Amikacin Minimum Inhibitory Concentrations and Mutational Resistance in Patients With Treatment-Refractory Nontuberculous Mycobacteria Lung Disease Treated With Liposomal Amikacin for Inhalation

Kenneth N. Olivier¹, Gina Eagle¹, John P. McGinnis II, Liza Micic³, Barbara A. Brown-Elliot¹, Richard J. Wallace, Jr⁶

¹National Heart, Lung, and Blood Institute / National Institutes of Health, Bethesda, MD, USA; ²Sponsored Incorporated, Bridgewater, NJ, USA; ³The University of Texas Health Science Center at Tyler, Tyler, TX, USA.

INTRODUCTION

- Nontuberculous mycobacterial (NTM) lung infections are increasing globally in both men and women.¹
- NTM lung infections are often chronic and may be refractory to current guideline-based antibiotic therapy.²
- Liposomal amikacin for inhalation (LAI) is a novel formulation of amikacin in development for the treatment of NTM lung infections.³
  - LAI is composed of charged, highly biocompatible liposomes (~0.3 µm) that encapsulate charge-positive amikacin for delivery through pulmonary mucociliary transport.
  - The high lung concentration and extended release of amikacin from liposomes enable once-daily dosing of LAI.
- The efficacy, safety, and tolerability of once-daily LAI were recently evaluated in a phase 2, randomized, double-blind, placebo-controlled study of patients with treatment refractory NTM lung infections (Study TRU-012, ClinicalTrials.gov identifier: NCT01813256).

AIMS

- To evaluate mutational resistance in patients with Mycobacterium avium complex (MAC) or Mycobacterium abscessus (Mabs) (Mycobacterium) lung infection who received LAI and the correlation between LAI administration and a mutation in the 16S rRNA gene, which encodes the ribosomal RNA component of the ribosome.
- To evaluate the relationship between the minimum inhibitory concentrations (MIC) of MAC or Mabs and the presence of a mutation.

METHODS

Study Design

- Study design is summarized in Figure 1.
- Study TRU-012 is the first, randomized, placebo-controlled, multicenter clinical trial in patients with NTM lung disease, conducted in 19 sites in North America.
- The study assessed the efficacy, safety, and tolerability of LAI 590 mg once daily vs. placebo in patients with treatment-refractory NTM on a stable multidrug regimen.
- In the 84-day double-blind period, patients were randomized 1:1 to LAI 590 mg pc or placebo once daily via a customized investigational ventilator (rFlow technology nebulizer (PART Pharma GmbH)) added to their ongoing, stable drug regimen.
- Participants continuing on ATS/IDSA guideline-based therapy.

Study Population

- Patients were eligible for enrollment if they had pulmonary NTM infection refractory to American Thoracic Society / Infectious Diseases Society of America (ATS/IDSA) guidelines-based therapy for 5 months prior to screening.
- Patients were stratified by the presence or absence of cystic fibrosis, and by the presence of MAC vs. Mabs infection.

Study Procedures

- Amikacin MICs were assessed by broth microdilution assay.

RESULTS

- Of the 178 patients evaluated, 90 were randomized, 89 were in the modified intent-to-treat (MITT) population (44 LAI, 45 Placebo) and 108 completed treatment in the double-blind phase and 59 completed treatment in the open-label phase.

SUMMARY AND CONCLUSIONS

- LAI and placebo addition increased the proportion of patients who were culture-negative for NTM to 54.6% and 34.2%, respectively.
- There was a very high correlation between an MIC >64 and the presence of a mutation.

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DISCLOSURES

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