Stability and Consistency of Treatment Effect With Liposomal Amikacin for Inhalation (LAI) as Add-on Therapy in Patients With Nontuberculous Mycobacterial (NTM) Lung Disease

Quanwu Zhang[1], George Georges[1], John P. McGinnis II[1], Keith Liu[1], Gina Eagle[1], David E. Griffith[2], Richard J. Wallace, Jr[2], Kenneth N. Olivier[3]

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

INTRODUCTION

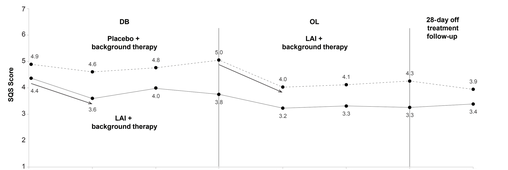
- Recent reports suggest that the incidence and prevalence of nontuberculous mycobacterial (NTM) lung disease and its burden are increasing in many regions of the world, with *Mycobacterium avium* complex (MAC) being the most common organism (MAC lung disease).[1-5]
- Treatment for MAC lung disease, according to the Statement of the American Thoracic Society/Infectious Diseases Society of America, includes a macrolide (clarithromycin or azithromycin), ethambutol, and a rifamycin (rifampin or rifabutin).[6] Clinical improvement and prolonged culture conversion (ie, 12 months of negative cultures for sputum NTM while on therapy) are the goals of therapy.
- Liposomal amikacin for inhalation (LAI) is a novel, once-daily formulation of amikacin currently in development for the treatment of MAC lung disease in adult patients who remain sputum culture–positive despite previous treatments. A phase 2, randomized, double-blind, placebo-controlled study of LAI in patients with recalcitrant NTM lung disease suggested that LAI may be effective in achieving negative sputum culture in patients with MAC lung disease when added to a multidrug regimen.[7]
- In this poster, we present a post hoc evaluation of the phase 2 study to describe the stability and consistency of treatment effect with LAI over the double-blind and open-label periods of this study.

METHODS

- Patients with treatment-refractory NTM lung disease (MAC and *Mycobacterium abscessus* [Mab]) on a stable multidrug regimen were randomized (1:1) to once-daily LAI 590 mg (n = 44) or placebo (n = 45) for 84 days in the double-blind phase followed by an additional 84 days of treatment with LAI (n = 78) in the open-label phase and assessed every 4 weeks. Safety assessments were performed during 28 days (n = 64) and 12 months (n = 45) off study drug. The primary study endpoint was change from baseline on a semiquantitative scale (SQS) for mycobacterial colony counts using a score ranging from 1 to 7, with a score of 1 representing a negative culture.
- Stability and consistency of SQS scores and the rate of negative sputum culture achievement were evaluated with repeated measures mixed effects models, adjusted for baseline SQS score.
- All-cause mortality was assessed through safety reports during the double-blind, open-label, and 12-month off-treatment safety follow-up periods until study completion, discontinuation, or event occurrence, whichever took place first. Rate ratio in mortality between patients who had ≥1 negative sputum culture and those who had positive results throughout the study follow-up was estimated using Poisson regression adjusting for treatment arm.

RESULTS

- The mean age of patients (N = 89) randomized to the study was 58 years; 88% of patients were women and more than 90% were Caucasian. Seventeen patients (19%) had cystic fibrosis. Fifty-seven patients (64%) had MAC, and 32 had Mab (36%) lung infection. Prespecified endpoint assessments have been reported elsewhere,[8] and the primary endpoint did not reach statistical significance.



Days	1	28	56	84	112	140	168	196
LAI: n	44	44	44	44	35	35	35	31
Placebo: n	45	45	45	45	43	43	43	33

Figure 1. Trends of divergence and convergence in semiquantitative scale (SQS) scores during double-blind and open-label periods.
DB, double-blind; LAI, liposomal amikacin for inhalation; OL, open-label.

- Mycobacterial load was numerically lower at baseline for LAI vs. placebo. This initial difference in SQS scores was adjusted for subsequent treatment group comparisons.
- By the end of the double-blind period (Day 84), mycobacterial load measured by SQS score decreased in the LAI group but slightly increased in the placebo group.
- During the first 4 weeks of the open-label period (Days 84-112), the rate of decline in SQS scores in the previously placebo group paralleled that seen in the LAI-treated group during the first 4 weeks of the double-blind period (baseline to Day 28).
- During the last 8 weeks of the open-label period (Days 112-168), both groups of patients (prior LAI and prior placebo) showed a lower level of mycobacterial load relative to the initial levels at baseline.

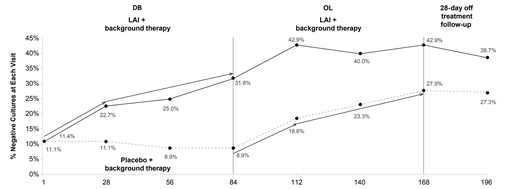


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Figure 2. Effect patterns of liposomal amikacin for inhalation (LAI) that were consistent with expected treatment effect trends.
DB, double-blind; OL, open-label.

- Rates of negative sputum culture diverged between the 2 treatment groups from baseline to Day 84, after which time the placebo group began to use LAI in the open-label period.
- Rate of negative sputum culture during the open-label period in the placebo group showed slopes over assessments performed every 4 weeks comparable to those in the LAI group during the double-blind period.

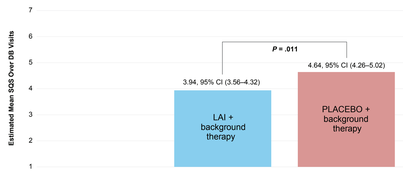

Figure 3. The difference in mean semiquantitative scale (SQS) scores during the double-blind study period between treatment arms.
CI, confidence interval; DB, double-blind.

- The mean follow-up SQS score was 3.94 (95% CI: 3.56-4.32) for liposomal amikacin for inhalation (LAI) vs. 4.64 for placebo (95% CI: 4.26-5.02) with adjustment for baseline SQS score (P = .011).

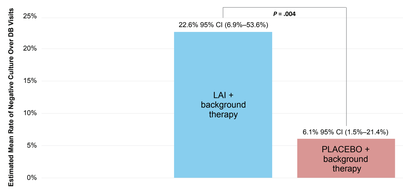

Figure 4. The mean rate of negative sputum culture over the double-blind study period for the liposomal amikacin for inhalation (LAI) and placebo treatment groups.
CI, confidence interval; DB, double-blind.

- The mean rate of negative sputum culture was 22.6% (95% CI: 6.9%-53.6%) in the LAI group vs. 6.1% (95% CI: 1.5%-21.4%) in the placebo group after adjustment for baseline SQS score (P = .004).

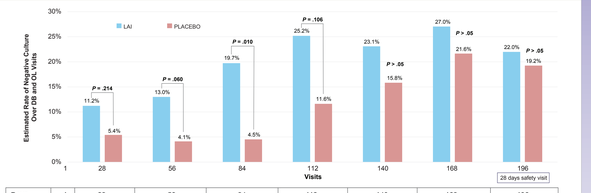

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Figure 5. Differences in the rate of negative sputum culture between treatment arms over visits in the double-blind and open-label periods after adjustment for baseline semiquantitative scale score.
CI, confidence interval; DB, double-blind; OL, open-label.
Note. In the modified intent-to-treat study sample (N = 89), 4 patients, 2 in each treatment group, achieved a sputum culture conversion and started conversion from baseline.

- During the double-blind period, numeric differences in the rate of negative sputum culture between LAI and placebo increased at every visit to Day 84 (end of double-blind phase).
- During the open-label period, numeric differences in the rate of negative sputum culture between the prior LAI and prior PLB treatment groups consistently decreased after Day 84, largely due to the increasing rate of negative sputum culture in the prior placebo group after exposure to LAI in the open-label period.
- The rate of negative sputum culture was maintained in the LAI group over the open-label visits, suggesting a numeric trend of effect stability with limited fluctuation.

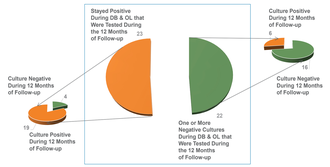

Figure 6. Proportions of patients who maintained or changed sputum culture status from the double-blind or open-label phase to 12 months off liposomal amikacin for inhalation (LAI).
DB, double-blind; OL, open-label.
Note. Of 89 patients who were randomized to the study, 45 had sputum culture test results available at the 12-months off-treatment long-term safety follow-up.

- Of the 22 patients who achieved ≥1 negative sputum culture during the double-blind and open-label phases and were assessed at 12 months off-treatment, 16 remained culture-negative and 6 converted to culture-positive.
- Of the 23 patients who stayed culture-positive during the double-blind and open-label phases, 19 had positive test results and 4 had negative results.

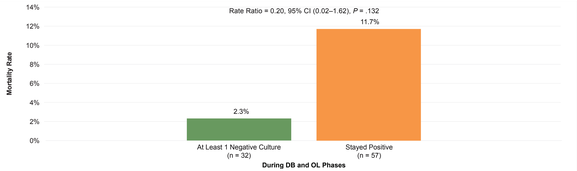

Figure 7. The annualized rate of all-cause mortality from the safety reports during the double-blind, open-label, and 12-month off-treatment safety follow-up study periods.
CI, confidence interval; DB, double-blind; OL, open-label.

- One subject died among patients who achieved ≥1 negative sputum culture during the double-blind and open-label periods (n = 32), with an annualized all-cause mortality rate of 2.3%.
- Eight subjects died among patients who did not achieve a negative sputum culture during the double-blind and open-label periods (n = 57), with an annualized all-cause mortality rate of 11.7%.

CAVEATS AND LIMITATIONS

- The study reports post hoc analytic results from a randomized, placebo-controlled, phase 2 clinical trial; hence, the findings are exploratory and hypothesis-generating in nature.
- To ensure transparency, confidence intervals are reported and statistical *P*-values should be considered as nominal because we did not account for prespecified endpoint hierarchy and multiplicity in hypothesis testing.
- All-cause mortality was not a prespecified endpoint but was assessed from study safety reports.

DISCUSSION

- The phase 2 clinical trial was conducted with a relatively small study sample and was of short duration.
- Though statistical testing in the post hoc analysis is nominal, the study data suggested trends of consistency and stability in treatment response over time and between randomized double-blind treatment groups that eventually were both administered LAI during the open-label phase.
- With available data from a subsample, the study suggested trends of durable negative sputum culture over a 12-month off-LAI assessment.
- Full safety results have been reported elsewhere.[7] The majority (~90%) of patients in both groups experienced ≥1 treatment-emergent adverse event. Most adverse events were mild or moderate in severity. During the double-blind phase, a greater percentage of patients treated with LAI vs. placebo experienced events of dysphonia, bronchiectasis exacerbation, cough, oropharyngeal pain, fatigue, chest discomfort, wheezing, and cystic fibrosis exacerbation. The frequency of respiratory symptoms declined with continued drug use in those patients who remained on the drug.
- The risk of mortality in the study patient population suggests a particularly heightened burden of illness associated with persistently positive MAC sputum cultures. This finding is consistent with those in a published article reporting a 34% (13/38) vs. 0% (0/13) 1-year mortality rate in patients with macrolide-resistant MAC lung disease who failed to convert vs. those who converted sputum cultures to negative.[8]

CONCLUSIONS

- These post hoc analyses support the stability and consistency of effect with LAI add-on therapy for refractory NTM lung disease (MAC and Mab) during a 6-month study period.

CLINICAL IMPLICATIONS

- LAI 590 mg once daily appears to have a stable and consistent effect in reducing mycobacterial burden in MAC or Mab lung disease, with a potentially flexible time window for drug initiation, in patients who remain sputum culture–positive despite previous multidrug treatment.

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DISCLOSURES

Quanwu Zhang, John P. McGinnis II, Keith Liu, and Gina Eagle are employees of Insmed Incoporated.
George Georges was an employee of Insmed Incorporated.
David E. Griffith is involved in clinical trials sponsored by Insmed Incorporated.
Richard J. Wallace, Jr, is Director of the Mycobacteriology Laboratory where the microbiology for the Insmed trial was performed.
Kenneth N. Olivier is supported by the Division of Intramural Research of the NHLBI-NIH, had a Cooperative Research and Development Agreement between Insmed Incorporated and NIAID/NIH, and is involved in clinical trials sponsored by Insmed Incorporated.

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