CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217417Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 124401

MEETING PRELIMINARY COMMENTS

Cidara Therapeutics, Inc.
Attention: Carol Waldo, MLA, RAC
Senior Vice President, Regulatory Affairs and Quality Assurance
6310 Nancy Ridge Drive, Suite 101
San Diego, CA 92121

Dear Ms. Waldo:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for rezafungin for injection.

We also refer to your January 3, 2022, correspondence, received January 3, 2022, requesting a meeting to discuss clinical, nonclinical, and regulatory topics related to the upcoming NDA filing, and reach agreement on the following:

- Topline safety and efficacy data from the Phase 3 ReSTORE study, along with data from the Phase 2 STRIVE study, to support an NDA for treatment of Candidemia/Invasive Candidiasis (C/IC).

- Clinical and nonclinical content provided in the NDA for treatment of C/IC.

Our preliminary responses to your meeting questions are enclosed. You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, please contact me at 301-796-0697.

Sincerely,

{See appended electronic signature page}

Eva Zuffova, MS, PhD
Regulatory Project Manager
Anti-Infectives Group 1
Division of Regulatory Operations for Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: March 3, 2022; 3:00 PM-4:00 PM EST
Meeting Location: Teleconference

Application Number: IND 124401
Product Name: Rezafungin for Injection

Indication: Treatment of Candidemia and/or Invasive Candidiasis

Sponsor Name: Cidara Therapeutics, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for March 3, 2022; 3:00 PM-4:00 PM EST, between Cidara Therapeutics, Inc., and the Division of Anti-Infectives. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

On January 3, 2022, the Sponsor, Cidara Therapeutics, Inc., submitted a meeting request for a Type-B teleconference to discuss clinical, nonclinical, and regulatory topics related to the upcoming NDA filing, and reach agreement on the following:

- Topline safety and efficacy data from the Phase 3 ReSTORE study, along with data from the Phase 2 STRIVE study, to support an NDA for treatment of Candidemia/Invasive Candidiasis (C/IC).
- Clinical and nonclinical content provided in the NDA for treatment of C/IC.

DISCUSSION

Question 1: Tabular summaries of nonclinical pharmacology, pharmacokinetic, and toxicology studies to support the NDA for treatment is provided in Appendix 1.
Does the Division agree that the type and nature of nonclinical studies listed are appropriate to support the treatment indication, without further studies required for filing and review?

FDA Response to Question 1: The adequacy of the nonclinical package to support the NDA for treatment without further studies will be determined during the review of the NDA. The type and nature of the data contained in the nonclinical package, including the three-month, once every three-day dosing study in juvenile monkeys will provide essential data for assessing the safety of the proposed weekly dosing regimen. Please indicate if any data from the weekly dosing study in adult animals will be included with the initial submission of this NDA.

Question 2: Cidara plans to present >6,000 rezafungin MIC values for >20 *Candida* species from nonclinical studies, including the annual international JMI Laboratories SENTRY Antimicrobial Surveillance Program (2014-2020), as well as clinical isolates from STRIVE and Phase 3 ReSTORE safety and efficacy studies.
Does the Division agree this information represents a range of clinically relevant fungi to inform an assessment of the potential clinical efficacy of rezafungin for the treatment indication?

FDA Response to Question 2: We agree. However, the determination of which fungal species would be included in the first and second lists of the microbiology section of the labeling will be a review issue.

Question 3: Does the Division agree that Rezafungin addresses unmet medical need?

FDA Response to Question 3: This will be a review issue. While there currently appears to be only modest differences between rezafungin's microbial activity and PK/PD characteristics compared to currently approved echinocandins, one of the focuses of the review will be to determine whether there may be other benefits of rezafungin use relative to current standard of care. An understanding of such benefits may help to define the parameters of any future approval.

Question 4: Does the Division agree it is reasonable for Cidara to proceed with an NDA for treatment of C/IC based on topline safety and efficacy data from Phase 3 ReSTORE, supported by data from Phase 2 STRIVE, expanded access, and clinical studies presented in Appendix 2?

FDA Response to Question 4: Upon preliminary review, there appears to be adequate data to file an NDA; the topline efficacy and safety results are acknowledged. However, as has been previously discussed, whether sufficient data are present to

support approval of a candidemia/invasive candidiasis indication, and if so, how such an indication would be defined, and whether all safety signals have been adequately explored will be a review issue.

Question 5: In the NDA, Cidara proposes to provide case report forms (CRFs) for serious adverse events (SAEs) adverse events of special interest (AESIs), deaths, and discontinuations from study drug or study due to adverse events. Additionally, Cidara proposes to provide subject narratives for SAEs and AESIs.
Is this proposal acceptable to the Division?

FDA Response to Question 5: This is generally acceptable.

Question 6: In the NDA, Cidara proposes to provide individual narratives for each of the expanded access patients. Is this proposal acceptable to the Division?

FDA Response to Question 6: This is acceptable.

Question 7: For the purposes of complying with the financial disclosure requirements, 21 CFR 54.2(e), Cidara considers the Phase 2 and Phase 3 studies as covered clinical studies and the Phase 1 clinical and clinical pharmacology studies as not covered.
Does the Agency agree?

FDA Response to Question 7: This is acceptable.

Question 8: Is the proposed rolling submission schedule acceptable to the Division?

FDA Response to Question 8: This is acceptable.

Question 9: To satisfy requirements for a 120-day safety update, Cidara proposes to submit the development safety update report (DSUR) to the NDA.
Is this acceptable to the Division?

FDA Response to Question 9: This is acceptable.

Additional Comments

Clinical Pharmacology

1. Regarding the submitted summary findings from PTA analyses and animal PK/PD studies, please note that the information on the growth of selected strains in the absence of treatment plays an important role in determining the suitability of the selected animal model and strains for evaluating a drug's activity and PK/PD target. Therefore, we recommend you submit information on the growth of selected strains in the absence of treatment in control mice in the nonclinical PK/PD study reports when submitting the NDA.

For example, the findings submitted to support rezafungin's activity against *C. glabrata* in a neutropenic mouse pharmacokinetic IC model. Visual inspection of Figure 4 of the meeting background material as well as the cited literature (Lepak 2018) suggests potential poor growth (fitness) of the three *C. glabrata* strains evaluated in the model compared to other strains. If this information is not available, we recommend you consider conducting additional animal PK/PD studies to further support the PTA analysis.

2. Please ensure traceability of source data for any dataset constructed using output files or postprocessed results from population PK analyses (e.g., exposure-response) providing definition files, reviewer guides, or codes utilized for dataset assembly. General expectations of model and data files format conformation can be found here: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/model-data-format. Results from population PK analyses should be accompanied with a structured population PK report. For expected content in each Section of the Population PK study report we refer you to the FDA Population PK guidance (https://www.fda.gov/media/128793/download)

3. Additionally, you should include the following information when submitting the NDA:
   - Population PK Reports
     - All (base, key intermediate, and final) population PK model files, parameter input files, data files, and control streams for the population PK and simulations reports and any codes (R, SAS, etc.) for PK/PD analyses;
     - The standard model diagnostic plots, tables with parameter estimates;
     - The output files for population PK models and simulations if applicable;
     - Include a USUBJID (unique subject ID) column in all the population PK datasets so that we can relate these datasets to the corresponding clinical efficacy/safety datasets.
   - PK-PD Reports
     - All datasets used for the PK-PD analyses in a SAS transport file (*.xpt) format;
     - Clinical: efficacy endpoints, baseline pathogen, MIC, and independent variables data;
     - Pre-Clinical: data from murine dose-fractionation studies (e.g., drug PK, fungal burden and associated time, inoculum size, etc.) and in vitro surveillance data. Also, provide clinical or laboratory strain identification;
     - The output files for PK-PD models if applicable;
     - IUSUBJID (unique subject ID) column to all PK-PD datasets so that we can relate these datasets to the corresponding clinical efficacy/safety datasets.
   - Bioanalytical Reports
     - Submit tables summarizing the bioanalytical methods and the life-cycle information using the templates available in the 'Bioanalytical Methods

Templates' Technical Specifications Document (https://www.fda.gov/media/131425/download) and submit the tables in the Appendix of the Summary of Biopharmaceutics located in eCTD 2.7.1.

Statistics

4. We note that the pooled phase 2 and phase 3 analyses presented in Table 16 of the meeting briefing package are adjusted by study. However, it does not appear that the phase 2 study analyses are adjusted by Part A and B. In comments dated October 5, 2017, we indicated for the phase 2 study that the differences in the randomization schemes (1:1:1 for Part A and 2:1 for Part B) would need to be addressed for the analyses that are conducted for Parts A and B combined. This should have also been taken into account for analyses of the phase 2 and phase 3 studies combined. Additionally, since the rezafungin dose was changed during the conduct of Part B of the Phase 2 study, we recommend that Part B be considered as having two parts: Part B1 and B2 based on when the rezafungin dose was changed. Integrated analyses for the rezafungin 400/200 mg group would then be based on and adjust for the phase 2 Part A, the phase 2 Part B2, and the phase 3 studies.

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/

EVA ZUFFOVA
02/25/2022 11:06:31 AM

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