Nontuberculous Mycobacterial Pulmonary Disease Caused by *Mycobacterium avium* Complex: Developing Drugs for Treatment

Guidance for Industry

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

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Clinical/Antimicrobial

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Contains Nonbinding Recommendations

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Nontuberculous Mycobacterial Pulmonary Disease Caused by *Mycobacterium avium* Complex: 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 nontuberculous mycobacterial pulmonary disease (NTM-PD) caused by *Mycobacterium avium* complex (MAC).

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 naïve and refractory NTM-PD caused by MAC. The design of clinical trials of new drugs for the treatment of NTM-PD 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 International Council for Harmonisation (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).[4] In addition, this guidance does not address drugs intended to treat patients with NTM-PD caused by pathogens other than MAC because the clinical characteristics of these patients may differ from patients with NTM-PD caused by MAC. Sponsors interested in

[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/drugs/development-antibacterial-drugs-treatment-nontuberculous-mycobacterial-disease-04082019-04082019.

[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.

developing drugs targeting non-MAC NTM-PD should discuss their plans with the Division of Anti-Infectives (the Division).

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

NTM-PD is a chronic and progressive pulmonary disease resulting in respiratory and nonrespiratory symptoms, such as cough, shortness of breath, and fatigue. In addition, NTM-PD decreases lung function and overall health-related quality of life. Most cases of NTM-PD are caused by MAC, but other species of NTM, such as *M. kansasii* and *M. abscessus*, can also cause lung disease. There are two main forms of NTM-PD: a nodular bronchiectatic form that has been classically associated with middle-aged and older nonsmoking females and a fibrocavitary form typically associated with preexisting pulmonary diseases such as chronic obstructive pulmonary disease. NTM-PD also occurs in patients with cystic fibrosis and certain types of immunodeficiencies. Treatment for NTM-PD involves multidrug regimens with durations lasting months to years that often cause drug-drug interactions and adverse reactions such as hepatotoxicity, nephrotoxicity, ocular toxicity, and skin reactions. Microbiological response to treatment, such as conversion of sputum culture to negative, is variable. Patients with treatment-naïve NTM-PD, who usually have macrolide-susceptible isolates, generally have high rates of microbiological response. In contrast, patients with NTM-PD caused by macrolide-resistant isolates generally have lower rates of microbiological response with salvage treatment regimens. In addition, microbiological recurrence (relapse or reinfection) and recurrence of NTM-PD associated symptoms are common after treatment cessation.

III. DRUG DEVELOPMENT CONSIDERATIONS

To support approval, FDA expects that drugs will provide benefit on a clinically meaningful endpoint. Sponsors considering a microbiological outcome as a surrogate endpoint that is reasonably likely to predict clinical benefit should discuss this with the Division.

A. Trial Design and Conduct

Sponsors should consider the following in their development programs for the treatment of NTM-PD caused by MAC:

Early Clinical Studies:

- Short-term, randomized, placebo-controlled proof-of-concept studies evaluating a single drug with subjects subsequently starting standard combination treatment may be appropriate in select subjects, provided there is adequate monitoring.

Phase 3:

- In general, sponsors should conduct two randomized, double-blind phase 3 trials. However, a single adequate and well-controlled trial showing robust evidence of efficacy with confirmatory evidence may also demonstrate substantial evidence of effectiveness.[5] Sponsors intending to seek approval of their drugs on the basis of a single trial and confirmatory evidence should discuss both the proposed phase 3 trial and a detailed and specific proposal for what they intend to provide as confirmatory evidence with the Division.

- The following are possible designs for phase 3 trials; however, there may be other acceptable options. Sponsors should discuss their clinical development plans with the Division.

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

  - Comparison of a new combination regimen to SOC in a superiority trial. In this case, sponsors should justify the contribution of each component of the combination to the overall efficacy.[6]

  - Comparison of a new combination regimen to placebo in a superiority trial in an appropriate population such as treatment-naïve subjects, provided that there are appropriate criteria for instituting rescue therapy. Sponsors should justify the contribution of each component of the combination to the overall efficacy.[6]

B. Trial Population

Sponsors developing drugs for the treatment of NTM-PD caused by MAC should consider the following regarding trial population:

[5] 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. 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.

[6] See the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* (June 2013).

Early Clinical Studies:

- Including both nodular bronchiectatic subjects and fibrocavitary subjects may be acceptable in early clinical studies to assess the response in each patient population. These trials will help to determine which patient population may be further studied in phase 3 trials.

Phase 3:

- Trial entry criteria should include a positive respiratory culture for MAC at screening plus a history of a positive culture in the past 6 months.

- Different NTM-PD patient populations (i.e., nodular bronchiectatic versus fibrocavitary or treatment naïve versus treatment refractory) 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 subject characteristics such as disease form (nodular bronchiectatic versus fibrocavitary), treatment experience (naïve versus refractory), and comorbidities.

  - If sponsors wish to develop their drugs for both the nodular bronchiectatic and the fibrocavitary forms of NTM-PD, they should discuss with the Division the need for separate trials in each patient population, based on the endpoint or endpoints of interest (see section III. C., Efficacy Endpoints). Given the differences between these subtypes of NTM-PD, the labeled indication will reflect the patient population studied. However, a single trial in each subtype of NTM-PD could be used to support a broader indication.

- Trials should include trial entry criteria defining the minimal baseline severity for NTM-PD-related symptoms.

- Racial and ethnic minorities should be represented in clinical trials. Sponsors should employ methods to recruit diverse populations to ensure representativeness of racial and ethnic minorities in clinical trials. However, FDA advises sponsors to seek diversity in clinical trial enrollment beyond populations defined by race and ethnicity, including other underrepresented populations defined by demographics such as sex, gender identity, age, socioeconomic status, disability, pregnancy status, lactation status, and comorbidity.

C. Efficacy Endpoints

As discussed below, phase 3 studies in the treatment of NTM-PD caused by MAC should generally have a clinical endpoint as the primary endpoint, with a microbiological endpoint as a key secondary endpoint. Sponsors should consider the following regarding efficacy endpoints:

- Primary efficacy endpoints should be based on clinical outcome assessments,[7] such as a Patient-Reported Outcome (PRO) instrument assessing symptoms of NTM-PD. Sponsors should discuss with the Division other appropriate clinical outcomes that could be used, such as observer-reported outcomes, clinician-reported outcomes, and performance outcomes. In addition to use in the primary efficacy endpoint, other clinical outcome assessments may also be appropriate for use in secondary endpoints.

- Microbiological endpoints, such as sputum culture conversion, are not generally recommended alone as primary endpoints for a phase 3 trial intended for traditional approval. There are limited data available, based mainly on retrospective, nonrandomized studies or exploratory analyses from nonrandomized subgroups, on the relationship of sputum culture conversion to clinical outcomes. The main limitation of these data is the difficulty in assessing if there are differences in subject characteristics between the converters and nonconverters that might impact the clinical outcomes. However, sponsors should include a microbiological endpoint that assesses sputum culture conversion as a key secondary endpoint. A discrepancy between the clinical and microbiological endpoints would be a review issue.

- Sponsors considering a microbiological outcome as a surrogate endpoint that is reasonably likely to predict clinical benefit should discuss this approach with the Division as clinical trials are being planned. If sponsors wish to use a microbiological endpoint as a coprimary endpoint, they should discuss their proposal with the Division.

- Currently, FDA is not aware of any specific PRO instruments that have been demonstrated to be fit-for-purpose[8] to assess symptoms of NTM-PD to support regulatory decision-making and medical product labeling.[9] Sponsors should discuss existing, new, or modified PRO instruments for this use with the Division.

- 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, as options for the primary endpoint are considered. 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

[7] See the draft guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments* (June 2022). When final, this guidance will represent the FDA's current thinking on this topic.

[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.

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

resolution of symptoms or meeting a prespecified extent of improvement. Sponsors should discuss endpoints with the Division.

- Sponsors should consider the following when developing, modifying, or selecting a PRO for NTM-PD trials. Additional information on PRO instrument development can be found at FDA's Patient-Focused Drug Development Guidance Series.[10]

  - Sponsors should evaluate commonly reported symptoms for patients, which include cough, shortness of breath, fatigue, night sweats, and chest pain.[3]

  - Heterogeneity in patients' symptoms (e.g., some patients have predominantly fatigue symptoms whereas others have predominantly pulmonary symptoms) may suggest an individualized endpoint approach.[11] 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. It is recognized that there are challenges with this approach, including that as one symptom resolves, other symptoms may emerge as more bothersome. Individualized endpoint methods and determination of which symptom(s) would be a part of this individualized endpoint approach should be discussed early in the drug development process with the Division.

  - Piloting the proposed PRO instrument in phase 2 trials 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.[10]

  - The timing 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. Sponsors should discuss these issues with the Division.

[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.

[11] Duke Margolis Center for Health Policy. Report of an event on April 5, 2017. Developing Personalized Clinical Outcome Assessments, available at https://healthpolicy.duke.edu/sites/default/files/2020-03/meeting_summary_4_5_17.pdf, accessed March 3, 2021.