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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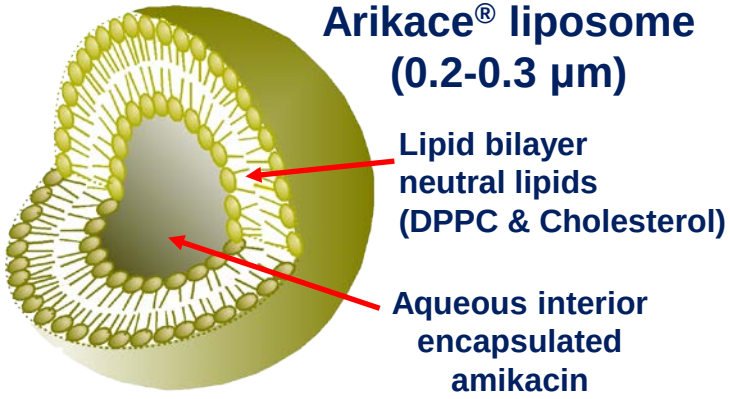
Arikace® - Non-Clinical Summary

- Arikace® is a liposomal 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
  - High lung Cmax, AUC, and t½ ➡ Improved AUC: MIC ratio
  - Penetration of drug into biofilm
  - Potent *Pseudomonas* killing, including resistant isolates
  - Virulence factors secreted by *Pseudomonas* facilitate further release of amikacin from Arikace®
  - Uniform drug distribution in rat lungs, including alveolar macrophages
  - Normal BAL macrophage activity
  - Toxicology in dogs and rats (3-6 months) supports long-term clinical studies

Arikace® - CF Open-Label Multi-Cycle Study: TR02-105 Extension

- Upon review of data from the Phase 2 randomized study of Arikace® versus placebo, DSMB recommended initiation of Multi-Cycle, Open-Label Extension Study of 560 mg of Arikace®
- Subjects randomized to Arikace® or Placebo in the main study were consented to participate in the open-label extension
- 49 eligible subjects were enrolled in the extension study

Arikace® - TR02-105 Extension: Open-Label Study Design

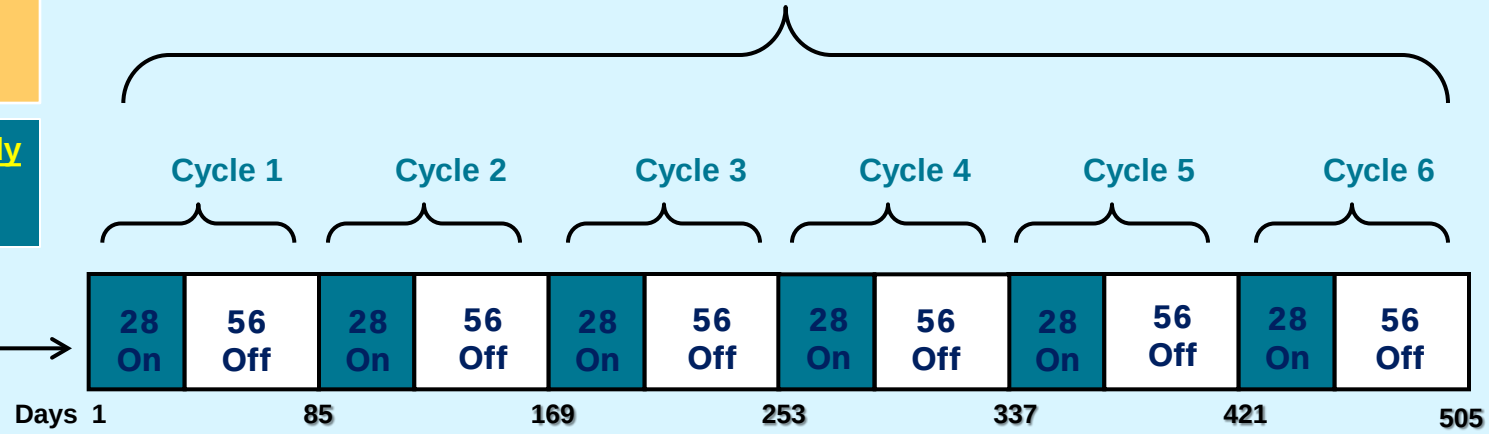
TR02-105: Main Study
Subjects Randomized to 280mg/560mg Arikace® or volume matched Placebo

Extension Study
Initiated 5-11 months later

28 days Run-in Period
Screening Day -14

Enrolled
N= 49

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



Key Inclusion Criteria

- FEV_1 ≥ 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)

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® - TR02-105 Extension: Overview of Adverse Events

	All Patients (N=49)
Number of Adverse Events	351
Patients with Adverse Events	48 (98.0%)
Number of Treatment-Related Adverse Events (Probably or Possibly Related)	33
Patients with Treatment-Related Adverse Events	15 (30.6%)
Deaths	0 (0.0%)
Patients with Serious Adverse Events	15 (30.6%)
Patients Interrupting Study Drug Due to Adverse Events	1 (2.0%)

Arikace® - Frequency of Adverse Events ≥8% Over 72 Weeks Period

Adverse Events by Descending Frequency

Preferred Term	All Patients (N=49)
Cystic Fibrosis lung	23 (46.9%)
Cough	14 (28.6%)
Nasopharyngitis	14 (28.6%)
Haemoptysis	11 (22.4%)
Productive cough	10 (20.4%)
Rhinitis	8 (16.3%)
Dysphonia	7 (14.3%)

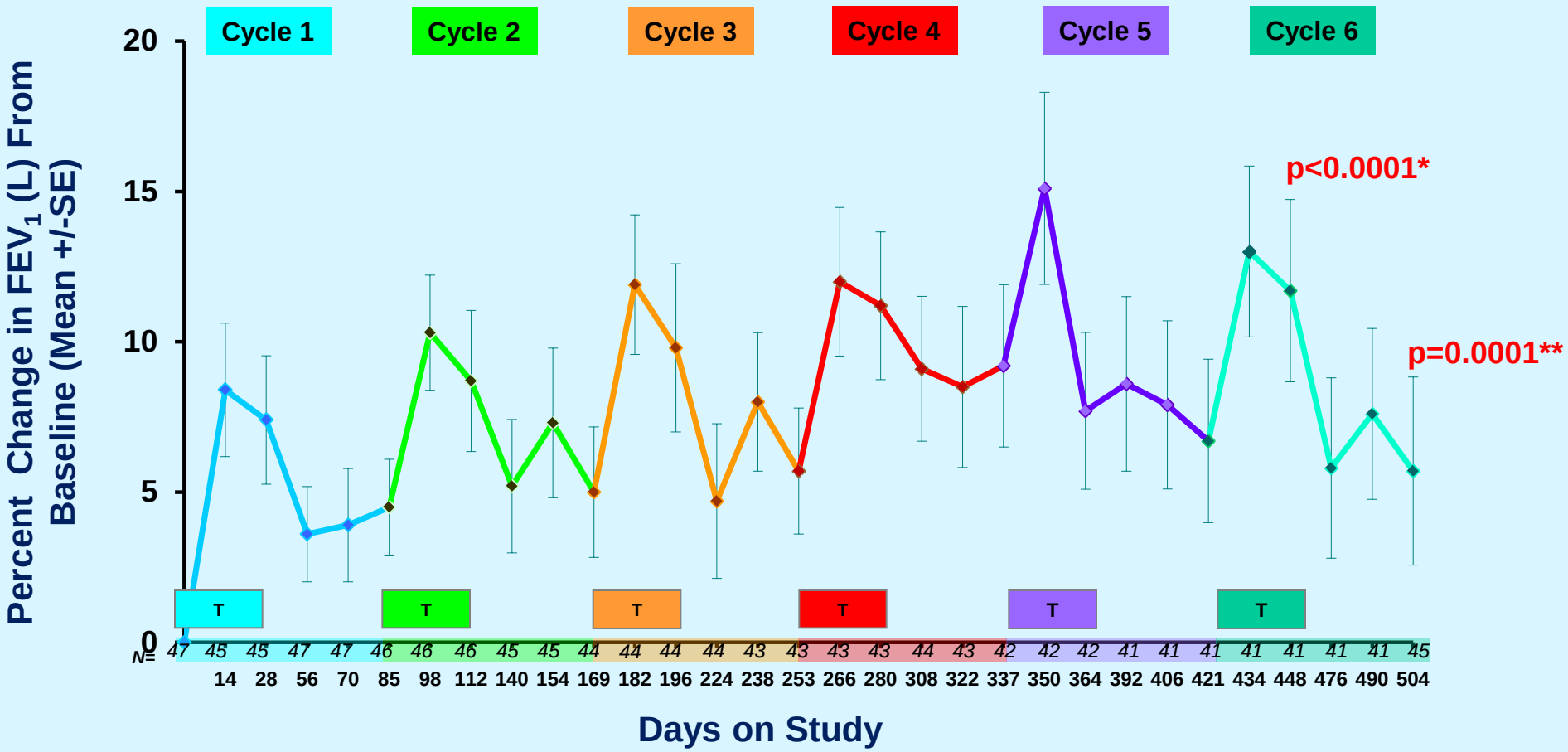
Arikace® - Frequency of Adverse Events ≥8% Over 72 Weeks Period

Adverse Events by Descending Frequency

Preferred Term	All Patients (N=49)
Influenza	6 (12.2%)
Oropharyngeal pain	5 (10.2%)
Pharyngitis	5 (10.2%)
Pyrexia	5 (10.2%)
Respiratory tract infection viral	5 (10.2%)
Abdominal pain	4 (8.2%)
Sinusitis	4 (8.2%)
Throat irritation	4 (8.2%)

Open Label Extension: Change in FEV_1 Over 72 Weeks Period

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

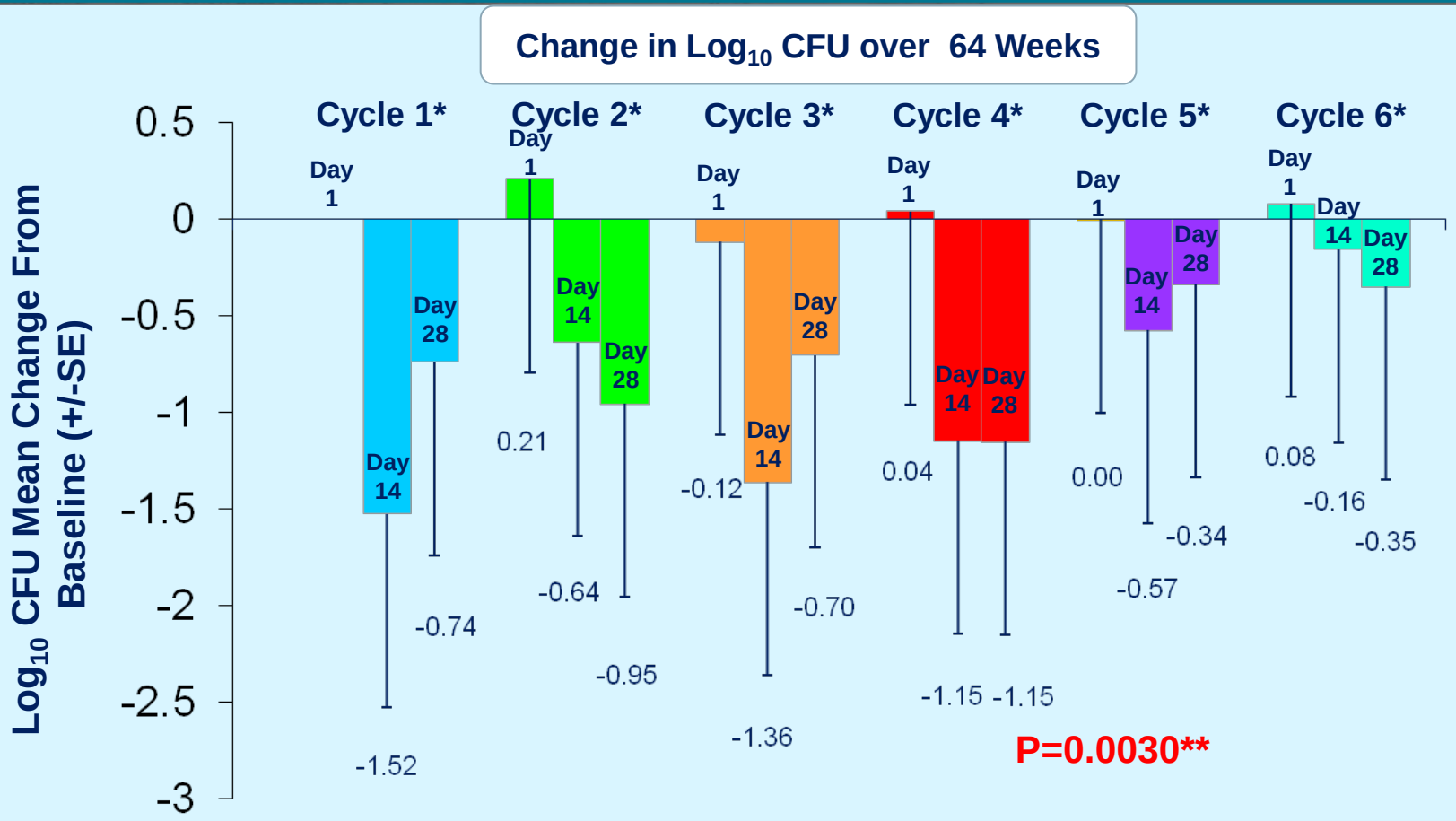


* Significance at end of treatment over 6 cycles

** Significance 56 days off-treatment over 6 cycles

T = Treatment Period

Arikace® - Change in *P. aeruginosa* Density from Baseline



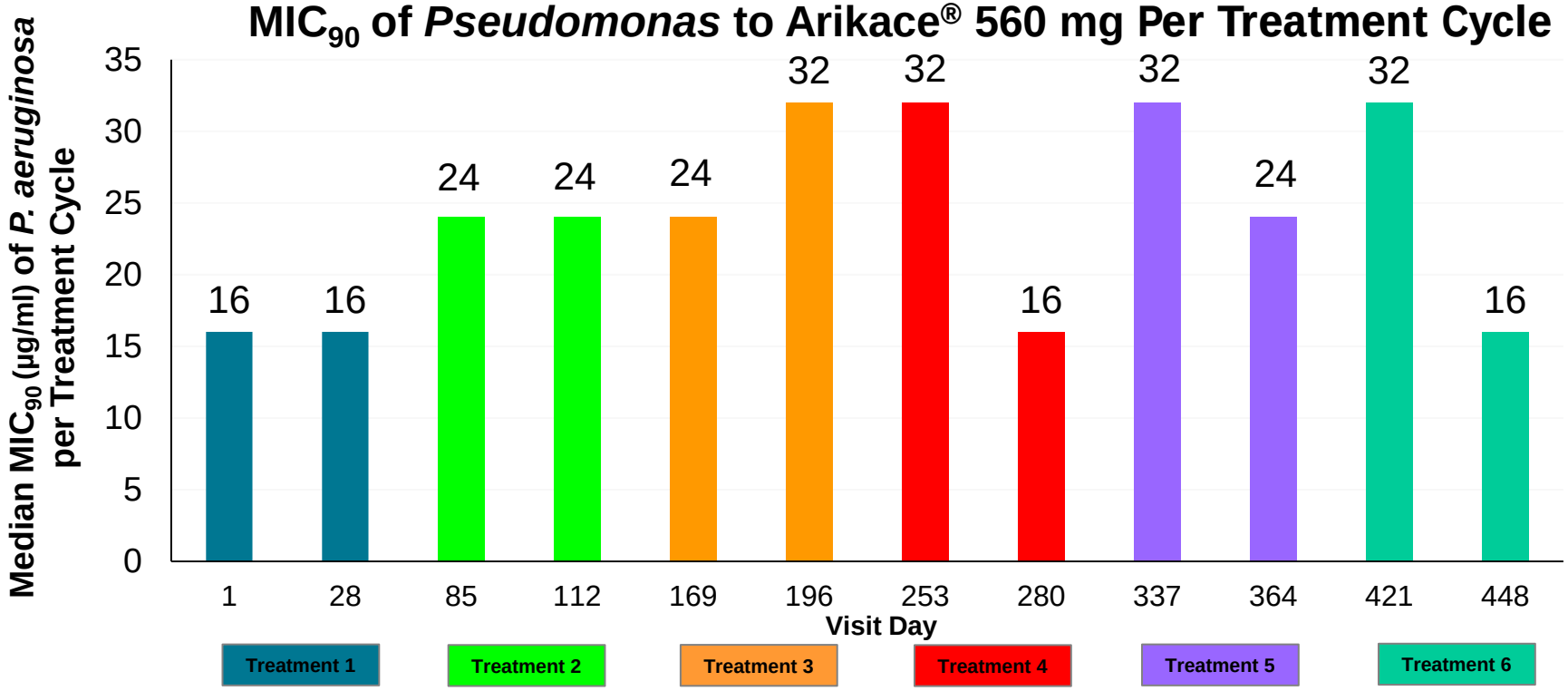
* Each cycle consists of 28 days of once daily treatment followed by 56 days off-treatment

* Day 1 values for Cycles 2, 3, 4, 5 and 6 are change from Baseline (Day 1 value of Cycle 1)

** Reduction in Log_{10} CFU is statistically significant during Cycles 1-6

Arikace® - TR02-105 Extension: Distribution of MIC_{90} (µg/ml) of *P. aeruginosa* to Arikace®

An open label extension study of Arikace® demonstrated no significant change in MIC_{90} over six cycles of therapy.



	Day 1/ Baseline	Day 28	Day 85	Day 112	Day 169	Day 196	Day 253	Day 280	Day 337	Day 364	Day 421	Day 448
# subjects contributing data	***41***	***41***	***40***	***40***	***32***	***32***	***33***	***33***	***36***	***36***	***33***	***33***

Arikace® - CF Open-Label Multi-Cycle Study Summary Observations: Safety

- Overall, Arikace® 560 mg administered once daily for 28 day periods, for six cycles was well tolerated
- No unexpected AEs were observed with longer term dosing
- In summary, nebulized Arikace® delivered using eFlow® is well-tolerated for 6 cycles 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 from baseline in *Pseudomonas aeruginosa* density, including mucoid strains. This is sustained over the treatment period of 6 cycles, with each cycle including 56 days off-treatment. The estimated change from baseline in Log_{10} CFU over time was -0.6 log (95% CI, -0.2 to -0.9 log) p=0.0030
- Inhalation of 560 mg of Arikace® for 6 cycles has demonstrated statistically significant sustained improvement in lung function. The estimated relative change in FEV_1 from baseline to end of treatment (Day 28) during Cycles 1-6 was 7.9% (95% CI +4.3, +11.7%) p<0.0001
- This effect was also sustained at the end of 56 days off-treatment during each of Cycles 1-6. The estimated relative change in FEV_1 was 5.7% (95% CI +3.0, +8.5%) p=0.0001

Arikace® - Summary and Conclusions

- Arikace® administered once daily using eFlow® has been well-tolerated for 6 cycles
- Data show statistically significant reduction from baseline in *P. aeruginosa* density, including mucoid strains. This effect was sustained over 6 cycles, including the 56 day interval between dosing ($p=0.0030$)
- No significant shift in MICs was observed
- Inhalation of 560 mg of Arikace® once daily for 28 days demonstrated statistically significant improvement in lung function over baseline that was sustained over a 72 week period.
  A mean increase in FEV_1(%) of 11.7% was observed at the end of treatment of 6 cycles ($p<0.0001$)
- Launch of Phase 3 studies is underway

Arikace® - Phase 2 Program: Acknowledgements

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