Full analyses of data from two phase II blinded and placebo-controlled studies of nebulized liposomal amikacin for inhalation (Arikace™) in the treatment of cystic fibrosis patients with chronic Pseudomonas aeruginosa lung infection

University of Alabama at Birmingham, CF Arikace™ Study Group & Transave, Inc., Monmouth Jct., NJ

Poster #227
**Arikace™ (Preclinical Summary)**

- Charge neutral highly biocompatible liposomes packed with amikacin
- Potent PsA killing, including resistant isolates
- High lung Cmax, T½, and AUC
- Low sputum binding
- Penetration of drug into biofilms
- Amikacin release by PsA byproducts
- Retained BAL macrophage killing
- Toxicology in dogs and rats (6 mos) supports long-term clinical studies

**Arikace™ liposome (0.2-0.3 μm)**

- Lipid bilayer - neutral lipids (DPPC and Cholesterol)
- Aqueous interior - encapsulated amikacin

~3 μm nebulized droplet (>300 liposomes/drop)
**Phase 2 Arikace™ Studies TR02-105 – TR02-106**

28 Days Off Inhaled Antibiotics

Run-in

N= 105

28 Days Daily Dosing

70, 140, 280 or *560 mg Arikace™
Once daily by PARI eFlow®

Placebo
Once daily by PARI eFlow®

*28-56 Days Follow Up

No inhaled antibiotics

**Key Inclusion Criteria**
- FEV₁ ≥ 40%
- Age ≥ 6 years
- Chronic Pa Infection
- 28 Days Off Inhalation Antibiotics
- Continued Azithromycin, DNAse, Hypertonic saline, Bronchodilators

**Weekly Safety Evaluation**
Assessments of PFT, CFU, Exacerbations, Time to Rescue Antibiotics, Hospitalizations, CFSD, CFQ-R and PK

*DSMB and FDA Evaluation of Interim Safety Data from 106; and Safety and Efficacy data from 105: Amended Study 106 to add 560 mg Cohort; Pediatric patients; and 56 days off treatment for durability of response*
## Arikace™ Phase 2 Study Features: Europe and US

<table>
<thead>
<tr>
<th>Study</th>
<th>Sites</th>
<th>Subjects</th>
<th>Doses</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR02-105 (Europe)</td>
<td>15</td>
<td>N = 66</td>
<td>560mg, 280mg, placebo</td>
<td>28 days on, 28 day f/u</td>
<td>Safety, PK/PD, efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: 16.5 yr (6.0), FEV1: 65.7% (20.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TR02-106 (US)</td>
<td>18</td>
<td>N = 19</td>
<td>140mg, 70mg, placebo</td>
<td>28 days on, 28 day f/u</td>
<td>Safety, PK/PD, efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: 30.5 yr (8.3), FEV1: 65.3% (19.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TR02-106 (US)</td>
<td>18</td>
<td>N = 22</td>
<td>560mg, placebo</td>
<td>28 days on, 56 day f/u</td>
<td>Safety, PK/PD, efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: 29.4 yr (11.9), FEV1: 67.4% (15.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Summary:**

- **Mucoid PsA:** 85% (TR02-105); 89% (TR02-106)
- **TOBI® use:** 19% (TR02-105); 35% (TR02-106)
Safety and Tolerability

- AEs were consistent with underlying CF disease although a trend towards mild to moderate dysphonia (8%) in the higher dose Arikace™ group

- **Acute Tolerability**: Percent Patients with $\geq 15\%$ decline in FEV$_1$
  - Arikace™: 2.8%
  - Placebo: 11.1%

- **Discontinuations**
  - Arikace™: four subjects (70 mg, 560 mg) – respiratory, laryngitis, tinnitus, dysphonia, (one of each)
  - One in placebo group (respiratory)

- **Distribution of adverse events** similar across Arikace™ and placebo groups
  - Ear/labyrinth disorder
  - Audiology

- **AEs** (relatedness)
  - Arikace™ (560 mg, n=36): 22% of subjects-possibly related
  - Placebo (n=36): 17% of subjects-possibly/probably related

- **CTC grade 3: AEs Not related** (pyrexia, laryngitis, tooth abscess, low wbc, arthralgia, exacerbation)
  - Arikace™ (560 mg, n=36): 11% of subjects
  - Placebo (n=36): 8%
Arikace™ TR02-105 and TR02-106: $\Delta$FEV$_1$

![Graph showing the percent change in FEV$_1$ (ml) from baseline for Arikace™ 280 (21), Placebo (36), Arikace™ 560 (36), Arikace™ TR02-105 and TR02-106.](image_url)

- **Arikace™ 280 (21)**: P=0.003
- **Arikace™ 560 (36)**: P=0.033
- **Placebo (36)**: P=0.003

**Study Day**:
- 21/34/35
- 20/34/34

**Percent Change in FEV$_1$ (ml) from Baseline**

**N:**
- 20/33/36

**Mean (SE):**
Arikace™ TR02-105 and TR02-106: $\Delta \log_{10} \text{CFU}$

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study Day</th>
<th>N:</th>
<th>Mean (SE)</th>
<th>$\Delta \log_{10} \text{CFU}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (36)</td>
<td>14</td>
<td>19/31/32</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Arikace™ - 280 mg (21)</td>
<td>28</td>
<td>19/32/28</td>
<td>-0.5</td>
<td>P=0.007</td>
</tr>
<tr>
<td>Arikace™ - 560 mg (36)</td>
<td>35</td>
<td>19/31/29</td>
<td>-1.5</td>
<td>P=0.007</td>
</tr>
</tbody>
</table>

Mean (SE)
PK and PD Relationships: $\Delta$FEV$_1$ and CFU vs AUC

*p<0.05 each treatment day vs pre

FEV$_1$ vs Day 1 AUC

CFU vs Day 1 AUC
Arikace™ - TR02-105 & 106
CFQR - Respiratory Scale - Clinical Response Rate

Clinical Response Rate of Arikace™ 560 mg vs Placebo

Day 1 to 28

Improved = Increase of >=4 points
Worsened = Decrease of >=4 points
Stable = Change (increase or decrease) of <4 points
MCID = 4 Points

66.7% (24/36) Arikace™ 560 mg
36.1% (13/36) Placebo
38.9% (14/36) Placebo

P = 0.006

Percent

0 10 20 30 40 50 60 70 80

Improved

Worsened
## Correlation Between Change in CFQ-R Respiratory Domain Scores and FEV₁

<table>
<thead>
<tr>
<th></th>
<th>Day 15</th>
<th>Day 28</th>
<th>Day 42</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>61</td>
<td>63</td>
<td>58</td>
</tr>
<tr>
<td><strong>FEV₁ % Predicted Day 28</strong></td>
<td>*r = 0.26, p = 0.0435</td>
<td>*r = 0.42, p = 0.0006</td>
<td>*r = 0.34, p = 0.0093</td>
</tr>
</tbody>
</table>

* Pearson Correlation Coefficients
In summary, nebulized Arikace™ is well-tolerated and demonstrates adverse effects that are consistent with those expected in a population of CF patients receiving inhalation medicines.

PK and PD data support mechanism of action *in vivo*
- High sputum Cmax, and AUC with low serum concentrations
- Prolonged t½: once daily dosing
- Dose proportional and statistically significant correlation between AUC; increasing FEV₁ and decreasing CFU
- No shift in MICs
Summary of Arikace™ Phase 2 Efficacy Data

- Patients receiving 560 mg of Arikace™ demonstrated improvement in lung function over baseline while patients on placebo declined over time. A treatment effect of relative change in FEV₁ of 12.5% was observed at one month after discontinuing study drug (p=0.003).

- Patients receiving Arikace™ demonstrated superior clinical benefit vs patients receiving placebo
  - Significant Improvement in patient reported respiratory symptoms (67% on Arikace™ improving versus 36% on placebo; p=0.006).
  - Statistically significant correlation between respiratory symptom score and FEV₁ at end of treatment (p=0.0006)
  - Statistically significant reduction in *Pseudomonas aeruginosa* density, including mucoid strains (~1.7 log reduction; p=0.007)
  - Patients receiving Arikace™ had prolonged time to exacerbation as compared to placebo (Arikace™ arm: Mean = 45.3 days vs Placebo arm: Mean = 31.4 days)
Global CF Program Acknowledgements

Principal Investigators
Dr. Clancy
Dr. Young
Dr. Ahrens
Dr. Aitken
Dr. Billings
Dr. Faro
Dr. Goss
Dr. Layish
Dr. Light

Dr. Miller
Dr. Nasr
Dr. Nick
Dr. Rubenstein
Dr. Sannuti
Dr. Sawicki
Dr. Taylor-Cousar
Dr. Trapnell
Dr. Wallace
Dr. Woo

Cystic Fibrosis Foundation Therapeutics
- Preston Campbell III, MD
- CFFT Protocol Review Committee
- CF Therapeutics Development Network Consulting Services Group
- Drug Safety Monitoring Board

University of Washington
Bonnie Ramsey, MD
Jane Burns, MD
Prof. Donald Patrick
Nicole Hamblett, PhD
James Lymp, PhD

University of Miami
Alexandra Quittner, PhD

Univ. of Edinburgh
Prof. John Govan

PARI Pharma GmbH
Accelsiors, AXIO, ICPD

European Investigators
Co-PIs
Prof. Dupont
Prof. Minic
Prof. Fustic

Co-PIs
Study Coordinators