
  - *route of administration:* intravenous infusion and/or oral
  - *regimen:* loading regimen every 8 hours for 6 doses followed by once daily maintenance dose as guided by the results from Study 1. Intravenous and oral formulations may be dosed interchangeably, as equivalence has been established in adults.

  Use an age-appropriate oral formulation in Study 2 described above. If an age-appropriate oral formulation is not currently available, you must develop and test an age-appropriate oral formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate oral formulation.

  In accordance with section 505A(e)(2), if

  1) you develop an age-appropriate oral formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);

2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

The pharmacokinetics of any age appropriate oral formulation used in Study 2 must be characterized in pediatric patients, and as needed, a relative bioavailability study comparing the approved oral capsule formulation to the age appropriate oral formulation may be conducted in adults.

- *Statistical information, including power of study(ies) and statistical assessments:*

  Study 1:
  The PK profile of intravenous Cresemba must be characterized. Plasma concentration data and PK parameters must be summarized by descriptive statistics and by each individual subject by treatment day. The incidence of treatment emergent adverse events must be summarized by relationship to study drug and overall. In addition, laboratory values and vital signs (if applicable) must be summarized.

  Study 2:
  The incidence of treatment emergent adverse events must be summarized by relationship to study drug and in general. The PK of IV and/or oral Cresemba

must be characterized based on a Population PK model. In addition, laboratory values and vital signs (if applicable) must be summarized. A descriptive summary of the efficacy outcomes must be provided.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that Cresemba is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document “Study Data Specifications,” which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in

the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before December 15, 2023. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated October 24, 2017, as amended by this letter must be submitted to the Agency on or before December 15, 2023, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION**

REQUESTED" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[6]

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

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

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Director
Office of Infectious Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Complete Copy of Written Request as Amended

[6] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN J FARLEY
10/06/2022 09:56:31 AM