A Multi-Cycle Open-Label Study of Nebulized Liposomal Amikacin (Arikace™) in the Treatment of Cystic Fibrosis Patients with Chronic Pseudomonas aeruginosa Lung Infection

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Cystic Fibrosis Arikace™ Study Group

ECFS Workshop 9, Abstract #236
June 17, 2010
Arikace™ is a sustained-release lipid 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
- Penetration of drug into biofilm
- High lung Cmax, AUC, and t½ \( \text{Improved AUC: MIC ratio} \)
- Potent PsA killing, including resistant isolates
- Virulence factors secreted by Pseudomonas facilitate further release of amikacin from Arikace™
- Normal BAL macrophage activity
- Toxicology in dogs and rats (3-6 months) supports long-term clinical studies
Arikace™ - TR02-105 Extension: Open-Label Study Design

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

Extension Study
Initiated 11 months later

28 days Run-in Period
Screening Day -14

560 mg Arikace™ Once Daily for 28 Days by eFlow® *
Followed by 56 Days Off-Treatment for 6 Cycles

Cycle 1
- Days 1 On
- Days 85 Off
- Days 169 On
- Days 253 Off

Cycle 2
- Days 56 On
- Days 337 On

Cycle 3
- Days 56 Off
- Days 421 On

Cycle 4
- Days 28 On
- Days 56 Off

Cycle 5
- Days 28 On
- Days 56 Off

Cycle 6
- Days 28 On
- Days 56 Off

Enrolled N= 49

Interim Data

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)
### Number of Cycles

<table>
<thead>
<tr>
<th>Number Of Patients Completed Cycle (N=49) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
</tr>
<tr>
<td>48</td>
</tr>
<tr>
<td>Cycle 2</td>
</tr>
<tr>
<td>46</td>
</tr>
<tr>
<td>Cycle 3</td>
</tr>
<tr>
<td>45</td>
</tr>
<tr>
<td>Cycle 4</td>
</tr>
<tr>
<td>32</td>
</tr>
</tbody>
</table>

* Subjects enrolled in the study over 5-10 months. Subjects currently continuing in Cycles 4 through 6
<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>All Patients (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>Female</td>
</tr>
<tr>
<td><strong>FEV&lt;sub&gt;1&lt;/sub&gt; (L)</strong></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td><strong>FEV&lt;sub&gt;1&lt;/sub&gt; (% Pred)</strong></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td><strong>FVC (L)</strong></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td><strong>FEF 25-75% (L/sec)</strong></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td><strong>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</strong></td>
<td>Mean (SD)</td>
</tr>
</tbody>
</table>
### Arikace™ - Frequency of Adverse Events ≥8% over 12 month Period

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Patients (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis pulmonary exacerbation</td>
<td>20 (40.8%)</td>
</tr>
<tr>
<td>Cough</td>
<td>10 (20.4%)</td>
</tr>
<tr>
<td>Rhinopharyngitis</td>
<td>9 (18.4%)</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>7 (14.3%)</td>
</tr>
<tr>
<td>Sputum increased</td>
<td>7 (14.3%)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>6 (12.2%)</td>
</tr>
<tr>
<td>Fever</td>
<td>5 (10.2%)</td>
</tr>
<tr>
<td>Influenza</td>
<td>5 (10.2%)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>5 (10.2%)</td>
</tr>
<tr>
<td>Acute pharyngitis</td>
<td>4 (8.2%)</td>
</tr>
<tr>
<td>Acute rhinitis</td>
<td>4 (8.2%)</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>4 (8.2%)</td>
</tr>
</tbody>
</table>
Arikace™ - Relative Change in FEV₁ Over 12 Months

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

Percent Change From Baseline in FEV₁

Days on Study

Mean (SE)

N= 45 45 28 47 46 66 46 96 112 140 154 169 182 196 224 238 253 266 280 308 322

* Significance at end of treatment over 4 cycles

** Significance 56 days after treatment over 4 cycles
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, and 4 are change from Baseline (Day 1 value of Cycle 1)

** Reduction in \( \log_{10} \) CFU is statistically significant during Cycles 1-4

\[ \text{Log}_{10} \text{ CFU Mean Change From Baseline (+/-SE)} \]

\[ \text{Change in } \log_{10} \text{ CFU from Study Day 1} \]

\( \text{P}=0.0025^{**} \)
Overall, Arikace™ 560 mg administered once daily for 28 day periods, for four cycles was well tolerated

No unexpected AEs were observed with longer term dosing

DSMB recommended continuation of study without modification

In summary, nebulized Arikace™ delivered using eFlow® is well-tolerated for 4 cycles over 12 months, and demonstrates adverse effects 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 in *Pseudomonas aeruginosa* density, including mucoid strains. This is sustained over the treatment period of 4 cycles, with each cycle including 56 days off-treatment. The estimated change from baseline in Log$_{10}$ CFU over time is -0.8 (95% CI -1.3, -0.39) p=0.0025

- Nebulization of 560 mg of Arikace™ for 4 cycles has demonstrated statistically significant sustained improvement in lung function. The estimated relative change from baseline in FEV$_1$ to end of treatment (Day 28) during Cycles 1-4 is 9.2% (95% CI +5.0%, +13.4%) p=<0.0001

- This effect is also sustained at the end of off-treatment period (56 days) during Cycles 1-4. The estimated relative change in FEV$_1$ is 4.7% (95% CI +1.0%, +8.5%) p=0.015
Arikace™ - Summary and Conclusions

- Arikace™ administered once daily using eFlow® has been well-tolerated for 4 cycles
- Data show statistically significant reduction in *P. aeruginosa* density including mucoid strains, that has been sustained over the 12 month study period
- No significant shift was observed in MICs
- Nebulization of 560 mg of Arikace™ once daily for 28 days followed by 56 days off-treatment for 4 cycles demonstrated improvement in lung function that is sustained during the two months off study drug. This treatment effect has been maintained in each of the 4 cycles over a 12 month period with statistically significant increase in FEV₁ over time (*p*<0.0001)
- Subjects continue in this study towards completion of 6 cycles (18 months)
- Preparations are underway to launch Phase 3 studies
Arikace™ - Acknowledgements

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PARI Pharma GmbH
Accelsiors CRO & Consultancy Services
Axio Research

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