**Evaluation of Two Phase II Blinded and Placebo-Controlled Studies of Nebulized Liposomal Amikacin (Arikace™) in the Treatment of Cystic Fibrosis Patients with Pseudomonas aeruginosa Lung Infection**

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**Arikace™-Liposomal Amikacin: Preclinical 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 highly biocompatible liposomes (~0.3 μm) packed with amikacin
  - Penetration of drug into biofilm
  - High lung Cmax, AUC, and f(t) Improved AUC: MIC ratio
  - Potent PA4 killing, including resistant isolates
  - Vascular factors mediated by liposomal formulation facilitate further release of amikacin from Arikace™
- Normal BAL macrophage activity
- Toxicology in dogs and rats (3.6 months) supports long-term clinical studies

**US and European CF Phase II Program with Arikace™**

- Arikace™ Doses tested: 70, 140, 280, 560 mg vs. Placebo
- Total N = 105
- Duration: 28 days on drug, 28-56 days off drug
- Safety: Safe and well tolerated
- AEs were consistent with underlying CF disease
- No differences between groups in the overall rates of AEs.
- A trend towards increase in reporting of mild/moderate dysphonia in the higher dose Arikace™ group
- PKPD:
  - High spuht Cmax and AUC with low serum concentrations
  - High Cmax and AUC, MIC ratio
  - Prolonged spuht 1%: once daily dosing
  - Dose proportional and statistically significant correlation between AUC and microbiologic activity and improvement in lung function
- No shift in MICs

**Arikace™– CF Phase 2 Study Design: TR02-105 & 106**

- 28 Days On DDM Antimicrobial
- 28-56 Days Follow-Up
- Placebo vs. Arikace™ Once daily by pMDI

**CF-PATIENT CHARACTERISTICS – COHORT 3**

- **Demographics:**
  - Europe – TR02-105
    - N = 64 enrolled (mITT)
    - Randomized, double-blind, placebo-controlled
    - 350 mg vs. 560 mg vs. placebo
  - US – TR02-106
    - N = 19 enrolled (mITT)
    - Randomized, double-blind, placebo-controlled
    - 70 mg vs. 410 mg vs. placebo

- **Mean (%)**
  - Age: 16 (6-29 yr)
  - Sex: Male 57 (62%); Female 29 (33%)
- **Study Days**
  - Day 0-56

**RESULTS: PK DATA**

- High levels of Amikacin achieved in Sputum
  - Cmax Mean (CV): 3496 (9.73%) mcg/g
  - AUC Mean (CV): 280 mg Cohort: 13120 (13.63%) μg/hr
    - 560 mg Cohort: 22445 (8.31%) μg/hr
  - High patient variability, but sputum AUC values are dose proportional

- Serum PK data demonstrate low systemic exposure
  - Cmax Mean (SD): 2.27 (1.58) μg/mL

**Change in FEV1 (ml) From Baseline: Pooled Data: TR02-105 & 106**

- Significant improvement in FEV1 observed in the Arikace™ group over placebo

**CF Phase 2 Summary Observations: Safety**

- Overall, Arikace™ 70 mcg, 140 mcg, 280 mg and 560 mg administered once daily for 28 days was well tolerated
- No unexpected AEs were observed
- There were no appreciable changes in acute tolerability
- There was improvement in oxygen saturation
- No differences between groups in overall rates of AEs
- AEs were consistent with underlying CF disease although a trend towards mild to moderate dysphonia was reported in the higher dose Arikace™ group

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.

**Summary Observations: Efficacy**

- Dose proportional and high levels of Amikacin achieved in Sputum with low systemic exposure
- PKPD:
  - High spuht Cmax and AUC with low serum concentrations
  - High Cmax and AUC, MIC ratio
  - Prolonged spuht 1%: once daily dosing
  - Dose proportional and statistically significant correlation between AUC and microbiologic activity and improvement in lung function
  - No appreciable shift in MICs

**Overall Conclusion**

Arikace™ technology provides the following:

- High levels of sustained release of antibiotic in the lung with drug concentrations well above the MICs for Pseudomonas aeruginosa during the dosing interval
- Penetration of drug into biofilm observed in non-clinical experiments
- Increased microbiologic activity, including against mucoid and resistant isolates: significantly superior to placebo
- Improvement in respiratory symptoms, and lung function: significantly superior to placebo
- Sustained clinical benefit up to one month after discontinuing dosing of Arikace™