Regulatory Aspects of Drug Development for Nontuberculous Mycobacteria Pulmonary Infections

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Disclosure

The views expressed in this presentation are those of the author and do not necessarily represent the views of the U.S. Food and Drug Administration.
Outline

• Introduction
• Regulatory standards for drug approval
• Challenges to development of drugs for non-tuberculous mycobacteria (NTM) pulmonary infections
• Possible regulatory approaches to facilitate approval of drugs for NTM pulmonary infections
Introduction

- Prevalence of NTM lung infections is increasing in the US.
- Treatment involves multi-drug regimens given for >1 year and is associated with significant toxicity.
- No drugs are FDA-approved for NTM infections.
- FDA is trying to facilitate the development of drugs for treatment of NTM infections.
  - Non-Tuberculous Mycobacterial (NTM) Lung Infection Public Meeting was sponsored by FDA in October 15, 2015.
Regulatory Standards for Drug Approval

- Federal Food, Drug, and Cosmetic Act (FD&C) requires substantial evidence of a drug effectiveness from adequate and well-controlled investigations for the drug approval.
- The purpose is to distinguish the effect of a drug from spontaneous change in the course of the disease, placebo effect, or biased observation.
- Types of controls (21 CFR 314.126):
  - Placebo concurrent control
  - Dose-comparison concurrent control
  - No treatment concurrent control
  - Active treatment concurrent control
  - Historical control
- Data from one adequate and well-controlled clinical investigation and confirmatory evidence may establish effectiveness (FDAMA 1997).
Assessment of Outcomes in Clinical Trials (Terms and Definitions)

- **Clinical outcome**: An outcome that reflects how an individual feels, functions or survives.
- **Biomarker**: A characteristic (e.g., laboratory or radiographic) that measures responses to therapeutic interventions. It is not an assessment of how an individual feels, functions, or survives.
- **Endpoint**: A precisely defined variable intended to reflect an outcome of interest that is analyzed to address a particular research question.
- **Surrogate endpoint**: a substitute (e.g., a biomarker) for a direct measure of how a patient feels, functions, or survives, which is expected to predict a clinical benefit.

Regulatory Mechanisms for Drug Approval

• **Standard approval**
  – based on an endpoint measuring how a patient feels, functions, or survives

• **Accelerated approval**
  – based on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality
  – postmarketing confirmatory trials may be required to verify the predicted clinical benefit

Challenges to Designing Trials in NTM Pulmonary Infections

• Clinical outcomes are difficult to assess due to symptoms related to underlying comorbidities (bronchiectasis, COPD, cystic fibrosis).

• Response to study drugs may vary by NTM species and underlying lung disease.

• Trials are lengthy, include multiple visits which raises issues with compliance and lost to follow-up.
Clinical Outcome Assessment in Trials in NTM Pulmonary Infections

• **Clinician reported outcome**: clinical assessment can be confounded by the progression or exacerbation of underlying diseases such as bronchiectasis, CF, or COPD.

• **Performance outcome measures**: a 6-minute walk test (6WT) has been used in pulmonary NTM clinical trials\(^1\) and may be included as a part of clinical assessment. Additional discussion of a clinically important difference in 6WT in NTM patients is needed.

• **Patient reported outcome measures**: an important aspect of clinical outcome assessment but may be confounded by underlying comorbidities and, in case of inhaled products, by respiratory adverse events. \(^1\)

• Overall, it may be challenging to define an endpoint in NTM pulmonary infection trials that is based on clinical assessment.

\(^1\) Olivier KN et al. Am J Respir Crit Care Med. 2017 Mar 15; 195(6):814-823
Potential Endpoints in Trials in NTM Pulmonary Infections

Microbiological assessment

• Culture conversion
  – May be defined as 3 consecutive negative respiratory cultures measured at defined post-randomization time points although the number of negative cultures needed is not firmly established
  – Correlation with clinical outcome needs to be established
  – May expedite clinical program but a longer follow-up (e.g., a 12-month) may still be needed

• 12 months of culture-negative sputum
  – Recommended treatment goal for MAC and *M. kansasii* infections
  – Culture conversion may reasonably well predict sustained microbiological response so a 12-months of negative culture endpoint may not be necessary.

Radiographic assessment - may be difficult because of limited potential for improvement of MAC-related radiological abnormalities.

Possible Designs of Comparative Trials for NTM Pulmonary Infections

• Superiority to demonstrate a greater response rate, shorter duration of therapy, decreased toxicity.
  – New drug combination vs. placebo (when delay in treatment is acceptable)
  – New drug combination vs. standard of care
  – A study drug + background regimen (BR) vs. BR alone
  – New drug combination vs. historical control

• Non-inferiority
  – Justification of a non-inferiority margin may be challenging
Possible Regulatory Approaches to Facilitate NTM Drug Approval

• Use of earlier surrogate endpoints, e.g., sputum culture conversion
• Potential use of a smaller clinical data package
• Contribution of individual components in a drug combination may be supported by in vitro and animal data
• The Division is happy to meet with sponsors early in drug development to discuss clinical trial design
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