**INTRODUCTION**

The increasing rate of nontuberculous mycobacterial (NTM) lung infection worldwide represents an important public health concern.1,2 NTM lung infections may include reactivation of current multidrug-resistant (MDR)-based antibiotic therapy, and are associated with significant morbidity and mortality.3

Liposomal amikacin for inhalation (LAI) is a novel inhalational formulation of amikacin in development for the treatment of NTM lung infections. LAI is composed of charged-liposomes, highly biocompatible liposomes (≤0.3 μm) that encapsulate amikacin and are able to be taken up by macrophages.4 The high lung concentration and extended release of amikacin from liposomes may enable once-daily dosing of LAI.5

A phase 2, randomized, double-blind, placebo-controlled clinical trial was conducted to evaluate the efficacy, safety, and tolerability of LAI in patients with treatments for NTM lung infections (Study TR02-112, ClinicalTrials.gov identifier: NCT01335280).

Here we report on data collected from patients enrolled in the 12-month long-term follow-up period of Study TR02-112 after their last dose of LAI.

**OBJECTIVES**

To collect long-term safety information on patients with NTM lung infection who had not received LAI treatment for 12 months after having been previously exposed to LAI for ≥78 days.

To evaluate the efficacy endpoints of change in Global Rating of Health (GRH), and from baseline on the full semi-quantitative scale (SQS) for 65 patients who entered the 12-month off-LAI follow-up phase of Study TR02-112 after their last dose of LAI.

**METHODS**

**Design of TR02-112**

TR02-112 was conducted at 19 sites in North America and is the first randomized, placebo-controlled, multicenter clinical trial in patients with NTM lung disease.

TR02-112 assessed the efficacy, safety, and tolerability of LAI 590 mg once daily vs. placebo in adults with NTM lung infection due to M. avium and/or M. intracellularare bacteria that had been refractory to a standard, guideline-based, multidrug regimen for ≥6 months. Patients prior continued in the open-label phase, including the main study and the 12-month safety follow-up period (Figure 1).

The design of TR02-112 included the main study and the 12-month safety follow-up period shown in Figure 1.

The main study included a double-blind phase, an open-label phase, and a 28-day follow-up period.

In the 84-day double-blind phase, patients were randomized 1:1 to receive once daily LAI 590 mg or placebo in a randomized investigational drug technology nebulizer (PARI Pharma GmbH) added to their ongoing, stable, multi-drug regimen. Patients continuing to the open-label phase received LAI 590 mg once daily as add-on therapy for 84 additional days.

There was also a 28-day follow-up period after the last dose of study drug for all patients.

Patients had the option to consent to return for a follow-up visit 1 year after the last dose of study treatment.

An SQS was used to assess relative mycobacterial growth, with a negative baseline score after the last dose of study drug.

**RESULTS**

**Main Study**

Of the 136 patients screened, 90 were randomized and 89 received 3 dose of study drug in the double-blind phase; 80 patients completed treatment in the double-blind phase, and 59 completed treatment in the open-label phase (Figure 2).

The primary endpoint of change from baseline on the SQS in the LAI group vs. placebo did not reach statistical significance (p = 0.072), although a positive numerical trend in favor of the LAI group was observed.

Of the 23 patients who achieved culture conversion by the 26-week’s end-of-study follow-up visit, 7 converted at baseline (Step 1) prior to administration of study drug, suggesting active culture conversion after baseline (Step 1), 10 of whom were randomized to LAI in the double-blind phase and 7 patients after entering the open-label phase; the remaining 2 patients achieved culture conversion while receiving add-on placebo during the double-blind phase.

Figure 2. Patient disposition

**Long-Term Safety Follow-up Phase**

After completing LAI treatment, 65 patients (LAI, 29; placebo, 36) entered the long-term safety follow-up period.

Of these, 57 patients completed the 12-month follow-up visit, 7 died prior to the 12-month follow-up visit, and 1 patient chose not to return for the visit.

Of the 10 patients who died during the safety follow-up phase, 6 had not achieved culture conversion and only 1 had achieved culture conversion (a 3 consecutive negative sputum cultures) during the study treatment phases (Table 1).

Patient demographics and disease characteristics:

- Patient baseline demographics and disease characteristics were comparable between treatment groups for the mITT population.
- CF, cystic fibrosis; LAI, liposomal amikacin for inhalation; Mabs, multidrug regimen.
- NTM, nontuberculous mycobacteria; PBO, placebo.

**DISCUSSION**

The modified intent-to-treat population (mITT) was defined as all patients who discontinued (3 during the double-blind [DB] phase; 11 during open-label [OL] phase) and 51 patients who completed (1 completed DB only and did not consent to OL, and 50 completed DB and OL phases) the study.

Among patients with available follow-up SQS data (n = 48), those who achieved culture conversion during the main study were more likely to demonstrate negative sputum cultures during the 12-month follow-up visit vs. those who did not achieve culture conversion (4/47 [82.6%] vs. 0/31 [0.0%], respectively).

Of the 65 patients who entered the 12-month off-LAI follow-up phase, those who achieved culture conversion were less likely to require antimycobacterial drugs at the time of the 12-month follow-up visit vs. those who did not achieve culture conversion (2/32 [6.3%] vs. 20/42 [47.6%], respectively).

**CONCLUSIONS**

These long-term follow-up data from Study TR02-112 show that, for patients with available follow-up SQS data, 84.2% who achieved culture conversion during the double-blind phase of LAI added on to guideline-based treatment for NTM lung infection had negative sputum culture results at 12 months after LAI, suggesting durability of culture conversion.

Six of the 7 deaths reported during the long-term follow-up occurred in patients who failed to achieve NTM sputum culture conversion, suggesting a link between persistent positivity and poor outcomes in patients with treatment-refractory disease.

Study findings continue to support the once-daily regimen role of LAI as a viable add-on treatment to standard multidrug regimens for NTM lung infections that are refractory to previous multidrug regimens.

**REFERENCES**


6. Data on file from Inhaled Therapeutics, Malvern, PA.

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