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

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Mukil Natarajan at 240-402-4626.

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

September 2021
Clinical/Antimicrobial

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

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

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

September 2021
Clinical/Antimicrobial

TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND 2

III. DRUG DEVELOPMENT CONSIDERATIONS 2

A. Trial Design and Conduct 2

B. Trial Population 3

C. Efficacy Endpoints 4

Nontuberculous Mycobacterial Pulmonary Disease Caused by *Mycobacterium avium* Complex: Developing Drugs for Treatment Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

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 study 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 ICH guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001)[4] and the ICH draft guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analyses in Clinical Trials* (May 2021).[5] In addition, this guidance does not address drugs intended to treat patients with

[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.

[5] 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.

NTM-PD caused by pathogens other than MAC, as the clinical characteristics of these patients may differ from patients with NTM-PD caused by MAC. Sponsors interested in developing drugs targeting non-MAC NTM-PD should discuss their plans with the Division of Anti-Infectives (the Division).

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, 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, fatigue, decreased lung function, and decreased 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 women 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.

III. DRUG DEVELOPMENT CONSIDERATIONS

To support approval, FDA expects that drugs will provide benefit on a clinically meaningful endpoint. Sponsors considering microbiologic 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 program for the treatment of NTM-PD caused by MAC:

Phases 1 and 2:

- Delay of therapy may be appropriate in select patients, provided there is adequate monitoring, supporting a short-term, randomized, placebo-controlled proof-of-concept study evaluating a single agent.

Phase 3:

- In general, sponsors should conduct two randomized, double-blind phase 3 trials. However, a single trial showing robust evidence of efficacy with confirmatory evidence may also demonstrate substantial evidence of effectiveness.[6] Sponsors intending to seek approval of their drug on the basis of a single trial and confirmatory data should discuss their development program with the Division.

- New drugs for NTM-PD are likely to be used in combination with other antibacterial drugs. As a result, phase 3 trials should study the test drug in combination with the other antibacterial drugs with which it is intended to be used. However, the added contribution of the test drug to the combination will need to be assessed, for example, using an add-on design study.

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

  - Comparison of a standard-of-care (SOC) regimen plus the new drug to SOC plus placebo in a superiority trial. Sponsors should discuss acceptable SOC regimens with the Division and define them in the study 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.[7]

  - Comparison of a new combination regimen to placebo in a superiority trial in an appropriate population such as treatment-naïve patients, 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.[7]

B. Trial Population

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

[6] 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 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.

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

Phases 1 and 2:

- Studying both nodular bronchiectatic and fibrocavitary patients may be acceptable in phases 1 and 2 trials 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 study endpoints.

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

  - If sponsors wish to develop their drug 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 C). Given the differences between these subtypes of NTM-PD, the labeled indication will reflect the patient population studied and may not cover all forms of NTM-PD.

- If applicable, trials should include trial entry criteria defining the minimal baseline severity for NTM-PD-related symptoms, preferably using the same patient-reported outcome (PRO) instrument used for the efficacy endpoint (see section C).

- Racial and ethnic minorities should be represented in clinical trials. Sponsors should ensure that clinical trial sites include geographic locations with higher proportions of racial and ethnic minorities to recruit a diverse study population.

C. Efficacy Endpoints

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

- Microbiological endpoints, such as sputum culture conversion, are not generally recommended as primary endpoints for a phase 3 trial. There are limited data available, based mainly on retrospective, nonrandomized trials or exploratory analyses from nonrandomized subgroups, on the relationship of sputum culture conversion to clinical outcomes. The main limitation of these trials is the difficulty in assessing if there are differences in patient characteristics between the converters and nonconverters that might impact the clinical outcomes. Sponsors considering a microbiologic 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. Microbiological endpoints that assess the clearance of the NTM pathogen may be included as secondary endpoints.

- Primary efficacy endpoints should be based on clinical outcome assessments, such as a PRO instrument assessing symptoms. Sponsors should discuss with the Division other appropriate clinical outcomes that could be used.

- 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 an a priori threshold (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 resolution of symptoms or meeting a prespecified extent of improvement. Sponsors should discuss endpoints with the Division.

- Sponsors should consider the following when developing 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

[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).

[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.

from baseline in the symptom or symptoms as the primary efficacy endpoint or at least as part of the endpoint.

- 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 study population and treatment effect of the drug or drugs. Sponsors should discuss these issues with the Division.