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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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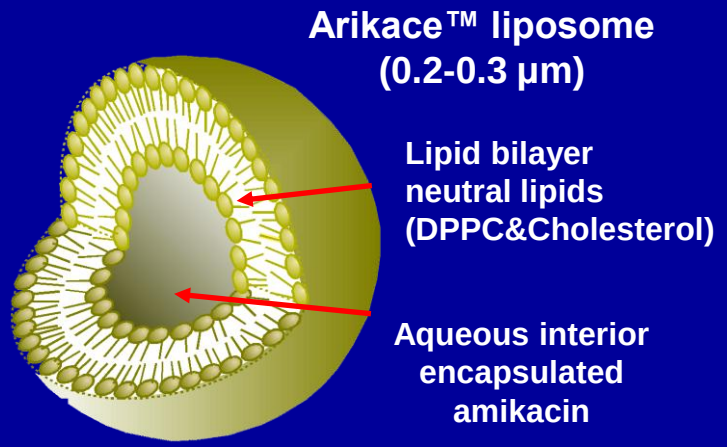
Poster #243

TRANSAVE
Inhalation Biotherapeutics

Cystic Fibrosis Foundation
| Adding *tomorrows* every day.

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

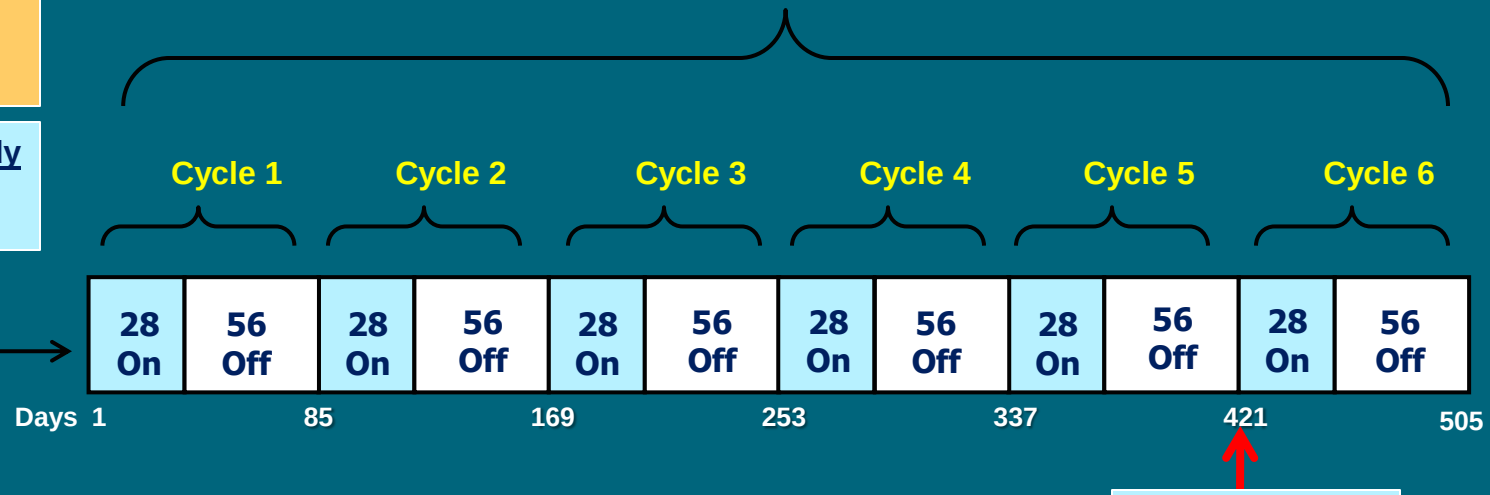
TR02-105: Main Study
Subjects Randomized to 280mg/560mg Arikace™ or volume matched Placebo

Extension Study
Initiated 11 months later

28 days Run-in Period
Screening Day -14

Enrolled
N= 49

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



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- September 2010

Number of Cycles	Number Of Patients Completed Cycle (N=49) *
Cycle 1	48
Cycle 2	46
Cycle 3	45
Cycle 4	44
Cycle 5	43

- Subjects enrolled in the study over 5-10 months. Subjects currently continuing in Cycles 5 through 6
- 4/49 (8.0%) discontinued study

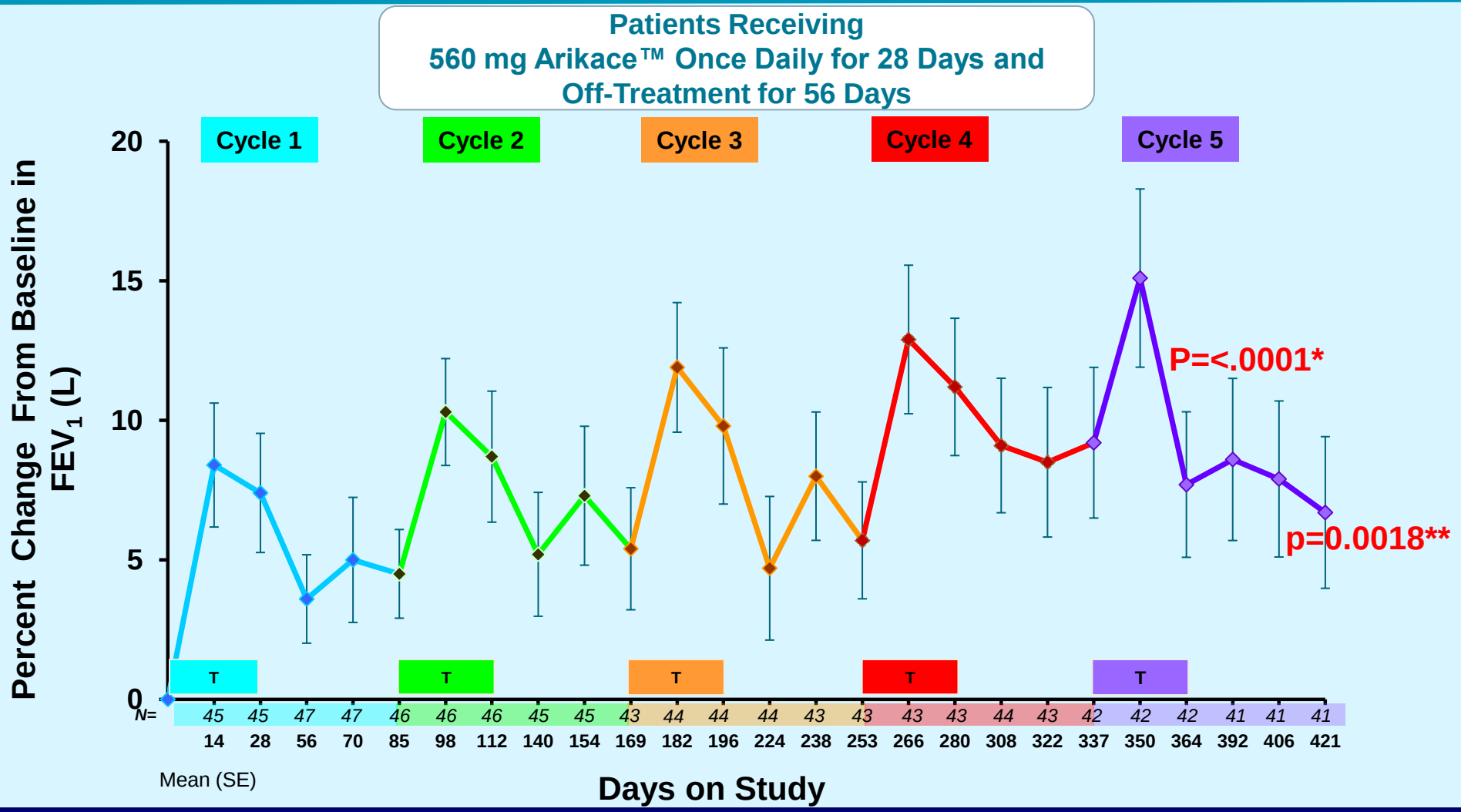
Patient Characteristics

		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™ - Safety Summary

- Overall, Arikace™ 560 mg administered once daily for 28 day periods, for five cycles was well tolerated
- No unexpected AEs were observed with longer term dosing
- There were no appreciable changes in acute tolerability
- DSMB review at 12 months recommended continuation of study without modification
- In summary, nebulized Arikace™ delivered using eFlow® is well-tolerated for 5 cycles, and demonstrates adverse effects that are consistent with those expected in a population of CF patients receiving inhalation medicines

Open Label Extension: Change in FEV_1 Over 5 Cycles

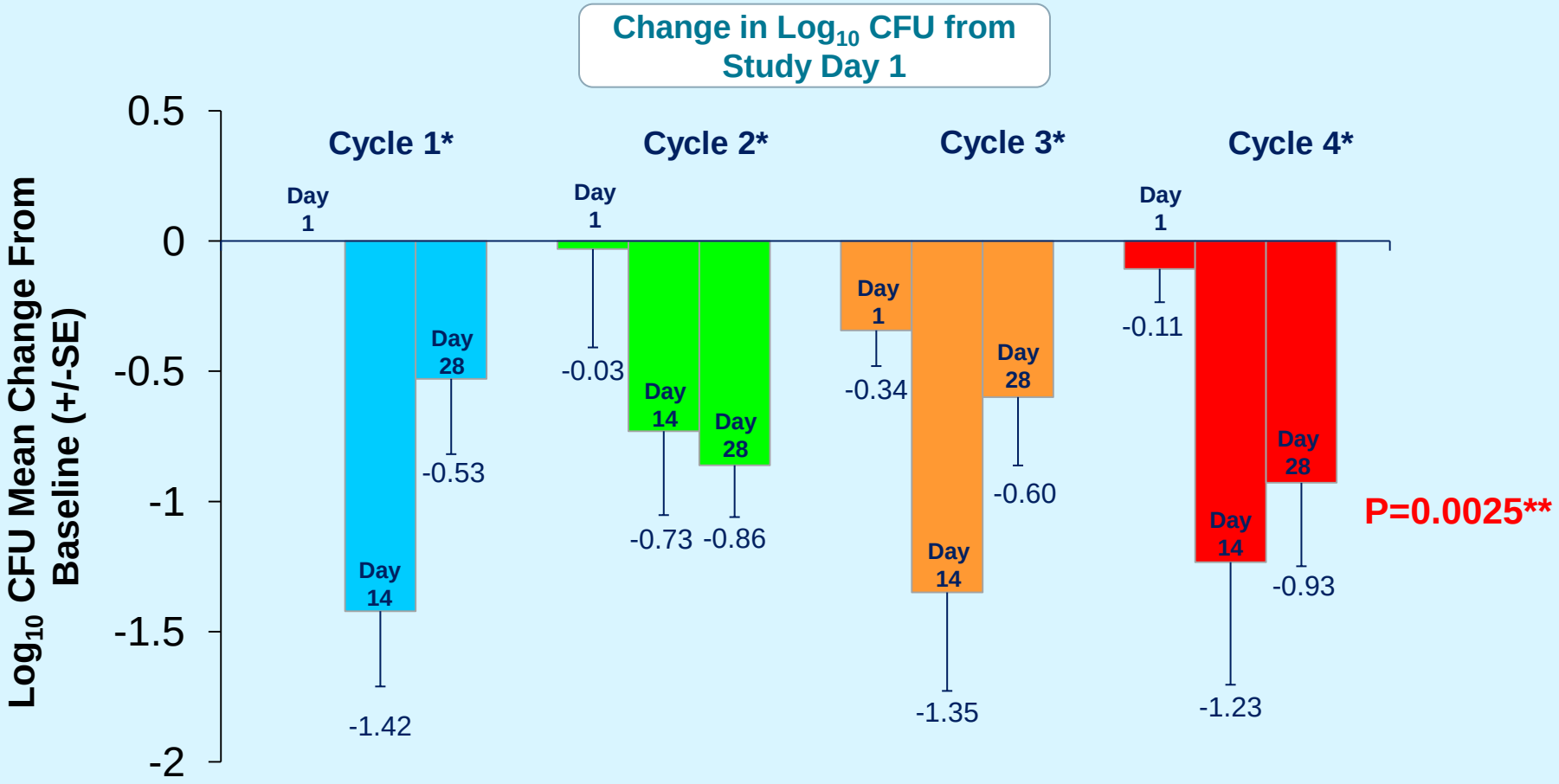


* Significance at end of treatment over 5 cycles

** Significance 56 days off-treatment over 5 cycles

T = Treatment Period

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



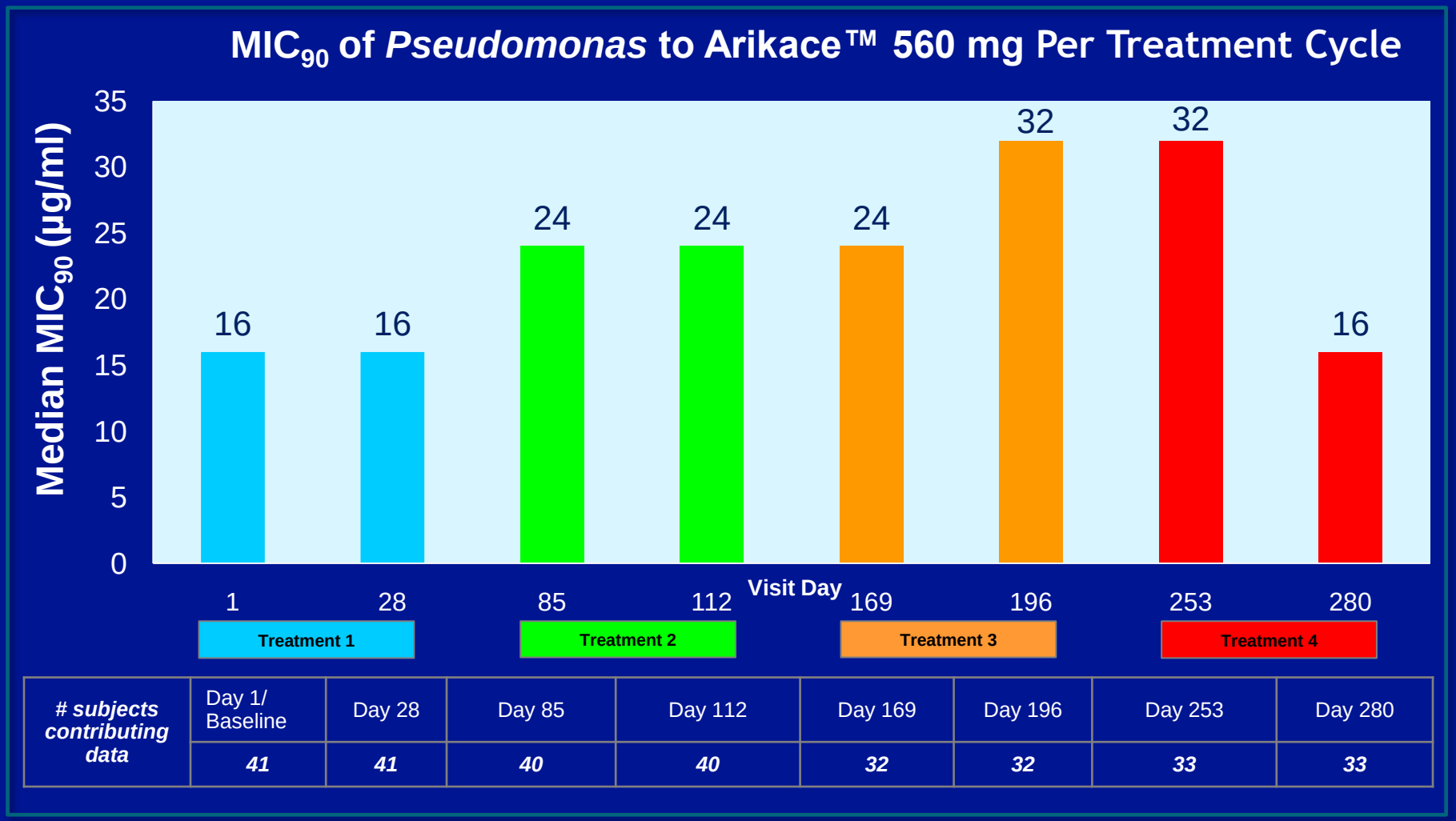
* Each cycle consists of 28 days of once daily treatment followed by 56 days off-treatment

* Day 1 values for Cycles 2, 3, 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™ - TR02-105 Extension - Distribution of MIC_{90} (µg/ml) of *P. aeruginosa* to Arikace™

No significant change observed in MIC_{90} over multiple cycles of therapy



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

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 5 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 5 cycles has demonstrated statistically significant sustained improvement in lung function. The estimated relative change in FEV_1 over time, from baseline to end of treatment (Day 28) during Cycles 1-5 is 8.4% (95% CI +4.7%, +12.0%) p=<0.0001
- This effect is also sustained at the end of off-treatment period (56 days) during Cycles 1-5. The estimated relative change in FEV_1 over time is 6.5% (95% CI +2.5%, +10.4%) p=0.0018

Arikace™ - Summary and Conclusions

- Arikace™ administered once daily using eFlow® has been well-tolerated for 5 cycles
- Data show statistically significant reduction in *P. aeruginosa* density including mucoid strains, that has been sustained over a 12 month 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 5 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 5 cycles over a 14 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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