A Multi-Cycle Open-Label Study of Nebulized Liposomal Amikacin (Arikace™) in the Treatment of Cystic Fibrosis Patients with Chronic *Pseudomonas aeruginosa* Lung Infection

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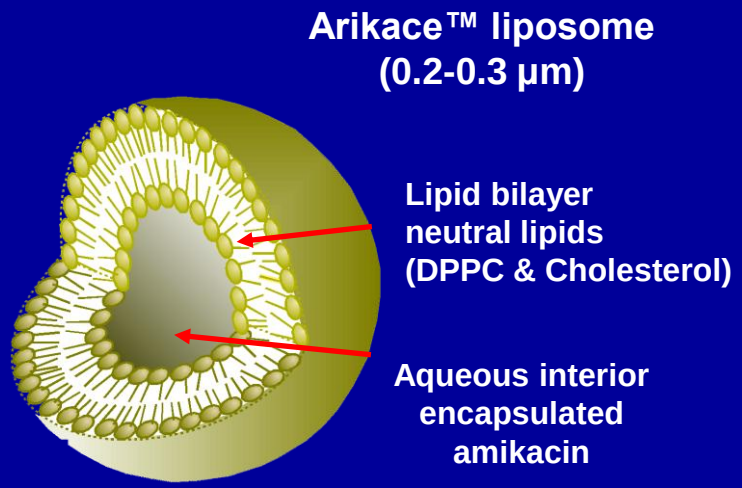
TRANSAVE
Inhalation Biotherapeutics

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 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

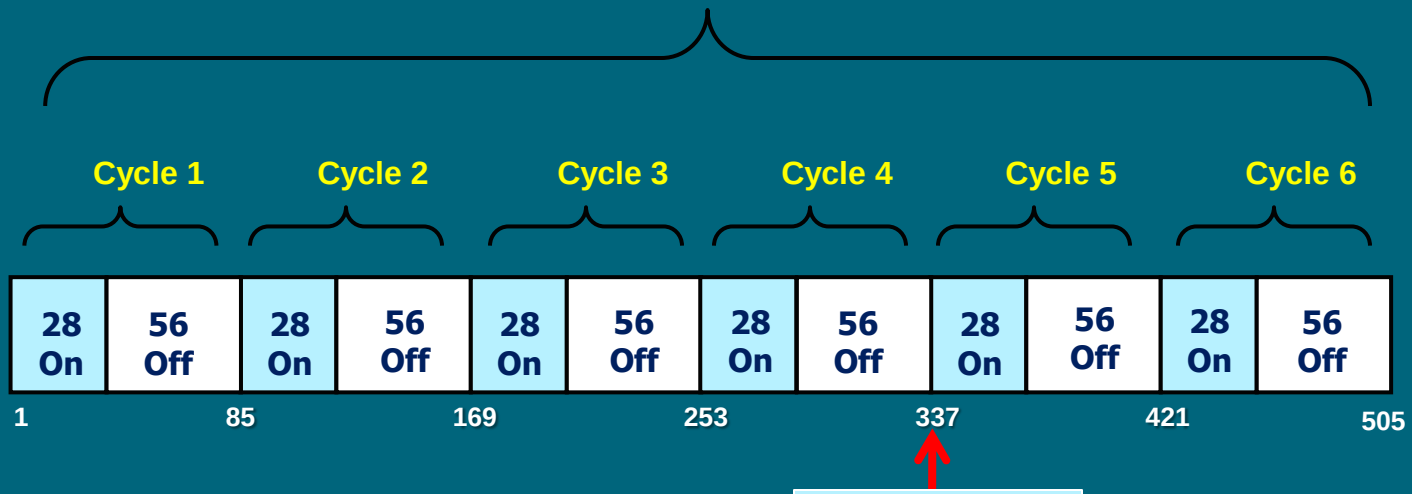
TR02-105: Main Study
Subjects Randomized to 280 mg/560 mg Arikace™ or volume matched Placebo

Extension Study
Initiated 11 months later

28 days Run-in Period
Screening Day -14

Enrolled
N= 49

560 mg Arikace™ Once Daily for 28 Days by eFlow® *
Followed by 56 Days Off-Treatment for 6 Cycles



Interim Data

Key Inclusion Criteria

- $FEV_1 \geq 40\%$
- 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: April 2010

Number of Cycles	Number Of Patients Completed Cycle (N=49) *
Cycle 1	48
Cycle 2	46
Cycle 3	45
Cycle 4	32

* Subjects enrolled in the study over 5-10 months.
Subjects currently continuing in Cycles 4 through 6

Patient Characteristics

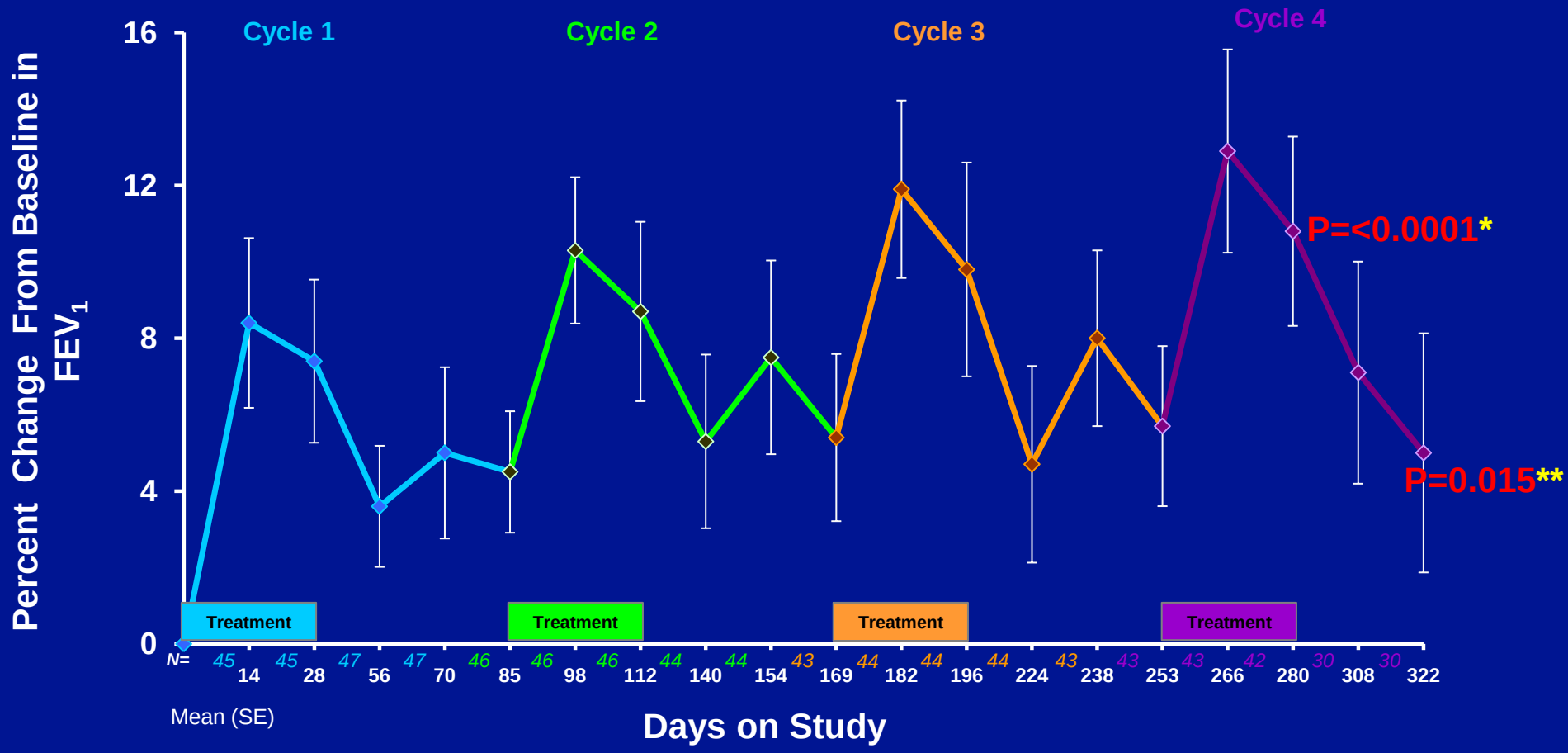
		All Patients (N=49)
Age (yrs)	Mean (SD)	17.4 (6.2)
Gender	Male	20 (40.8%)
	Female	29 (59.2%)
FEV_1 (L)	Mean (SD)	1.871 (0.772)
FEV_1 (% Pred)	Mean (SD)	59.2 (19.3)
FVC (L)	Mean (SD)	2.693 (1.109)
FEF 25-75% (L/sec)	Mean (SD)	1.336 (0.766)
BMI (kg/m^2)	Mean (SD)	18.425 (3.114)

Arikace™ - Frequency of Adverse Events ≥8% over 12 month Period

	Number of Patients (N=49)
Cystic fibrosis pulmonary exacerbation	20 (40.8%)
Cough	10 (20.4%)
Rhinopharyngitis	9 (18.4%)
Haemoptysis	7 (14.3%)
Sputum increased	7 (14.3%)
Dysphonia	6 (12.2%)
Fever	5 (10.2%)
Influenza	5 (10.2%)
Sore throat	5 (10.2%)
Acute pharyngitis	4 (8.2%)
Acute rhinitis	4 (8.2%)
Throat irritation	4 (8.2%)

Arikace™ - Relative Change in FEV_1 Over 12 Months

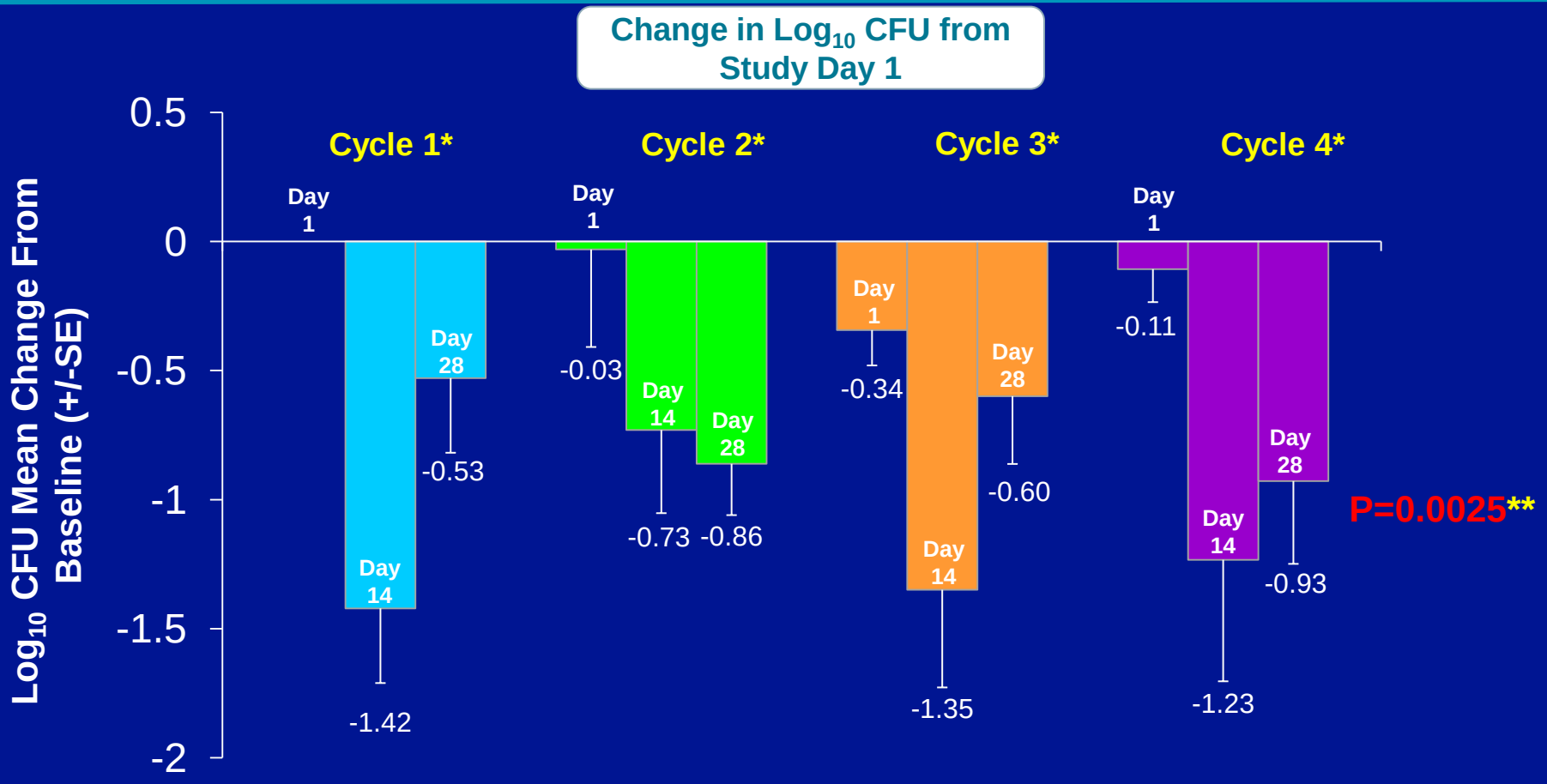
Patients Receiving
560 mg Arikace™ Once Daily for 28 Days
and Off-Treatment for 56 Days



* Significance at end of treatment over 4 cycles

** Significance 56 days after treatment over 4 cycles

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™ - CF Open-Label Multi-Cycle Study Summary Observations: Safety

- Overall, Arikace™ 560 mg administered once daily for 28 day periods, for four cycles was well tolerated
- No unexpected AEs were observed with longer term dosing
- DSMB 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-Label Multi-Cycle Study Summary Observations: Efficacy

- Data show statistically significant reduction in *Pseudomonas 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_{10} CFU over time is -0.8 (95% CI -1.3, -0.39) 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_1 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_1 is 4.7% (95% CI +1.0%, +8.5%) p=0.015

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_1 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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