Disseminated Coccidioidomycosis: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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TABLE OF CONTENTS

Disseminated Coccidioidomycosis: Developing Drugs for Treatment Guidance for Industry[1]

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I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs[2] for the treatment of disseminated coccidioidomycosis caused by *Coccidioides* species (i.e., *C. immitis* and *C. posadasii*).

Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding clinical trial design issues, choice of trial population, and endpoints for the treatment of patients with disseminated coccidioidomycosis caused by *Coccidioides* species. The design of clinical trials of new drugs for the treatment of disseminated coccidioidomycosis was discussed during an FDA public workshop.[3]

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998), *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021), and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001), respectively.[4] Additionally, this guidance does not address considerations that may be relevant for developing anti-infective drugs to address unmet medical need. For those considerations, please refer to the guidance for industry *Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases – Questions and Answers* (June 2025).

[1] This guidance has been prepared by the Division of Anti-infectives in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] Workshop materials can be found at https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/coccidioidomycosis-valley-fever-considerations-development-antifungal-drugs-08052020-08052020.

[4] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Coccidioidomycosis (Valley Fever) is caused by the dimorphic fungi of the genus *Coccidioides* that includes two species, *C. immitis* and *C. posadasii*, which have similar clinical presentations. Coccidioidomycosis is endemic to the Western Hemisphere, including the southwest of the United States, northern Mexico, and areas of Central and South America. Coccidioidomycosis is acquired by inhaling fungal elements and presents most commonly as pulmonary infection, ranging from asymptomatic or minimally symptomatic infection to diffuse pneumonia. Patients with early coccidioidal infection may develop systemic symptoms with fever, drenching night sweats, weight loss and fatigue associated with respiratory, dermatologic, and rheumatologic signs and symptoms. Disseminated coccidioidomycosis may present as soft tissue, bone and joint, genital tract, peritoneal, and central nervous system (i.e., meningitis) infections. Treatment of disseminated coccidioidomycosis depends on the presentation of the disease and the immune status of the host.[5] The recommended duration of treatment for disseminated coccidioidomycosis is generally at least 6 to 12 months but may be longer.

III. DRUG DEVELOPMENT CONSIDERATIONS

A. Trial Design and Conduct

To support approval, FDA expects that drugs will provide benefit on a clinically meaningful endpoint. Sponsors should consider the following in their development programs for the treatment of disseminated coccidioidomycosis:

1. Early Clinical Studies

- Proof-of-concept studies may evaluate tolerability, pharmacokinetics, and preliminary clinical efficacy in the target patient population and provide data to inform the design of phase 3 trials. For studies using a combination of antifungal drugs, nonclinical assessments of potential interactions between the drugs (i.e., antagonism or synergy) are recommended. The potential for in vitro interaction can be determined using fractional inhibitory concentrations in a checkerboard titration assay or in a time kill assay. Early clinical studies can provide an opportunity to capture data to aid the development of

[5] Galgiani, JN, NM Ampel, JE Blair, A Catanzaro, F Geertsma, SE Hoover, RH Johnson, S Kusne, JD MacDonald, SL Meyerson, PB Raskin, J Siever, DA Stevens, R Sunenshine, and N Theodore, 2016, 2016 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for the Treatment of Coccidioidomycosis, Clin Infect Dis, 63(6):e112-e146.

clinical outcome assessments (COAs) to be used in pivotal efficacy trials (see section III.C). Primary endpoints should evaluate clinical outcomes. Secondary endpoints may include serological markers and radiological evaluations.

- Given that a prolonged duration of antifungal therapy is generally used for treatment of disseminated coccidioidomycosis, sponsors may consider a proof-of-concept study design evaluating the investigational drug, either alone or as an add-on to standard of care (SOC), for the initial part of disseminated coccidioidomycosis therapy, with an early evaluation of clinical response, followed by SOC therapy to complete the full treatment course. Sponsors should prospectively discuss the timing of the early clinical response assessment with the Division.

- A dose-ranging study design can be considered as an option for clinical studies early in development to weigh the benefits and risks of various doses and to ensure that suboptimal doses or excessive doses (beyond those that add to efficacy) are not used in a phase 3 trial.

2. Phase 3 Trials

- In general, sponsors should conduct two randomized, double-blind, controlled, phase 3 trials. However, a single adequate and well-controlled trial showing robust evidence of efficacy with confirmatory evidence[6] may also demonstrate substantial evidence of effectiveness.[7] Sponsors intending to seek approval of their drug or drugs on the basis of a single trial plus confirmatory evidence should discuss with the Division both the proposed phase 3 trial and a detailed and specific proposal for what they intend to provide as confirmatory evidence.

- Given the extended duration of disseminated coccidioidomycosis treatment, sponsors may consider incorporating prospectively planned criteria to stop the trial for futility (lack of efficacy) or harm.

- FDA anticipates that phase 3 trials will include a superiority trial design; however, there may be other acceptable options. Sponsors should prospectively discuss their clinical development plans with FDA. Additional considerations for superiority trials include the following:

[6] See the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[7] See section 505(d) of the Federal Food, Drug, and Cosmetic Act and the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998); see also the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic.

- *Comparison of an SOC regimen plus the investigational drug to SOC plus placebo in a superiority trial.* Sponsors should discuss with the Division acceptable SOC regimens and define them in the trial protocol.

- *Comparison of investigational drug to SOC in a superiority trial.* Sponsors should discuss with the Division whether the preclinical and early clinical data support the use of the investigational drug as monotherapy for the treatment of disseminated coccidioidomycosis.

B. Trial Population

Sponsors developing drugs for the treatment of disseminated coccidioidomycosis should consider the following regarding trial population:

1. Early Clinical Studies

- While proof-of-concept studies in the target patient population (e.g., disseminated coccidioidomycosis) may be most informative, patients at lower risk of mortality, or limited sites of dissemination (e.g., skin and soft tissue, bone), may be considered in early clinical studies given uncertainty with the clinical efficacy of the new drug or drugs. Sponsors may also consider enrolling patients in early phase clinical studies who are refractory to or unable to tolerate SOC therapy, given the limited treatment options available for these patient populations.

2. Phase 3 Trials

- Trial entry criteria should include a diagnosis of disseminated coccidioidomycosis based on typical symptoms and radiographic abnormalities, with enzyme immunoassay and immunodiffusion or complement fixation (CF) testing to detect immunoglobulin M and immunoglobulin G antibodies. The diagnosis of disseminated coccidioidomycosis should be confirmed based on the presence of *C. immitis* or *C. posadasii* in culture of bone, joint or tissue lesions, sputum, bronchial wash, or lung tissue or pleural fluid, or identification of endosporulating spherules in histological preparations.

- Different disseminated coccidioidomycosis patient populations (e.g., nonmeningeal coccidioidomycosis versus coccidioidal meningitis) may have different disease manifestations and different responses to treatment and may require different trial endpoints.

  - Sponsors should consider whether phase 3 trials should limit enrollment based on patient characteristics such as disease form (nonmeningeal coccidioidomycosis versus coccidioidal meningitis), treatment experience (naïve versus refractory), and comorbidities.

158 – Given the differences between the disease forms of disseminated coccidioidomycosis,
159 the labeled indication will reflect the patient population studied and may not cover all
160 forms of disseminated coccidioidomycosis.
161
162 • If applicable, trial entry criteria should define the minimal baseline severity for
163 disseminated coccidioidomycosis symptoms, preferably using the same clinical criteria
164 used in efficacy outcome assessments (see section III.C).
165
166 **C. Efficacy Endpoints**
167
168 Phase 3 trials evaluating new drugs for the treatment of disseminated coccidioidomycosis should
169 generally have a clinical endpoint as the primary endpoint, with a microbiological endpoint as a
170 key secondary endpoint. As disseminated coccidioidomycosis is a heterogeneous disease,
171 endpoints should represent the outcomes that are most meaningful to the target population, can
172 be improved with treatment, and are expected to be sensitive to detect a treatment effect.
173 Sponsors should consider the following regarding efficacy endpoints:
174
175 *1. Primary Endpoints*
176
177 • Primary efficacy endpoints should be based on COAs, such as a patient-reported outcome
178 (PRO) instrument assessing symptoms of disseminated coccidioidomycosis. Sponsors
179 should discuss with the Division other appropriate COAs that could be used, such as
180 observer-reported outcomes, clinician-reported outcomes, and performance outcomes. In
181 addition to use in the primary efficacy endpoint, COAs may also be appropriate for use in
182 secondary endpoints.
183
184 • Currently, FDA is not aware of any specific PRO instruments that have been
185 demonstrated to be fit-for-purpose[8] to assess symptoms of disseminated
186 coccidioidomycosis to support regulatory decision-making and medical product labeling.
187 Sponsors should discuss with the Division existing, new, or modified PRO instruments
188 for this use.
189

[8] For additional information on the definition of *fit-for-purpose*, refer to the BEST (Biomarkers, EndpointS, and other Tools) Resource glossary, available at https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/glossary.fitforpurpose/. Additional information on FDA's Fit-for-Purpose Initiative is available at https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tools-fit-purpose-initiative.

- For considerations on developing, modifying, or selecting a COA for disseminated coccidioidomycosis trials, refer to FDA's Patient-Focused Drug Development Guidance Series.[9,10]

  - Commonly reported symptoms often vary based on the site of dissemination and may include the following:[11,12]

    - Systemic symptoms: fever, chills, night sweats, fatigue, weight loss, nausea or vomiting, generalized weakness or pain, swollen lymph nodes

    - Musculoskeletal-related symptoms: joint pain or stiffness, muscle pain or stiffness, swelling of extremities, pain in arms or back, bone pain

    - Respiratory symptoms: shortness of breath, cough, chest or rib pain, chest pressure, pain with breathing, wheezing, hoarseness of voice

    - Neurological symptoms: headache, vertigo, loss of consciousness, seizures, cognitive impairment, hallucinations, delirium

  - Given the heterogeneous nature of disseminated coccidioidomycosis, determination of which subset of symptoms to investigate will depend on what aspect or aspects of the condition the study drug is expected to improve as well as symptomatology associated with the site of dissemination.

  - Heterogeneity in patients' symptoms may support the use of a personalized endpoint approach.[13] One possible approach would be for subjects, at baseline, to identify their most bothersome symptom or symptoms and use the change from baseline in the symptom or symptoms as the primary efficacy endpoint or at least as part of the endpoint. FDA recognizes that there are challenges with this approach, including that

[9] See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009) (2009 Final PRO guidance).

[10] Information on this guidance series is available at https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical. These guidances are part of FDA's patient-focused drug development efforts in accordance with the 21st Century Cures Act and the Food and Drug Administration Reauthorization Act of 2017, Title I. When all guidances are final, the Patient-Focused Drug Development Guidance Series will replace the 2009 Final PRO guidance.

[11] See the Centers for Disease Control and Prevention's Valley Fever (Coccidioidomycosis) web page, available at https://www.cdc.gov/valley-fever/signs-symptoms/index.html

[12] Harvey, EL, M Bresnik, T Symonds, E Blatt, S Hughes, R Purdie, and JL Clegg, 2023, Development of a de novo Patient-Reported Outcome (PRO) Measure to Assess the Impacts of Disseminated Coccidioidomycosis [Valley Fever] on Patients Living with the Condition, Open Forum Infect Dis, 10(Suppl 2):ofad500.2134.

[13] See the Duke-Margolis Center for Health Policy's Developing Personalized Clinical Outcome Assessments, available at https://healthpolicy.duke.edu/sites/default/files/2020-03/meeting_summary_4_5_17.pdf.

as one symptom resolves, other symptoms may emerge as more bothersome. The process to construct a personalized endpoint should be standardized, and the criteria for selecting the outcome assessments should be consistent across sites and patients. The same set of outcome assessments should be assessed for all patients, regardless of their own personalized endpoint, to allow for an assessment of any new or worsening symptoms and/or functional limitations during the trial. Personalized endpoint methods and determination of which symptom or symptoms would be a part of this personalized endpoint approach should be discussed with the Division early in the drug development process. For further information on a personalized endpoint approach, please refer to the draft guidance for industry *Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints For Regulatory Decision-Making* (April 2023).[14]

- An appropriate endpoint could be the time to sustained symptom alleviation or resolution assessed over an appropriate duration. Sustained symptom alleviation or resolution can be defined as occurring when no key disseminated coccidioidomycosis-related symptom scored higher than a prespecified threshold over a clinically meaningful time period (as documented using a PRO instrument).

- Piloting the proposed PRO instrument in early clinical studies provides an opportunity to evaluate the instrument's measurement properties (reliability, validity, and ability to detect change), to evaluate clinically meaningful within-patient change in scores (using methods such as anchor-based methods), and to confirm the endpoint definition before use in phase 3 trials.[15]

- Based on the role of the PRO instrument and data obtained during its development, establishing a range of a priori thresholds (i.e., the change in the individual PRO score over a predetermined time period that should be interpreted as a clinically meaningful within-patient change) is useful when considering options for the primary endpoint. A variety of primary endpoint options are appropriate. For example, if a total symptom score can be computed for the PRO, possible endpoints might include time to sustained resolution of symptoms or meeting a prespecified extent of clinically meaningful improvement. Sponsors should discuss endpoints with the Division.

- The timing and frequency of the primary endpoint assessment and duration of follow-up will depend on the nature of the chosen trial population and treatment effect of the drug or drugs. Given the protracted nature of disseminated coccidioidal infections, the primary outcome assessment should be performed after at least 6 to 12 months of study drug treatment. Sponsors should prospectively discuss these issues with the Division.

[14] When final, this guidance will represent the FDA's current thinking on this topic.

[15] See footnote 10.

2. Secondary Endpoints

- Microbiological endpoints, such as negative cultures or decline in CF titers could be included as secondary endpoints. Serial monitoring of serum CF titers to *Coccidioides* species should be performed every 1 to 3 months for at least 1 year. A decline (≥2 dilution reduction) in quantitative CF titers measured at a central laboratory over the duration of the trial or at months 6 or 12 could serve as a secondary endpoint.