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 & Transave, Inc., Monmouth Junction, NJ, USA

Poster #243
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 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

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

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)
### Arikace™ - TR02-105 Extension Subject Status Status - September 2010

<table>
<thead>
<tr>
<th>Number of Cycles</th>
<th>Number Of Patients Completed Cycle (N=49) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td>48</td>
</tr>
<tr>
<td>Cycle 2</td>
<td>46</td>
</tr>
<tr>
<td>Cycle 3</td>
<td>45</td>
</tr>
<tr>
<td>Cycle 4</td>
<td>44</td>
</tr>
<tr>
<td>Cycle 5</td>
<td>43</td>
</tr>
</tbody>
</table>

- Subjects enrolled in the study over 5-10 months.
- Subjects currently continuing in Cycles 5 through 6
- 4/49 (8.0%) discontinued study
### Patient Characteristics

The table below presents the characteristics of all patients (N=49) with mean and standard deviation (SD) for various parameters:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Patients (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>Mean (SD) 17.4 (6.2)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Male 20 (40.8%)</td>
</tr>
<tr>
<td></td>
<td>Female 29 (59.2%)</td>
</tr>
<tr>
<td><strong>FEV&lt;sub&gt;1&lt;/sub&gt; (L)</strong></td>
<td>Mean (SD) 1.871 (0.772)</td>
</tr>
<tr>
<td><strong>FEV&lt;sub&gt;1&lt;/sub&gt; (% Pred)</strong></td>
<td>Mean (SD) 59.2 (19.3)</td>
</tr>
<tr>
<td><strong>FVC (L)</strong></td>
<td>Mean (SD) 2.693 (1.109)</td>
</tr>
<tr>
<td><strong>FEF 25-75% (L/sec)</strong></td>
<td>Mean (SD) 1.336 (0.766)</td>
</tr>
<tr>
<td><strong>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</strong></td>
<td>Mean (SD) 18.425 (3.114)</td>
</tr>
</tbody>
</table>
Overall, Arikace™ 560 mg administered once daily for 28 day periods, for five cycles was well tolerated.

No unexpected AEs were observed with longer term dosing.

There were no appreciable changes in acute tolerability.

DSMB review at 12 months recommended continuation of study without modification.

In summary, nebulized Arikace™ delivered using eFlow® is well-tolerated for 5 cycles, and demonstrates adverse effects that are consistent with those expected in a population of CF patients receiving inhalation medicines.
Open Label Extension: Change in FEV$_1$ Over 5 Cycles

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

Days on Study

Percent Change From Baseline in FEV$_1$ (L)

Mean (SE)

* Significance at end of treatment over 5 cycles
** Significance 56 days off-treatment over 5 cycles
T = Treatment Period

N= 45 47 45 46 47 46 46 45 43 44 46 47 46 46 45 44 43 43 43 43 44 43 42 42 42 41 41 41

Days: 14 28 56 70 85 98 112 140 154 169 196 224 238 253 280 308 322 337 350 364 392 406 421

P=<.0001*
p=0.0018**
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
Arikace™ - TR02-105 Extension - Distribution of MIC\(_{90}\) (µg/ml) of *P. aeruginosa* to Arikace™

No significant change observed in MIC\(_{90}\) over multiple cycles of therapy

**MIC\(_{90}\) of *Pseudomonas* to Arikace™ 560 mg Per Treatment Cycle**

<table>
<thead>
<tr>
<th>Day 1/ Baseline</th>
<th>Day 28</th>
<th>Day 85</th>
<th>Day 112</th>
<th>Day 169</th>
<th>Day 196</th>
<th>Day 253</th>
<th>Day 280</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment 1</td>
<td>16</td>
<td>16</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Treatment 2</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>32</td>
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<td>Treatment 3</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Treatment 4</td>
<td>16</td>
<td>16</td>
<td>24</td>
<td>24</td>
<td>24</td>
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</tr>
</tbody>
</table>

# subjects contributing data:

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<tr>
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<tbody>
<tr>
<td>41</td>
<td>41</td>
<td>40</td>
<td>40</td>
<td>32</td>
<td>32</td>
<td>33</td>
<td>33</td>
</tr>
</tbody>
</table>
Data show statistically significant reduction in *Pseudomonas aeruginosa* density, including mucoid strains. This is sustained over the treatment period of 5 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 5 cycles has demonstrated statistically significant sustained improvement in lung function. The estimated relative change in FEV$_1$ over time, from baseline to end of treatment (Day 28) during Cycles 1-5 is 8.4% (95% CI +4.7%, +12.0%) $p=<0.0001$

This effect is also sustained at the end of off-treatment period (56 days) during Cycles 1-5. The estimated relative change in FEV$_1$ over time is 6.5% (95% CI +2.5%, +10.4%) $p=0.0018$
Arikace™ administered once daily using eFlow® has been well-tolerated for 5 cycles.

Data show statistically significant reduction in *P. aeruginosa* density including mucoid strains, that has been sustained over a 12 month 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 5 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 5 cycles over a 14 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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and sites who participated in the main study

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Accelsiors CRO & Consultancy Services
Axio Research

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