Efficacy of Liposomal Amikacin for Inhalation (LAI) in Achieving Negative Sputum Cultures for Nontuberculous Mycobacteria (NTM) in Patients Whose Lung Infection Is Refractory to Guideline-Based Therapy

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INTRODUCTION

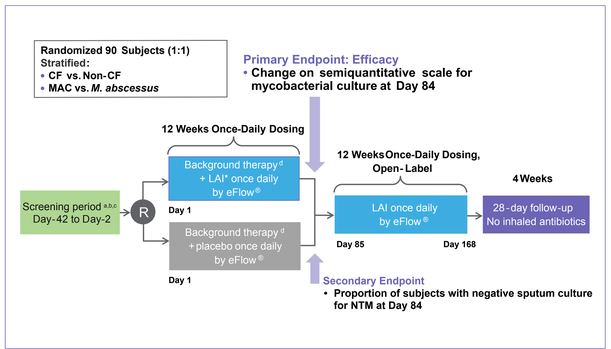
- Management of pulmonary disease caused by nontuberculous mycobacteria (NTM) infection includes lengthy multidrug regimens, which are often associated with drug toxicity and suboptimal outcomes.[1-5]
- Achieving negative sputum cultures for NTM is one of the objectives of treatment and represents the most clinically important microbiologic endpoint in patients with NTM lung infection.[1,3]
- Liposomal amikacin for inhalation (LAI) is a novel, once-daily formulation of amikacin currently in development for the treatment of lung infections caused by NTM (ie, *Mycobacterium avium* complex [MAC] and *M. abscessus*).[6,7]
- This analysis demonstrates the efficacy of LAI in achieving negative sputum cultures for NTM in the subgroup of patients with MAC lung infection that has been refractory to guideline-based treatment for ≥6 months.

METHODS

Study Design

- This randomized, double-blind, placebo-controlled clinical trial evaluated the efficacy and safety of LAI in adults with NTM lung infection refractory to American Thoracic Society / Infectious Disease Society of America (ATS/IDSA) guideline–based therapy for ≥6 months **(Figure 1)**.
- Patients were stratified by the presence or absence of cystic fibrosis (CF) and by the presence of MAC or *M. abscessus* infection.
- In the 84-day double-blind phase, eligible patients received LAI 590 mg or placebo once daily via eFlow® nebulizer (PARI Pharma GmbH) added onto their ongoing, stable, guideline-based treatment.
- After completing the double-blind phase, patients who consented to continue into the open-label phase received LAI 590 mg once daily for 84 additional days.
- Early morning sputum samples were collected at screening and prior to the administration of the study drug at baseline and every 28 days thereafter, up to the 28-day follow-up visit at Day 196.
- The primary efficacy endpoint was assessed by evaluating the change from baseline on the semiquantitative scale for mycobacterial culture for the LAI arm compared with the placebo arm at Day 84.
- One of the key secondary endpoints was the proportion of patients with negative sputum culture for NTM for the LAI arm compared with the placebo arm at Day 84.

Figure 1. Study design



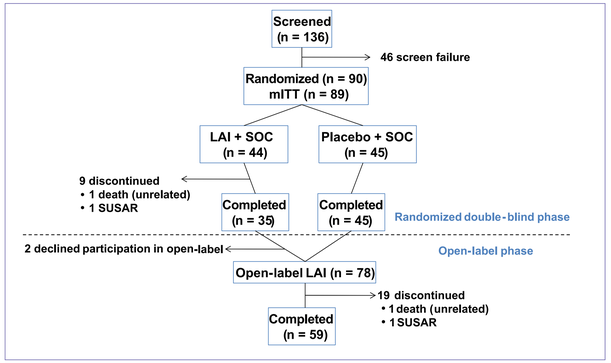
CF, cystic fibrosis; LAI, liposomal amikacin for inhalation; MAC, *Mycobacterium avium* complex.
[a] 2007 ATS/IDSA criteria with evidence of nodular bronchiectasis and/or fibrocavitary disease by chest CT.
[b] At least 2 documented positive cultures in the prior 2 years, of which at least one was obtained 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 (CF infection, 19%; non-CF infection, 81%; MAC infection, 64%; *M. abscessus* infection, 36%); 89 of the 90 patients were included in the modified intent-to-treat (mITT) population (ie, patients who received ≥1 dose of study drug) **(Figure 2** and **Table 1)**.
- A total of 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
Stratification at screening, n (%)			
MAC with CF	2 (5)	1 (2)	3 (3)
MAC without CF	27 (61)	27 (60)	54 (61)
MAB with CF	6 (14)	8 (18)	14 (16)
MAB without CF	9 (21)	9 (20)	18 (20)

CF, cystic fibrosis; FEV_1, forced expiratory volume in 1 second; MAB, *Mycobacterium abscessus*; MAC, *Mycobacterium avium* complex; mITT, modified intent-to-treat; SD, standard deviation.
[a] Percentages may not add up to 100 due to rounding.

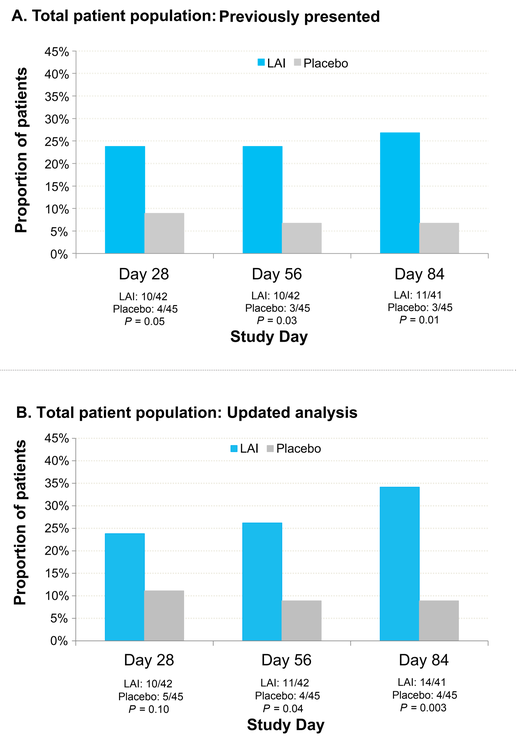
UPDATED ANALYSIS

- 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 1 and in most cases 2 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

- 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.
- **Previously presented:** Based on the analysis of missing values excluded, LAI demonstrated statistical significance in achieving 1 negative sputum culture for NTM in the total patient population at Day 28 (LAI, 10/42 patients vs. placebo, 4/45 patients; $P = 0.05$); Day 56 (LAI, 10/42 patients vs. placebo, 3/45 patients; $P = 0.03$); and Day 84 (LAI, 11/41 patients vs. placebo, 3/45 patients; $P = 0.01$) **(Figure 3A)**.
- **Updated analysis:** Based on the analysis of missing values excluded, LAI demonstrated statistical significance in achieving 1 negative sputum culture for NTM in the total patient population at Day 56 (LAI, 11/42 patients vs. placebo, 4/45 patients; $P = 0.04$) and Day 84 (LAI, 14/41 patients vs. placebo, 4/45 patients; $P = 0.003$) **(Figure 3B)**.

Figure 3. Proportion of patients with negative sputum culture at Days 28, 56, and 84 (mITT population)

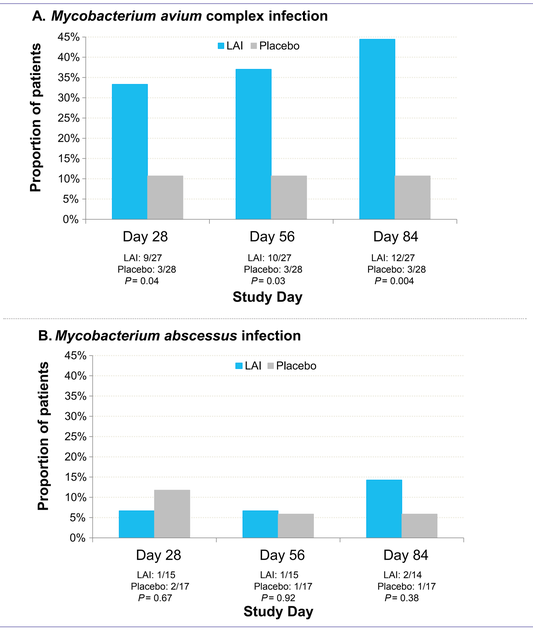


LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat.

Based on updated analyses:

- Compared with placebo, LAI demonstrated statistical significance with regard to the proportion of patients with MAC infections who achieved 1 negative sputum culture for NTM at Day 28 (LAI, 9/27 patients vs. placebo, 3/28 patients; $P = 0.04$; Day 56 (LAI, 10/27 patients vs. placebo, 3/28 patients; $P = 0.03$), and Day 84 (LAI, 12/27 patients vs. placebo, 3/28 patients; $P = 0.004$) **(Figure 4A)**.
- For the subgroup of patients with *M. abscessus* infection, no statistically significant difference was observed in negative sputum cultures for NTM after treatment with LAI vs. placebo at any of the 3 time points over 84 days **(Figure 4B)**.

Figure 4. Proportion of patients with negative sputum culture at Days 28, 56, and 84 (mITT population)



LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat.

CONCLUSIONS

- 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 was effective in achieving negative sputum culture for NTM in patients with NTM lung infection caused by MAC, suggesting that LAI could be an important add-on therapeutic option for this population.
- An effect was not seen in the *M. abscessus* population. Further exploration in a separate study that examines patient factors may be warranted.

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DISCLOSURES

Julie A. Biller has been a non-branded speaker and advisory board participant for Gilead and Genentech, and was a clinical investigator for 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. Stephen Ruoss 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. Barbara A. Brown-Elliott is the Supervisor of the Mycobacteria/Nocardia Laboratory which performed mycobacterial identification and susceptibility testing for this study. Richard J. Wallace, Jr. is the Director of the Mycobacteria/Nocardia Laboratory at the University of Texas which performed molecular and microbiologic testing for this study. 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.

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