A multi-cycle open-label study of nebulized liposomal amikacin (Arikace®) in the treatment of cystic fibrosis patients with chronic *Pseudomonas aeruginosa* lung infection


CF Arikace® Study Group & Insmed Incorporated, M. & W. Junction, NJ, USA

### Arikace® - Non-Clinical Summary

- Arikace® is a liposomal formulation of amikacin for inhalation, being developed for lung infections due to susceptible pathogens
- Key Features of Arikace®
  - Charge neutral highly bioavailable liposomes (−0.3 μm) packed with amikacin
  - High lung Cmax, AUC, and t½
  - Improved AUC: MIC ratio
  - Penetration of drug into biofilm
  - Potent *Pseudomonas* killing, including resistant isolates
  - Virulence factors secreted by *Pseudomonas* facilitate further release of amikacin from Arikace®
  - Uniform drug distribution in rat lungs, including alveolar macrophages
  - Normal BAL macrophage activity
  - Toxicology in dogs and rats (3-6 months) supports long-term clinical studies

### Arikace® - CF Open-Label Multi-Cycle Study: TR02-105 Extension

- Upon review of data from the Phase 2 randomized study of Arikace® versus placebo, DSMB recommended initiation of Multi-Cycle, Open-Label Extension Study of 560 mg of Arikace®
- Subjects randomized to Arikace® or Placebo in the main study were consented to participate in the open-label extension study
- 49 eligible subjects were enrolled in the extension study

### Arikace® - TR02-105 Extension: Open-Label Study Design

- **Study Design**: Toch 56 days off-treatment for 6 cycles
- **Enrolled Subjects**: 49
- **Assessments of Clinical Safety, PFT, CFU, CFG-R and PK**: Ongoing

### Arikace® - Frequency of Adverse Events ≥8% Over 72 Weeks Period

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>All Patients (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic Fibrosis lung</td>
<td>23 (46.9%)</td>
</tr>
<tr>
<td>Cough</td>
<td>14 (28.6%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>14 (28.6%)</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>11 (22.4%)</td>
</tr>
<tr>
<td>Productive cough</td>
<td>10 (20.4%)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>8 (16.3%)</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>7 (14.3%)</td>
</tr>
<tr>
<td>Influenza</td>
<td>6 (12.2%)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>5 (10.2%)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>5 (10.2%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5 (10.2%)</td>
</tr>
<tr>
<td>Respiratory tract infection viral</td>
<td>5 (10.2%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4 (8.2%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>4 (8.2%)</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>4 (8.2%)</td>
</tr>
</tbody>
</table>

### Arikace® - CF Open-Label Multi-Cycle Study Summary Observations: Safety

- Overall, Arikace® 560 mg administered once daily for 28 day periods, for six cycles was well tolerated
- No unexpected AEs were observed with longer term dosing
- In summary, nebulized Arikace® delivered using eFlow® is well-tolerated for 6 cycles and demonstrates adverse events that are consistent with those expected in a population of CF patients receiving inhalation medicines

### Arikace® - CF Open-Label Multi-Cycle Study Summary Observations: Efficacy

- Data show statistically significant reduction from baseline in *Pseudomonas aeruginosa* density, including mucoid strains. This is sustained over the treatment period of 6 cycles, with each cycle including 56 days off-treatment. The estimated change from baseline in Log10 CFU over time was −0.6 log (95% CI: −0.2 to −0.9 log) p=0.0030
- Inhalation of 560 mg of Arikace® for 6 cycles has demonstrated statistically significant sustained improvement in lung function. The estimated relative change in FEV1 from baseline to end of treatment (Day 28) during Cycles 1-6 was 7.9% (95% CI +4.3, +11.5%) p<0.0001
- This effect was also sustained at the end of 56 days off-treatment during each of Cycles 1-6. The estimated relative change in FEV1 was 5.7% (95% CI +3.0, +8.5%) p=0.0001

### Arikace® - Summary and Conclusions

- Arikace® administered once daily using eFlow® has been well-tolerated for 6 cycles
- Data show statistically significant reduction from baseline in *P. aeruginosa* density, including mucoid strains. This effect was sustained over 6 cycles, including the 56 day interval between dosing (p=0.0030)
- No significant shift in MICs was observed
- Inhalation of 560 mg of Arikace® once daily for 28 days demonstrated statistically significant improvement in lung function over baseline that was sustained over a 72 week period. A mean increase in FEV1 (%) of 11.7% was observed at the end of treatment of 6 cycles (p<0.0001)
- Launch of Phase 3 studies is underway

### Arikace® - Phase 2 Program: Acknowledgements

- **Investigating Teams**
  - Predrag Minic, MD, PhD
  - Yuri Antipkin, MD, PhD
  - Eszter Csizser, MD
  - Anna Feketeova, MD
  - Henryk Mazurek, MD, PhD
  - Aleksandar Sovtic, MD
  - Aleksandar Sovtic, MD
  - Eniko Solyom, MD
  - Alexandar Sovtic, MD
  - Roman Takac, MD
  - Rita Ujhelyi, MD

- **Co-PIs and Study Sites**
  - Cystic Fibrosis Foundation
  - University of Washington
  - University of Edinburgh
  - University of Miami

**Principal Investigators**

- Cystic Fibrosis Foundation Therapeutics
- CF-FTDN Study Review Committee
- CF Therapeutics Development Network Consulting Services Group
- Drug Safety Monitoring Board

**Data**

- EeCS
- University of Washington
- James Library, PhD
- University of Edinburgh
- John R.W. Govan, DSc
- Catherine Doherty
- University of Miami
- Alexandra Quilter, PhD

**Research**

- ICDD-Ordway Research Institute