Randomized, Double-Blind, Placebo-Controlled Study and Open-Label Extension of Liposomal Amikacin for Inhalation (LAI) in Patients with Recalcitrant Nontuberculous Mycobacterial Lung Disease (NTM-LD)


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INTRODUCTION

- Nontuberculous mycobacteria (NTM) lung infections are increasing worldwide. NTM is associated with increased morbidity and mortality, and represents an emerging public health concern.
- Liposomal amikacin for inhalation (LAI) is a novel formulation of amikacin that is currently being developed for the treatment of lung infections caused by NTM and Pseudomonas aeruginosa.1-4 LAI is composed of charge-neutral, highly biocompatible liposomes (~0.3 µm) that encapsulate amikacin and penetrate the bathillium to achieve a high drug concentration at the site of infection.
- The high lung concentration (Cmax) and area under the curve (AUC) of amikacin are improved due to the half-life (t1/2) of liposomes, which enables once-daily dosing of LAI.
- The efficacy and favorable tolerability of LAI have been demonstrated in phase 3 studies of patients with cystic fibrosis (CF) and chronic bronchopulmonary infections due to P. aeruginosa.5
- The current study evaluates the efficacy, safety, and tolerability of LAI in patients with refractory NTM lung disease.

METHODS

Study Design

- The TR0-112 study design is summarized in Figure 1. Study TR0-112 is the first randomized, controlled, multicenter study in patients with NTM lung disease, conducted at 19 sites in the United States and Canada. For the 84-day double-blind phase, patients were eligible if they had been refractory to American Thoracic Society / Infectious Disease Society of America (ATS/IDSA) guidelines-based therapy for 6 months prior to screening.
- Patients were stratified by presence of CF, and by Mycobacterium avium complex (MAC) versus Mycobacterium abscessus infection.
- Patients were randomized 1:1 to LAI 500 mg or placebo once daily via flornethulizer (PARI Pharma GmbH) to obtain their stable drug regimen.
- After completing the double-blind phase, all patients who consented to and continued in the open-label phase received LAI 500 mg once daily for 84 additional days.

Efficacy endpoints during the double-blind and open-label phases included:
- Change from baseline on the semi-quantitative scale for mycobacterial culture
- NTM culture conversion to negative
- Cough frequency
- Absolute changes in 6 minute walk test (6MWT).

RESULTS

Efficacy Summary

- Primary endpoint of change from baseline in the full semi-quantitative scale did not achieve statistical significance, although there was a positive trend in favor of the LAI arm (Figure 4).
- LAI achieved statistical significance in achieving a negative culture at day 84, with 11 of 44 patients on LAI versus 3 of 45 patients on placebo (P = .01) (Figures 5 and 6).
- Six of the 31 patients who culture-converted on LAI had sustained negative sputum cultures throughout the open-label phase, including at the 28-day off-treatment follow-up visit.
- Two patients on LAI achieved their first negative culture at day 32 and sustained negative sputum cultures throughout the open-label phase, including at the 28-day off-treatment follow-up visit.
- Two patients on placebo achieved their first negative culture after entering the open-label phase and sustained negative sputum cultures through the 28-day off-treatment follow-up visit.
- One patient on placebo had fluctuating culturing results between negative and low positivity ( broth-positive) during the double-blind phase. After entering the open-label phase, the patient achieved negative sputum cultures from day 12 to the 28-day off-treatment follow-up visit.
- One patient entering the open-label phase from the placebo arm showed sustained negative sputum cultures from day 84 to the 28-day off-treatment follow-up visit.
- Patients with treatment-refractory NTM have a symptomatology that includes consistent sputum, cough frequency, and exacerbations. The 6MWT was used to assess the impact of LAI on overall physical function or capacity (Figure 7).
- LAI demonstrated statistical significance in the 6MWT in the double-blind phase (LAI vs placebo: 23.880 vs 25.052 meters, P = .009).
- In the open-label phase, patients in the LAI arm continued to improve on the 6MWT and patients in the placebo group who started LAI showed a decrease in the rate of deterioration.

Safety and Tolerability Summary

- Most treatment-emergent adverse events (TEAEs) were mild or moderate in severity, and the majority were respiratory in nature (Table 2 and Figure 8). Local respiratory events and infective exacerbation of the underlying lung disease were the most common TEAEs.
- Few patients discontinued the study drug as a result of these events.

CONCLUSIONS

- In patients with refractory NTM, LAI achieved statistical significance in culture conversion at day 84 in the double-blind phase.
- LAI demonstrated effectiveness in sustaining negative sputum cultures.
- LAI demonstrated improvement versus placebo in the 6MWT.
- The majority of TEAEs in the LAI arm were respiratory in nature; however, few patients discontinued study drug due to these events.
- These data increase our understanding of NTM disease management, including incorporating of new treatments in future NTM clinical trials, and creating potential new NTM management paradigms.

References


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