Introduction

Liposomal Amikacin for Inhalation (LAI): Nonclinical Summary

- LAI is a novel lipid formulation of amikacin (Figure 1) for inhalation that is being developed for lung infections due to Pseudomonas aeruginosa (Pa) and nontuberculous mycobacteria (NTM).

- Key Features of LAI:
  - Charge neutral high biocompatible liposomes (~0.3 um) encapsulating amikacin
  - Penetration of drug into biofilm
  - High lung concentration (Cmax), area under the curve (AUC), and half-life (t1/2) improved AUC:
    - Maximum inhibition concentration (MIC) ratio
  - Potent Pa killing, including resistant isolates
  - Virulence factors secreted by Pa facilitate further release of amikacin from LAI
  - Potent in vitro and in vivo NTM killing that is superior to amikacin solution

CLEAR-108: Primary Objective

- To evaluate the efficacy, safety, and tolerability of 3 cycles of LAI administered once daily compared to TOBI® administered twice daily in patients with cystic fibrosis (CF) with chronic bronchopulmonary infections due to Pa

Methods

Figure 2. CLEAR-108 Study Design

- A multicenter study was conducted in 73 sites in Europe and Canada
- Upon completion of CLEAR-108, eligible patients were rolled over to a multicyle (up to 2 years) study of LAI (CLEAR-110)

Results

CLEAR-108: Safety Summary

- LAI administered once daily was generally safe and well tolerated in patients with CF with chronic bronchopulmonary infection due to Pa
- The majority of patients in the LAI (84.5%) and tobramycin inhalation solution (TOBI®; 78.8%) treatment groups experienced >1 treatment-emergent adverse event (TEAE)
- Most were mild or moderate. There were no unexpected adverse events, and the TEAEs were consistent with underlying CF disease
- Serious adverse events (SAEs), primarily hospitalizations for the treatment of pulmonary exacerbations, were experienced by 17.6% and 19.9% of LAI and TOBI® patients, respectively; SAEs were considered related to study drug in 1 patient given LAI (FEV1 decreased) and 1 patient given TOBI® (infective pulmonary exacerbation of CF)

Figure 3. Patient Disposition

CLEAR-108: Efficacy Summary

- The study achieved its primary endpoint by demonstrating that LAI administered once daily was noninferior to TOBI® administered twice daily with respect to the relative change in FEV1 from baseline to end of study (Day 168)
- Relative change in FEV1 observed at the end of the treatment period in Cycle 3 (Day 140) was similar to that observed at the end of the treatment period in Cycle 1 (Day 58), suggesting that the treatment effect was maintained over the course of 3 cycles

Table 1. Demographic and Baseline Characteristics (mITT Population)

Table 2. Summary of AE s (Safety Population)

Figure 4. Primary Endpoint: Relative Change in FEV1 (Per Protocol Population)

Figure 5. Change from Baseline in Sputum Density of Pseudomonas aeruginosa (mITT Population)

Figure 6. CRO-R Percent Change in Respiratory Symptoms (mITT Population)

Figure 7. CRO-R Scale Response at Day 140, Based on Minimal Clinically Important Difference (mITT Population)

Figure 8. CRO-R Percent Change in Treatment Burden (mITT Population)

Conclusions

- LAI was generally safe and well tolerated, and no unexpected adverse events were observed
- LAI administered once daily is comparable to TOBI® administered twice daily in improving lung function, the standard of care in patients with CF chronically infected with Pa
- Patients maintained on LAI reported significantly greater improvement in respiratory symptoms compared with the TOBI® arm at the end of the treatment period of the study
- Patients also reported less treatment burden in the LAI arm, which is administered once daily and is associated with a significantly lower rate of treatment discontinuation

Support

This research was funded by Insmed Incorporated, Monmouth Junction, NJ. Editorial assistance was provided by The Curry Rockefeller Group, LLC, Tarrytown, NY, and was funded by Insmed Incorporated.

Acknowledgments

The LAI Study Group: PIs, Co-Pi’s, and Study Coordinators who participated in the study. Principal Investigator: Diana Bilton, MD; Arikace Steering Committee Members: Bonnie Ramsey, MD; Co-Principal Investigator: Diana Bilton, MD; P. J. Clancy MD; J. Stuart Elborn, MD; Nicole Hamblett, PhD; Michael Konstan, MD; Lisa Salinan, MD, MPH; H. A. W. M. (Harm) Tiddens, MD, PhD. Acknowledgments CRO & Consultancy Services: Biotics International Ltd; Chiltern International Ltd; ICON Central Laboratories; PARI Pharma GmbH; Vitalgraph Ltd; Xerixus Inc; Cystic Fibrosis Foundation Therapeutics (CFFT), Inc; CFFT/Therapeutics Development Network (TIDN) Study Review Committee; Preston Campbell III, MD; CF TIDN Coordinating Services Group Data Safety Monitoring Board; European Cystic Fibrosis Society (ECFS)-Clinical Trials Network; Seattle Children’s Hospital (Kase Burns, MD; Anne Marie Burcis, MD, MSc/ACCP). Patients who contributed their time and faith to participate in the study.