Analysis of Functional Exercise Capacity (via the Six-Minute Walk Test [6MWT]) and Negative Sputum Culture for Nontuberculous Mycobacteria (NTM) in Patients With NTM Lung Infection Refractory to Guideline-Based Therapy Treated With Liposomal Amikacin for Inhalation (LAI)

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INTRODUCTION

- The increasing rate of pulmonary disease caused by nontuberculous mycobacteria (NTM) lung infections is an emerging public health concern worldwide.[1,2]
- NTM lung infection refractory to treatment can be debilitating, with symptoms of persistent productive cough, fatigue, and malaise.[3]
- The six-minute walk test (6MWT) is used for the objective evaluation of functional exercise capacity.[4]
  - The 6MWT is a practical, simple test that measures the distance that a patient can walk in a period of 6 minutes.[4]
- The limited choice of effective treatments for patients with NTM lung infection refractory to multidrug therapy represents a therapeutic challenge.[5,6]
- Liposomal amikacin for inhalation (LAI) is a novel, once-daily formulation of amikacin currently in development to treat lung infections caused by NTM.[7-9]
  - LAI is composed of charge-neutral, highly biocompatible liposomes (~0.3 µm) that encapsulate charge-positive amikacin and penetrate the macrophages.
  - High lung concentration and the extended release of amikacin from liposomes enable once-daily dosing of LAI.
- In the current study, the 6MWT was analyzed to address the clinical significance of culture conversion (ie, 3 consecutive negative sputum samples collected 1 month apart) in patients with NTM lung infection refractory to treatment.

OBJECTIVE

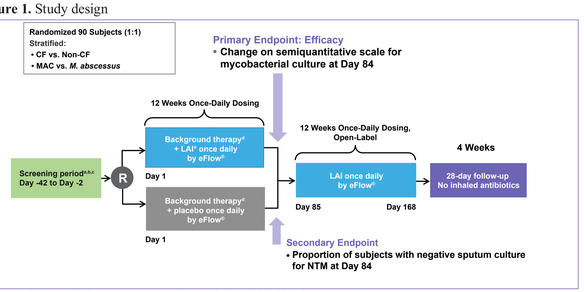
- To evaluate functional exercise capacity using the 6MWT and its correlation with culture conversion (ie, 3 consecutive negative sputum samples collected 1 month apart) in patients with treatment-refractory NTM lung infection.

METHODS

Study Design

- Study TR02-112, the first randomized, placebo-controlled, multicenter clinical trial to evaluate the safety and efficacy of LAI in adults with NTM lung infections refractory to treatment, was conducted at 19 sites in the United States and Canada **(Figure 1)**.
- Patients were eligible if they had pulmonary NTM infection that was refractory to American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guideline-based therapy for ≥6 months prior to screening.
- For the 84-day double-blind phase, patients were randomized 1:1 to LAI 590 mg or placebo once daily via eFlow® nebulizer (PARI Pharma GmbH) added to their ongoing, stable, guideline-based drug regimen.
- After completing the double-blind phase, all patients who consented to continue in the open-label phase received LAI 590 mg once daily for 84 additional days.
- The 6MWT was completed at baseline (Day 1), Day 84, and Day 168, at which times, patients had no knowledge of their culture results.
- This subanalysis evaluated the effect of LAI vs. placebo on the 6MWT at Day 84, and the 6MWT change from baseline to Days 84 and 168 in patients with culture conversion vs. those without culture conversion.

Figure 1. Study design



CF, cystic fibrosis; LAI, liposomal amikacin for inhalation; MAC, *Mycobacterium avium* complex.

[a] 2007 ATS/IDSA criteria with evidence of nodular bronchiectasis and/or fibrocavitary disease by chest CT.

[b] At least 2 documented positive cultures in the prior 2 years, of which at least one was obtained in the 6 months prior to screening.

[c] Receiving ATS/IDSA guideline−based treatment for at least 6 months prior to screening with persistently positive cultures.

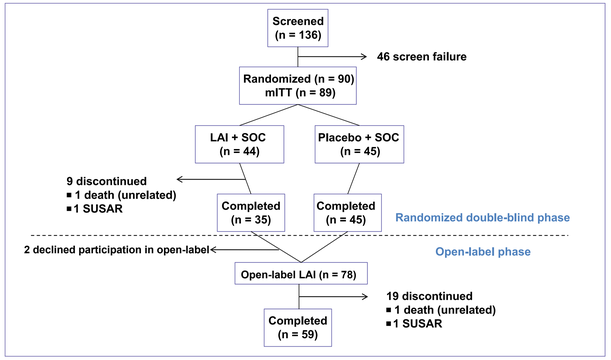
[d] Continuing on ATS/IDSA guideline−based therapy.

STUDY DISPOSITION

Patient Characteristics

- Of 136 screened patients, 90 were randomized to double-blind treatment (19% CF; 81% non-CF; 64% with *Mycobacterium avium* complex [MAC] infection; and 36% with *M. abscessus* infection); 89 of the 90 patients were included in the modified intent-to-treat (mITT) population (ie, all patients who received ≥1 dose of LAI) **(Figure 2** and **Table 1)**.
- 80 patients completed treatment in the double-blind phase and 59 patients completed treatment in the open-label phase **(Figure 2)**.

Figure 2. Patient disposition



LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat; SOC, standard of care; SUSAR, suspected unexpected serious adverse reaction.

Table 1. Demographics and Baseline Characteristics of mITT Population

Characteristic	LAI (n = 44)	Placebo (n = 45)	Overall (N = 89)
Gender, n (%)			
Male	6 (14)	5 (11)	11 (12)
Female	38 (86)	40 (89)	78 (88)
Race/ethnicity, n (%)[a]			
Caucasian (not of Hispanic origin)	42 (96)	40 (89)	82 (92)
Hispanic	0	2 (4)	2 (2)
African	0	1 (2)	1 (1)
Asian	2 (5)	2 (4)	4 (5)
Other	0	0	0
Baseline age, years			
n	44	45	89
Mean (SD)	58.0 (16.6)	59.1 (15.2)	58.5 (15.8)
Median	61.5	63.0	63.0
Min, Max	18, 85	19, 80	18, 85
Baseline FEV_1 percent predicted			
n	44	45	89
Mean (SD)	63.6 (21.3)	62.6 (17.2)	63.1 (19.2)
Median	61.3	61.0	61.0
Min, Max	30.2, 114.9	34.4, 101.6	30.2, 114.9

FEV_1, forced expiratory volume in 1 second; mITT, modified intent-to-treat; SD, standard deviation.

[a] Percentages may not add up to 100 due to rounding.

UPDATED ANALYSIS

- Analyses of preliminary top-line data from this study have previously been presented. Closer inspection of the primary data revealed that specimens negative for AFB but positive for ordinary bacteria, indicating bacterial contamination, were categorized as 'positive for mycobacteria' in liquid media in the preliminary analysis; however, there was no growth of mycobacteria on subculture.
- Pursuant to standard practice, such specimens should be considered negative. In the updated analyses, the re-categorization was adopted. The appropriateness of this corrected categorization was further supported at each time point with at least one and in most cases two additional negative cultures.
- Appropriate categorization of these specimens does affect the efficacy outcomes such that the drug now appears to be more effective than was originally reported.

RESULTS

Culture Results

- The primary endpoint of change from baseline in the full semiquantitative scale did not achieve statistical significance, although there was a positive trend in favor of the LAI arm.
- LAI reached significance for negative sputum culture for NTM at Day 84.
- **Previously presented:** LAI demonstrated effectiveness in achieving culture conversion in 16 patients. Of these 16 patients, 15 were non-CF patients with MAC infection and 1 was a non-CF patient with *M. abscessus* infection.
- **Updated analysis:** LAI demonstrated effectiveness in achieving culture conversion in 20 patients. Of these 20 patients, 17 were non-CF patients with MAC infection, 1 was a non-CF patient with *M. abscessus* infection, and 2 were CF patients with *M. abscessus* infection.

Six-Minute Walk Test Results

- The least squares (LS) mean change from baseline to Day 84 in distance walked (meters) in the 6MWT was significantly higher for patients receiving LAI vs. placebo (14.4 m vs. -36.9 m; $P = 0.009$) **(Figure 3)**.
- A significant difference was not seen in the LS mean change from baseline to Day 168 in the distance walked in the 6MWT for patients with culture conversion (n = 20); however, there was a positive trend **(Figure 4)**.
- There was a significant difference seen in the LS mean change for the non-CF patients with MAC infection (37.3 m vs. -18.5 m; $P = 0.032$) **(Figure 5)**.

CONCLUSIONS

- Patients with NTM lung infections refractory to treatment showed improvement in distance walked in the 6MWT when LAI was added to their background of guideline-based therapy.
- Patients with culture-negative status during the study achieved better physical functional capacity as assessed by the 6MWT, which was conducted when patients were unaware of their culture results. This supports the clinical importance and significance of culture conversion.

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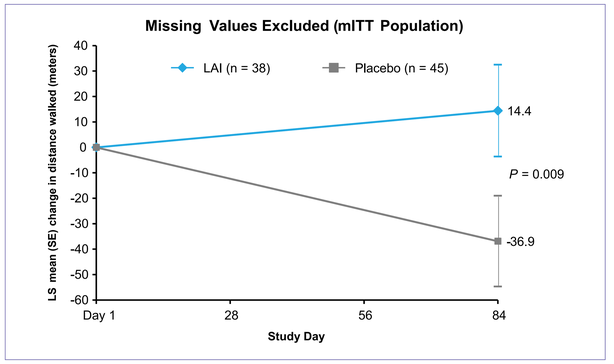
DISCLOSURES

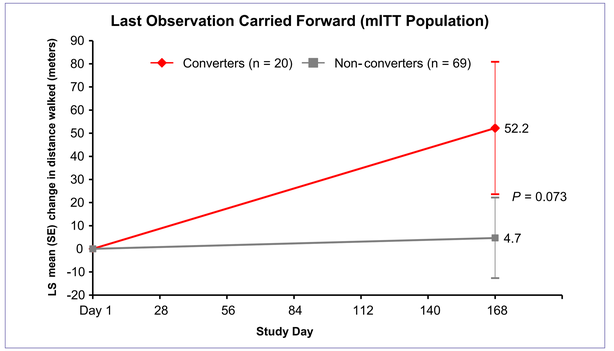
Stephen Ruoss is involved in clinical trials sponsored by, and is a consultant of Insmed Incorporated. Gina Eagle, John P. McGinnis II, and Liza Micioni are employees of Insmed Incorporated. Charles L. Daley is involved in clinical trials sponsored by Insmed Incorporated. Kevin L. Winthrop is involved in clinical trials sponsored by, and is a consultant of Insmed Incorporated. Doreen J. Addrizzo-Harris is involved in clinical trials sponsored by Aradigm Corporation and Insmed Incorporated. Patrick Flume has received grant support from, and is a consultant of Insmed Incorporated. Daniel Dorgan has no disclosures. Matthias Salathe has served on the advisory panel of Insmed Incorporated. David E. Griffith is involved in clinical trials sponsored by Insmed Incorporated. Kenneth N. Olivier is supported by the Division of Intramural Research of the NHLBI-NIH, and had a Cooperative Research and Development Agreement between Insmed Incorporated and NIAID/NIH.

Figure 3. Mean change in distance walked (meters) in the 6MWT: End of double-blind phase (Day 84)



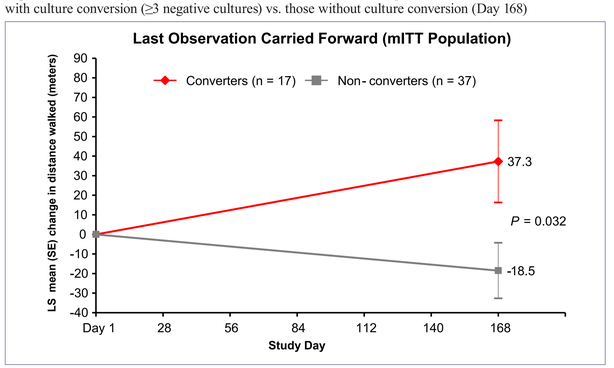
6MWT, six-minute walk test; LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat.

Figure 4. Mean change in distance walked (meters) in the 6MWT in patients with culture conversion (≥3 negative cultures) vs. those without culture conversion (Day 168)



6MWT, six-minute walk test; LS, least squares; mITT, modified intent-to-treat.

Figure 5. Mean change in distance walked (meters) in the 6MWT in patients with non-CF MAC infection with culture conversion (≥3 negative cultures) vs. those without culture conversion (Day 168)



6MWT, six-minute walk test; CF, cystic fibrosis; LS, least squares; MAC, *Mycobacterium avium* complex; mITT, modified intent-to-treat.

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