ATS Abstract #1836 – Poster Session
A53 Cystic Fibrosis: Clinical Pediatric Studies

TRANSAVE
Inhalation Biotherapeutics

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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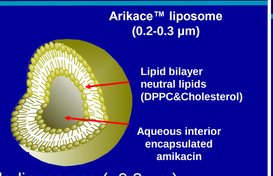
Arikace™-Liposomal Amikacin: Preclinical Summary

- Arikace™ is a sustained-release lipid formulation of amikacin for inhalation, being developed for lung infections due to susceptible pathogens

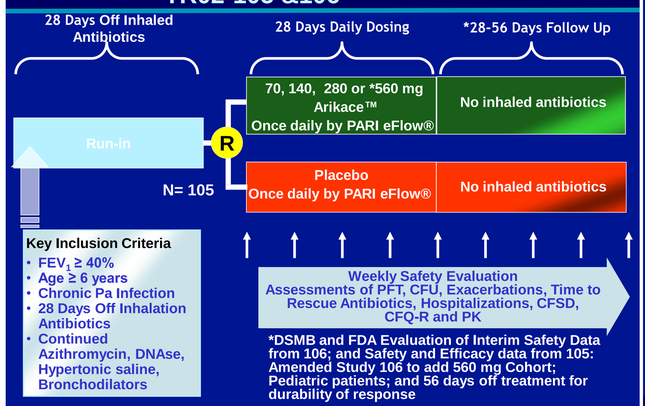


- **Key Features of Arikace™**
  - Charge neutral highly biocompatible liposomes (~0.3 μm) packed with amikacin
  - Penetration of drug into biofilm
  - High lung Cmax, AUC, and t½ ⇒ Improved AUC: MIC ratio
  - Potent *PsA* killing, including resistant isolates
  - Virulence factors secreted by Pseudomonas facilitate further release of amikacin from Arikace™
  - Normal BAL macrophage activity
  - Toxicology in dogs and rats (3-6 months) supports long-term clinical studies

US and European CF Phase II Program with Arikace™

- Arikace™ Doses tested: 70, 140, 280, 560 vs. Placebo (via e-Flow® Nebulizer System PARI Pharma GmbH)
- 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 slight trend towards increase in reporting of mild-moderate dysphonia in the Arikace™ group
- PK/PD:
  - High sputum Cmax and AUC with low serum concentrations
  - High Cmax and AUC: MIC ratio
  - Prolonged sputum t½: once daily dosing
  - Dose proportional and statistically significant correlation between AUC and microbiologic activity and improvement in lung function
  - No shift in MICs

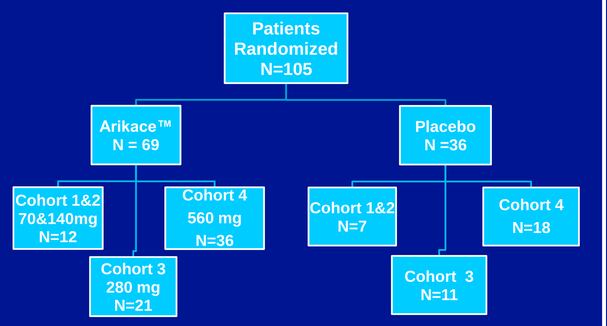
Arikace™ – CF Phase 2 Study Design: TR02-105 &106



Arikace™ - TR02-105: STATISTICAL ASSUMPTIONS

Primary Endpoint	◆ Safety and tolerability of study drug
Secondary Objectives	◆ Pulmonary Function – Change from baseline to Day 28 and 56 for FEV_1 (L), FEV_1 % Predicted, $FEF_{25-75\%}$, and FVC ◆ Sputum Bacterial Density – Change from baseline ◆ Time to and duration of systemic anti-pseudomonal rescue treatment ◆ QOL/PRO (change in CFQR)
Sample Size	◆ Safety and tolerability: ~80% power to observe adverse events with a true toxicity rate as low as 8% ◆ Efficacy: Power to detect between treatment groups difference in FEV_1 of 100ml is 31%; for a difference of 190ml, the power is 80%

Arikace™ - CF Program: PATIENT DISTRIBUTION



Demographics: European and US Phase 2 Studies Total Number of Patients =105

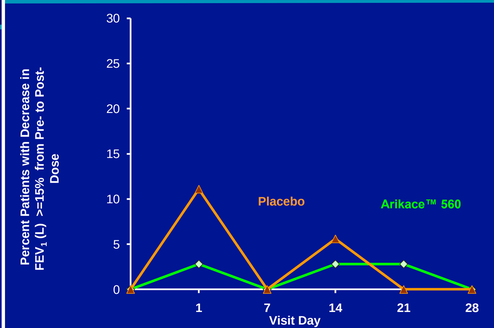
- **Europe – TR02-105**
  - N = 15 sites
  - N = 64 enrolled (mITT)
  - Randomized, double-blind placebo controlled
  - 280 mg, 560 mg vs placebo Once daily x 28 days f/u x 28 days
    - N = 42 (active)
    - N = 22 (placebo)
  - Age: 16 (6-29 yr)
  - TOBI® use ~18%
  - Mucoid *PsA* ~85%
- **US – TR02-106**
  - N = 18 sites
  - N = 41 enrolled (mITT)
  - Randomized, double-blind placebo controlled
  - 70 mg, 140 mg vs placebo Once daily x 28 days f/u x 28 days
    - N = 12 (active)
    - N = 7 (placebo)
  - DSMB review and FDA recommendation
    - Drop low doses
    - Prolong off drug observation
  - 560 mg vs placebo x 28 days f/u x 56 days
    - N = 15 (active)
    - N = 7 (placebo)
  - Age: 27 (9-68 yr)
  - TOBI® use ~35.0%. Median 5 cycles in prior 12 months
  - Mucoid *PsA* ~89%

CF-PATIENT CHARACTERISTICS – COHORT 3

		Arikace™ 560 mg (N=36)	Pooled Placebo (N=36)
Age (yrs)	Mean (SD)	23.0 (12.6)	20.3 (7.7)
Gender	Male	21 (58.3%)	16 (44.4%)
	Female	15 (41.7%)	20 (55.6%)
FEV_1 (L)	Mean (SD)	2.190 (0.873)	2.133 (0.702)
FEV_1 (% Predicted)	Mean (SD)	66.389 (17.443)	67.861 (19.357)
$FEF_{25-75\%}$ (L/sec)	Mean (SD)	1.692 (0.933)	1.528 (0.874)
FVC (L)	Mean (SD)	3.014 (1.196)	3.077 (1.089)
BMI (kg/m²)	Mean (SD)	20.379 (4.064)	19.900 (3.458)

P-value assessed by ANOVA for continuous variables and chi-square statistic for categorical

Acute Tolerability: Decrease in FEV_1 (L) of >=15% from Pre- to Post-dose: Pooled Data: TR02-105 & 106

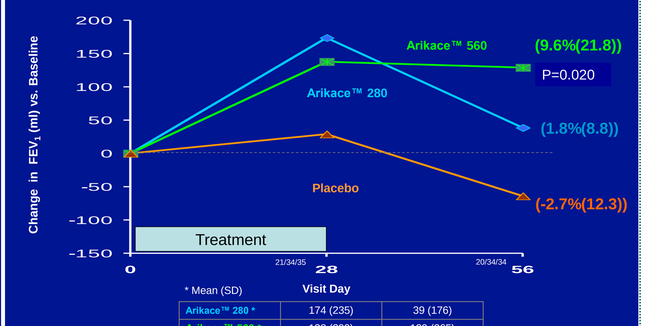


	1	7	14	21	28
560 mg Arikace™ *	2.8%	0%	2.8%	2.8%	0%
Pooled Placebo *	11.1%	0%	5.6%	0%	0%

RESULTS: PK DATA

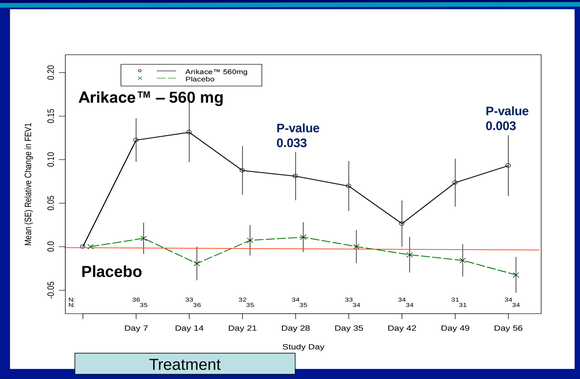
- High levels of Amikacin achieved in Sputum
  - C_{max} Mean (CV): 3496 (0.973) mcg/g
  - AUC Mean (CV):
    - 280 mg Cohort: 13120 (1.63) μg/g*hr
    - 560 mg Cohort: 22445 (0.831) μg/g*hr
- High patient variability, but sputum AUC values are dose proportional
- Serum PK data demonstrate low systemic exposure C_{max} Mean (SD): 2.27 (1.58) μg/mL

Change in FEV_1 (mL) From Baseline: Pooled Data: TR02-105 & TR02-106

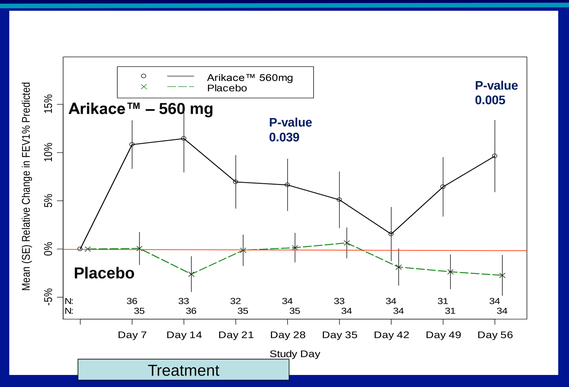


* Mean (SD)	21/34/35	28	20/34/34	56
Arikace™ 280 *	174 (235)			39 (176)
Arikace™ 560 *	138 (299)			129 (265)
Placebo *	29 (221)			-64 (226)

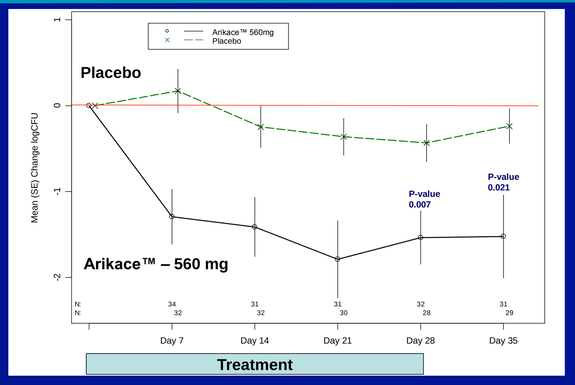
Relative Change in FEV_1 (L) from Baseline Pooled Data: TR02-105 & TR02-106



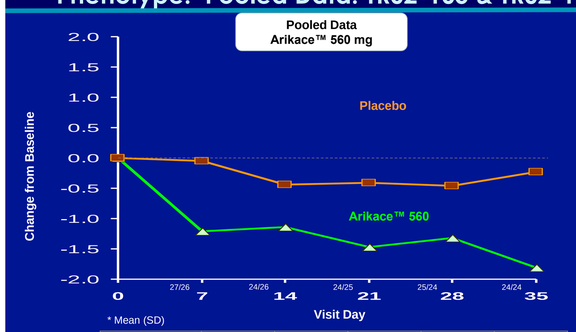
Relative Change in FEV_1% Predicted: Pooled Data TR02-105 and TR02-106



Change in Bacterial Density (Log_{10} CFU): All Phenotypes Pooled Data: TR02-105 & TR02-106



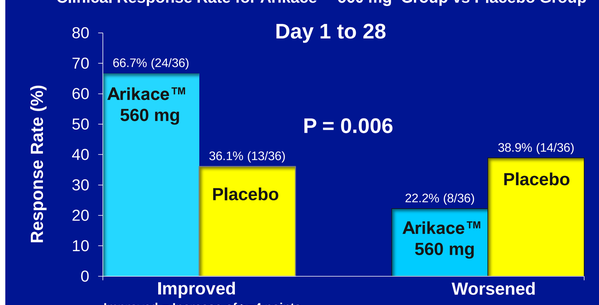
Change in Bacterial Density (Log_{10} CFU): Mucoid Phenotype: Pooled Data: TR02-105 & TR02-106



* Mean (SD)	0	7	14	21	28	35
		27/26	24/26	24/25	25/24	24/24
Arikace 560™ *		-1.210 (1.989)	-1.136 (1.907)	-1.473 (2.581)	-1.316 (1.690)	-1.809 (2.781)
Pooled Placebo *		-0.051 (1.256)	-0.442 (0.923)	-0.412 (1.267)	-0.461 (1.205)	-0.233 (1.000)

CFQR - Respiratory Scale: Clinical Response Rate Pooled Data: TR02-105 & TR02-106

Clinical Response Rate for Arikace™ 560 mg Group vs Placebo Group



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

CF Phase 2 Summary Observations: Safety

- Overall, Arikace™ 70 mg, 140 mg, 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

CF Phase 2 Summary Observations: Efficacy

- Patients receiving Arikace™ demonstrated superior clinical benefit vs patients receiving placebo
  - Statistically superior and sustained reduction in *Pseudomonas aeruginosa* density, including mucoid strains(~2.0 log reduction)
  - Clinically meaningful and statistically significant evidence of clinical benefit as measured by improvement in respiratory symptoms of CFQR- Respiratory Scale (67% on Arikace™ improving versus 36% on placebo)
- Patients receiving 560 mg of Arikace™ demonstrated improvement in lung function over baseline while patients on placebo declined over time. A statistically significant treatment effect of FEV_1% predicted of 12.5% was observed at one month after discontinuing study drug.

Summary Observations: Efficacy

- Dose proportional and high levels of Amikacin achieved in Sputum with low systemic exposure
- PK/PD
  - High sputum Cmax and AUC with low serum concentrations
  - High Cmax and AUC:MIC ratio
  - Prolonged t½: 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™

Arikace™ - Global CF Program Acknowledgements

Principal Investigators
Dr. Clancy
Dr. Young
Dr. Ahrens
Dr. Aitken
Dr. Billings
Dr. Faro
Dr. Goss
Dr. Layish
Dr. Lechtzin
Dr. Light
Dr. Miller
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Dr. Rubenstein
Dr. Sannuti
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PARI Pharma GmbH

Accelsiors, AXIO, ICPD