Two Hypothetical Cases of Drug Development Programs for Treatment of Pulmonary *Mycobacterium avium* Complex (MAC) Disease

Hiwot Hiruy, MD, PhD
Division of Anti-Infective Products
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Introduction

- The case studies are **hypothetical** and are not intended to cover every developmental stage and requirement for a specific drug program
- There should not be a head to head comparison of the two cases; our intent is to discuss two patient populations in the pulmonary MAC disease spectrum
- Assume the necessary nonclinical work has been completed and the development programs have successfully transitioned to the clinical space

Introduction

- Assume the drugs mentioned in the case studies have acceptable safety profiles hence the discussion will mainly focus on assessment of efficacy of these drugs
- The case studies present broad topics/ideas as we would like the discussion to focus on key topics such as clinically-oriented primary endpoints and the timing of assessment of the primary endpoints
- Assume the clinical outcome assessment (COA) tools, including patient reported outcomes (PROs), mentioned in the cases are “fit-for-purpose”(appropriate and validated for patients with pulmonary MAC disease)

Drug X: Novel Drug Developed as Add-on to Background Regimen (BR) for Treatment of Refractory Pulmonary MAC Disease

Drug X

- Oral formulation of a new molecular entity with novel mechanism of action
- Potent *in vitro* activity against *M. avium, M. intracellulare* and *M. abscessus*
- Murine models of pulmonary infection using clinical isolates of MAC comparing treatment with Drug X vs. placebo and treatment with Drug X + BR vs. BR show reduction in bacterial burden in mice treated with Drug X and Drug X + BR, respectively

Phase 1 Studies

- First-in-human, randomized, double-blind, placebo-controlled study to assess the safety, tolerability and PK of single and multiple ascending doses in healthy volunteers
- Concentration of Drug X in epithelial lining fluid (ELF) and plasma are assessed in healthy volunteers
- PK and potential drug-drug interaction of Drug X, clarithromycin, and rifampin are evaluated in healthy volunteers
- Main adverse events (AEs)
  - Gastrointestinal (nausea, abdominal discomfort) were mild-moderate in severity
  - No serious adverse events noted

Phase 2 Trial

- Dose ranging study to evaluate the PK, tolerability, safety, and efficacy of 3 different doses of Drug X (10 mg, 20 mg, 40 mg) as an add-on to BR vs. BR + placebo in patients with refractory pulmonary MAC disease
  - Refractory MAC disease is defined as failing to achieve 3 consecutive negative monthly sputum cultures after 6 months of ATS/IDSA guideline based multi-drug regimens
  - Study duration: 24 Months
- Primary endpoint: Culture conversion at Month 6
  - Culture conversion is defined as 3 consecutive negative monthly sputum cultures without reversion

Phase 2 Trial

- Secondary endpoints:
  - Change in a patient reported outcome (PRO) at Months 6, 12, 18 and 24
  - Sputum culture conversion at Months 12, 18 and 24
  - Change from baseline in 6MWT at Months 6, 12, 18 and 24
  - Changes from baseline for Quality of Life Bronchiectasis (QOL-B) NTM module at Months 6, 12, 18 and 24
  - Treatment emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Result :
  - The 20 mg dose is chosen for the Phase 3 trial
    - Proportion of patients with culture conversion and proportion of patients with improvement in a PRO score are higher in the 20 mg and 40 mg arms compared to the 10 mg and BR + placebo arms at Month 6
    - Dose-dependent GI disturbance noted; safety profile of the 20 mg dose is more favorable

Phase 3 Trial

- Multi-center, double-blind, randomized (2:1) trial evaluating the efficacy and safety of Drug X added to BR compared to BR + placebo in patients with refractory pulmonary MAC disease
  - BR will adhere to ATS/IDSA guidelines but will vary based on investigator's discretion and patient characteristics (e.g., prior therapy)
  - Study duration is 24 months→16 months on treatment and then follow-up off treatment for an additional 8 months
    - Monthly clinical and microbiological assessments for the first 16 months
    - Clinical and microbiological assessments every 3 months from Months 16-24
  - No study arm cross-over permitted
  - Treatment assignment and culture conversion status remain blinded as long as the patients remain clinically stable and rescue therapy is not deemed necessary

Phase 3 Trial

- Primary endpoint: A patient reported outcome (PRO) at Month 16
- Secondary endpoints:
  - Culture conversion without reversion at Month 16
  - Sustainability of improvement in PRO at Month 19 and 24
  - Durability of culture conversion at Months 19 and 24
  - Change from baseline in 6-minute walk test (6MWT) at Months 16 and 24
- Sample size adequate to show meaningful difference in PRO between the two arms with 90% power

Phase 3 Trial Results

- Primary endpoint: Drug X + BR met the pre-specified meaningful improvement in PRO compared to BR + placebo
- Secondary endpoint: No significant difference in culture conversion at Month 16
- No significant difference in reported treatment-emergent adverse events (TEAEs), serious adverse events and mortality

Questions for the Panel

1. What are the knowledge gaps in our understanding of:
   - Patient population to be studied (definition of refractory pulmonary MAC disease, disease subtypes)
   - Primary endpoint to assess direct clinical benefit for this patient population
   - Length of trial and timing of endpoints
   - Feasibility of making clinical decisions based solely on patient's clinical status without sputum culture results
   - Limiting cross-over from control arm to test arm
   - Feasibility of standardizing the BR regimen
2. How can we address these knowledge gaps?
3. Despite these gaps in knowledge, what can be done to move forward to design scientifically sound clinical trials for pulmonary MAC patients?

Regimen Y: A New Drug Regimen for Treatment of Newly Diagnosed Bronchiectatic Nodular Pulmonary MAC Disease

Regimen Y

- Contains two anti-mycobacterial drugs
- Clinical microbiology studies were conducted to rule out antagonistic effects and resistance development
- Contribution of each drug demonstrated by hollow-fiber model and animal model studies
- Phase 1 studies to assess safety, tolerability and PK of single and multiple doses were completed
  - PK and potential drug-drug interaction were also evaluated in healthy volunteers

Phase 2 Trial

- Randomized (1:1), double-blind, placebo-controlled trial in patients newly diagnosed with bronchiectatic nodular pulmonary MAC disease in accordance with ATS/IDSA criteria
  - Study duration is 18 months
- Primary endpoint: Culture conversion at Month 6
  - Culture conversion is defined as 3 consecutive negative monthly sputum cultures without reversion

Phase 2 Trial

- Secondary endpoints:
  - Change in a clinical outcome assessment (COA) at Months 6, 12 and 18
  - Sputum culture conversion at Months 12 and 18
  - Change from baseline in 6MWT at Months 6, 12 and 18
  - Changes from baseline Quality of Life Bronchiectasis (QOL-B) NTM module at Months 6, 12 and 18

Phase 2 Trial

- Result :
  - 45% more patients treated with Regimen Y achieved culture conversion at Month 6 compared to placebo-treated patients
  - A higher proportion of patients on Regimen Y had a clinically meaningful improvement on the COA
  - More TEAEs in patients treated with Regimen Y compared to placebo
    - Serious adverse events, including mortality, are comparable in the two arms

Phase 3 Trial

- Multi-center, randomized (2:1), double-blind, placebo-controlled trial
  - Adult treatment naïve patients with bronchiectatic nodular MAC infection who meet ATS/IDSA 2007 pulmonary disease criteria
  - Study duration is 24 months: 12 months of treatment and then follow-up off treatment for an additional 12 months
  - Culture conversion status is blinded throughout the study
  - Unblinding and rescue therapy only in clinically deteriorating patients
- Primary endpoint: COA at Month 12

Phase 3 Trial

- Secondary endpoints:
  - Change in COA at Months 18 and 24
  - Culture conversion at Months 12, 18 and 24
  - Change from baseline in 6MWT at Months 12, 18 and 24
- Sample size adequate to show meaningful difference in COA between the two arms with 90% power

Phase 3 Trial Result

- Primary endpoint: Regimen Y meets the pre-specified clinically meaningful improvement in the COA compared to placebo
- Secondary endpoint: 40% more patients treated with Regimen Y achieve culture conversion compared to placebo at Month 12, and sustained conversion at Month 24 is 20% higher in patients treated with Regimen Y
- Higher incidence of reported TEAEs, but no significant difference in serious adverse events and mortality

Questions for the Panel

1. What are the knowledge gaps in our understanding of:
   - Acceptability and duration of placebo use in the control arm
   - Preferred primary endpoint (e.g., COA tools such as symptom-based or function-based PROs, functional assessment such as 6MWT) to assess direct clinical benefit for this patient population
   - Potential use of COA tool and microbiological outcome as co-primary endpoints
   - Length of trial and timing of endpoints
2. How can we address these knowledge gaps?
3. Despite these gaps in knowledge, what can be done to move forward to design scientifically sound clinical trials for pulmonary MAC patients?