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**

### Arikace™ - Non-Clinical Summary

- **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 highy biocompatible liposomes (~0.3 µm) packed with amikacin
  - Penetration of drug into biofilm
  - High lung Cmax, AUC, and t½ Improved AUC: MIC ratio
  - Potent Pseudomonas 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 (~6 months) supports long-term clinical studies

### Arikace™ - TR02-105 Extension: Open-Label Multi-Cycle Study Design

#### 560 mg Arikace™ Once Daily for 28 Days

#### Followed by 16 Days Off-Treatment for 6 Cycles

- **Critical Pathway**
- **Subjects Randomized**
- **Assessments of Clinical Safety, PFT, CFU, CFD-R and PK**
- **20 mg Arikace™ Once Daily by eFlow®**

### Key Inclusion Criteria

- Age ≥ 3 years
- Cystic Fibrosis
- 36 Days On-Demand Inhalation Treatment including mucoid strains
- Not anemic or hypotensive (solute continued)

### Acknowledgements

**Principal Investigators**

- Predrag Minic, MD, PhD
- Yuriy Antipkin, MD, PhD
- Ezséter Csizsér, MD
- Anna Feketeová, MD
- Stojka Fustik, MD, PhD
- Victoria Kostromina, MD, PhD
- Henrik Mazurek, MD, PhD
- Anna Senatorová, MD, PhD
- Eniko Solomy, MD
- Aleksandar Sovtíc, MD
- Branka Tavas, PhD
- Rita Ujhelyi, MD
- Co-PIs and Study Coordinators and sites participated in this main study

**Affiliations**

- **Transave Inhalation Biotherapeutics**
- **PARI Pharma GmbH**
- **Ordway Research Institute**
- **CFTR Foundation**
- **Cystic Fibrosis Canada**
- **University of Washington**
- **Emory University**
- **University of Miami**
- **AFS**
- **University of Edinburgh**
- **Johns Hopkins University School of Medicine**
- **ICPD-Ordway Research Institute**

### Patient Characteristics

<table>
<thead>
<tr>
<th>All Patients (N=49)</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong> Mean (SD)</td>
<td>17.4 (6.2)</td>
<td>16.7 (6.2)</td>
<td>17.4 (6.4)</td>
<td>18.3 (6.8)</td>
</tr>
<tr>
<td><strong>Gender</strong> Male</td>
<td>20 (41.8%)</td>
<td>22 (45.8%)</td>
<td>20 (40.8%)</td>
<td>18 (37.3%)</td>
</tr>
<tr>
<td>Female</td>
<td>29 (58.2%)</td>
<td>18 (38.3%)</td>
<td>25 (50.0%)</td>
<td>20 (40.8%)</td>
</tr>
<tr>
<td><strong>FEV1 (%)</strong> Mean (SD)</td>
<td>1.871 (0.772)</td>
<td>1.776 (0.933)</td>
<td>1.891 (0.976)</td>
<td>1.832 (0.926)</td>
</tr>
<tr>
<td><strong>BMI (kg/m2)</strong> Mean (SD)</td>
<td>21.396 (3.198)</td>
<td>21.283 (3.224)</td>
<td>21.325 (3.239)</td>
<td>21.378 (3.213)</td>
</tr>
</tbody>
</table>

### Change in Distribution of MIC<sub>50</sub> (µg/ml) of *P. aeruginosa* to Arikace™

<table>
<thead>
<tr>
<th>Day 1 (Baseline)</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Subjects</strong></td>
<td>41</td>
<td>40</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td><strong>Lower</strong></td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Upper</strong></td>
<td>36</td>
<td>36</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td><strong>MIC (µg/ml)</strong> Mean (SD)</td>
<td>0.004 (0.003)</td>
<td>0.004 (0.003)</td>
<td>0.004 (0.003)</td>
<td>0.004 (0.003)</td>
</tr>
</tbody>
</table>

### Change in Lung Function

<table>
<thead>
<tr>
<th>Days on Study</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Days on Treatment</strong></td>
<td>Cycle 1</td>
<td>Cycle 2</td>
<td>Cycle 3</td>
<td>Cycle 4</td>
</tr>
<tr>
<td><strong>FEV1 (%)</strong> Mean (SD)</td>
<td>1.354 (0.773)</td>
<td>1.349 (0.768)</td>
<td>1.347 (0.772)</td>
<td>1.346 (0.771)</td>
</tr>
<tr>
<td><strong>FVC (L)</strong> Mean (SD)</td>
<td>2.693 (1.109)</td>
<td>2.690 (1.110)</td>
<td>2.688 (1.111)</td>
<td>2.685 (1.112)</td>
</tr>
<tr>
<td><strong>BMI (kg/m2)</strong> Mean (SD)</td>
<td>0.398 (0.206)</td>
<td>0.397 (0.207)</td>
<td>0.396 (0.208)</td>
<td>0.395 (0.209)</td>
</tr>
<tr>
<td><strong>THI</strong></td>
<td>4 (6.2%)</td>
<td>4 (6.2%)</td>
<td>4 (6.2%)</td>
<td>4 (6.2%)</td>
</tr>
</tbody>
</table>

### Change in *P. aeruginosa* Density from Baseline

<table>
<thead>
<tr>
<th>Days on Treatment</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 0 (Baseline)</strong></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>Day 1</strong></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>Day 2</strong></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>Day 3</strong></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>Day 4</strong></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>Day 5</strong></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### Significance

- **Significance at end of treatment over 4 cycles**
- **Significance 56 days after treatment over 4 cycles**

- **Data show statistically significant reduction in *P. 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<sub>10</sub> CFU over time is -0.8 (95% CI -1.31,-0.29) 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<sub>1</sub> 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<sub>1</sub> is 4.7% (95% CI +1.0%, +8.5%) p=0.012.

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

- Overall, Arikace™ 560 mg administered once daily for 28 days per cycle, for four cycles was well tolerated.
- No unexpected AEs were observed with longer term dosing.
- There were no appreciable changes in acute tolerability.
- DSMR 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 Multi-Cycle Study Summary Observations: Efficacy

- Data show statistically significant reduction in *P. 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<sub>10</sub> CFU over time is -0.8 (95% CI -1.31,-0.29) 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<sub>1</sub> 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<sub>1</sub> is 4.7% (95% CI +1.0%, +8.5%) p=0.012.

### 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 FEV<sub>1</sub> 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