INTRODUCTION

- Liposomal amikacin for inhalation (LAI) is a novel formulation of amikacin currently in development for the treatment of patients with lung infections caused by Pseudomonas aeruginosa and nontuberculous mycobacteria (NTM).
- LAI is composed of charge-neutral, highly biocompatible liposomes (~0.3 µm) that encapsulate amikacin and penetrate the bronchi to achieve a high drug concentration at the site of infection (Figure 1).

- Key features of LAI include:
  - High lung concentration ($C_{Lung}$) and area under the curve (AUC), as well as longer half-life ($t_{1/2}$), which result in improved AUC and minimum inhibitory concentration (MIC) ratio that enables once-daily dosing.
  - Potent $P$. aeruginosa killing, including resistant isolates.
  - Additional release of amikacin from LAI when virulence factors are secreted by $P$. aeruginosa.
  - Potent in vitro and in vivo NM killing that is superior to amikacin solution.

- In preclinical studies, the lung level of LAI administered once daily (QD) was approximately 5 times greater than the level of an equivalent amount of tobramycin inhalation solution (TIS), USP, given twice daily (BD).

RESULTS

Efficacy Summary

- Patients in both treatment groups entered CLEAR-108 with a higher baseline FEV$_1$ than their respective baseline values in CLEAR-108 (Figures 4 and 5).
- At the end of the six-off-treatment cycle in CLEAR-108, FEV$_1$ showed sustained improvement above baseline values, with a relative mean change of 3.39% and 1.11% for patients previously treated with LAI and TIS, respectively.
- Patients who previously received LAI in CLEAR-108 appear to have sustained a improvement in FEV$_1$, with longer-term exposure.

- Overall, reductions in $P$. aeruginosa sputum density were similar in all patients regardless of prior treatment (Figure 6).
- In CLEAR-108, LAI continues to show the ability to manage $P$. aeruginosa colonies, as demonstrated by the maintained reduction in $P$. aeruginosa sputum density at levels that were below baseline levels in both surgery.

- Because the study was ongoing at the time of the data cut as March 17, 2014, the number of patients at day 377 does not represent the complete dataset. Therefore, although trends may be observed, conclusions cannot be drawn at the present time.

Safety and Tolerability Summary

- In CLEAR-108, the number of patients who experienced $≥$1 adverse event during cycles LAI 590 mg once daily was 77 (52.0%) in Cycle 1 to 53 (39.6%) in Cycle 3 on LAI; the proportion of patients who experienced $≥$2 TEAEs on TIS was similar between Cycle 1 (52 [35.6%]) and Cycle 3 (47 [34.6%]).
- A similar trend was observed in CLEAR-100, with continued reductions in TEAEs from Cycle 1 to Cycle 6 for both treatment groups (Table 2).

- The majority of adverse events were respiratory in nature, with the highest frequency occurring in Cycle 1 for patients entering CLEAR-100 from the TIS arm (21.1% vs. 8.6% for Cycles 1 and 6, respectively). For patients entering from the LAI arm, respiratory adverse event numbers were 76% vs. 8.5% for Cycles 1 and 6, respectively (Table 2).

CONCLUSIONS

- Based on the available data included in this analysis:
  - LAI provides sustained improvement in pulmonary function in patients with CF who have bronchiolpulmonary infection caused by $P$. aeruginosa.
  - LAI has a favorable tolerability profile with prolonged exposure, with most adverse events being respiratory in nature. Bacterial load and sputum density were maintained at baseline levels.
  - Data from ongoing analyses will provide further understanding of factors that may have an impact on patient response.
  - Additional studies are warranted in patients for whom LAI may afford additional benefits.

REFERENCES


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DISCLOSURES

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John P. Clancy, MD, has received research grant support from Insmed Incorporated and has served on the Arikaye Clinical Program Steering Committee. Amparo Solé, MD, PhD has served on the Advisory board for Gilead Sciences and Vertex.