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, Monmouth Junction, NJ, USA
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 biocompatible 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
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

49 eligible subjects were enrolled in the extension study
Arikace® - TR02-105 Extension: Open-Label Study Design

TR02-105: Main Study
Subjects Randomized to 280mg/560mg Arikace® or volume matched Placebo

Extension Study
Initiated 5-11 months later

28 days Run-in Period
Screening Day -14

560 mg Arikace® Once Daily by eFlow® *
Followed by 56 Days Off-Treatment for 6 Cycles

Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6

Days 1
85
169
253
337
421
505

28 On
56 Off
28 On
56 Off
28 On
56 Off
28 On
56 Off
28 On
56 Off

Enrolled
N= 49

Key Inclusion Criteria
• FEV₁ ≥ 40%
• Age ≥ 6 years
• Chronic Pa Infection
• 28 Days Off Inhalation Antibiotics
• AZI, DNAse and/or hypertonic saline continued

Assessments of Clinical Safety, PFT, CFU, CFQ-R and PK

* eFlow® Nebulizer System (PARI Pharma GmbH)
# Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td>17.4 (6.2)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20 (40.8%)</td>
</tr>
<tr>
<td>Female</td>
<td>29 (59.2%)</td>
</tr>
<tr>
<td><strong>FEV$_1$ (L)</strong></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td>1.871 (0.772)</td>
</tr>
<tr>
<td><strong>FEV$_1$ (% Pred)</strong></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td>59.2 (19.3)</td>
</tr>
<tr>
<td><strong>FVC (L)</strong></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td>2.693 (1.109)</td>
</tr>
<tr>
<td><strong>FEF 25-75% (L/sec)</strong></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td>1.336 (0.766)</td>
</tr>
<tr>
<td><strong>BMI (kg/m$^2$)</strong></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td>18.425 (3.114)</td>
</tr>
</tbody>
</table>
## Arikace® - TR02-105 Extension: Overview of Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N=49)</th>
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</thead>
<tbody>
<tr>
<td>Number of Adverse Events</td>
<td>351</td>
</tr>
<tr>
<td>Patients with Adverse Events</td>
<td>48 (98.0%)</td>
</tr>
<tr>
<td>Number of Treatment-Related Adverse Events (Probably or Possibly Related)</td>
<td>33</td>
</tr>
<tr>
<td>Patients with Treatment-Related Adverse Events</td>
<td>15 (30.6%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Patients with Serious Adverse Events</td>
<td>15 (30.6%)</td>
</tr>
<tr>
<td>Patients Interrupting Study Drug Due to Adverse Events</td>
<td>1 (2.0%)</td>
</tr>
</tbody>
</table>
## Arikace® - Frequency of Adverse Events

### ≥8% Over 72 Weeks Period

#### Adverse Events by Descending Frequency

<table>
<thead>
<tr>
<th>Preferred Term</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>Dysphonia</td>
<td>7 (14.3%)</td>
</tr>
</tbody>
</table>
**Arikace® - Frequency of Adverse Events ≥8% Over 72 Weeks Period**

**Adverse Events by Descending Frequency**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>All Patients (N=49)</th>
</tr>
</thead>
<tbody>
<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>
Open Label Extension: Change in FEV₁ Over 72 Weeks Period

Patients Receiving 560 mg Arikace® Once Daily for 28 Days and Off-Treatment for 56 Days

Percent Change in FEV₁ (L) From Baseline (Mean +/-SE)

- Cycle 1
- Cycle 2
- Cycle 3
- Cycle 4
- Cycle 5
- Cycle 6

Days on Study

* Significance at end of treatment over 6 cycles
** Significance 56 days off-treatment over 6 cycles

T = Treatment Period
Arikace® - Change in \( P. \) aeruginosa Density from Baseline

* Each cycle consists of 28 days of once daily treatment followed by 56 days off-treatment

* Day 1 values for Cycles 2, 3, 4, 5 and 6 are change from Baseline (Day 1 value of Cycle 1)

** Reduction in Log\(_{10}\) CFU is statistically significant during Cycles 1-6
An open label extension study of Arikace® demonstrated no significant change in MIC$_{90}$ over six cycles of therapy.

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</thead>
<tbody>
<tr>
<td># subjects contributing data</td>
<td>41</td>
<td>41</td>
<td>40</td>
<td>40</td>
<td>32</td>
<td>32</td>
<td>33</td>
<td>33</td>
<td>36</td>
<td>36</td>
<td>33</td>
</tr>
</tbody>
</table>

**MIC$_{90}$ of Pseudomonas to Arikace® 560 mg Per Treatment Cycle**
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 effects that are consistent with those expected in a population of CF patients receiving inhalation medicines.
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 Log$_{10}$ CFU over time was -0.6 log (95% CI, -0.2 to -0.9 log) $p=0.0030$

Inhalation of 560 mg of Arikace$^\text{®}$ for 6 cycles has demonstrated statistically significant sustained improvement in lung function. The estimated relative change in FEV$_1$ from baseline to end of treatment (Day 28) during Cycles 1-6 was 7.9% (95% CI +4.3, +11.7%) $p<0.0001$

This effect was also sustained at the end of 56 days off-treatment during each of Cycles 1-6. The estimated relative change in FEV$_1$ 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 FEV$_1$ (%) 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

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