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Full analyses of data from two phase II blinded and placebo-controlled studies of nebulized liposomal amikacin for inhalation (Arikace™) in the treatment of cystic fibrosis patients with chronic *Pseudomonas aeruginosa* lung infection

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Poster #227

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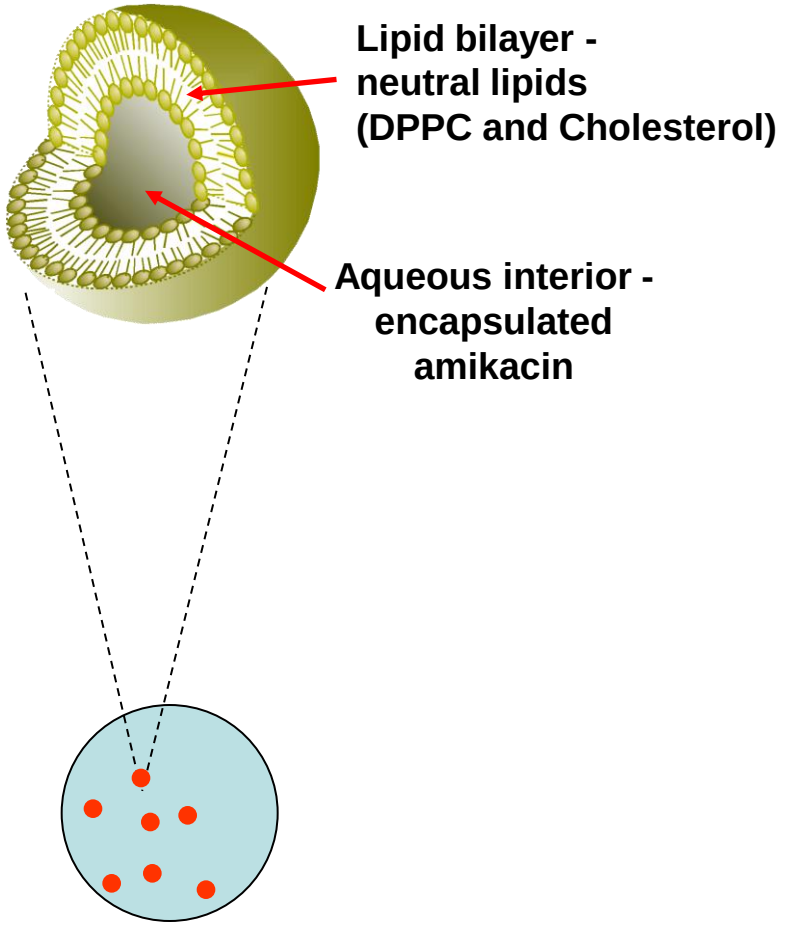
| Adding *tomorrows* every day.

Arikace™ (Preclinical Summary)

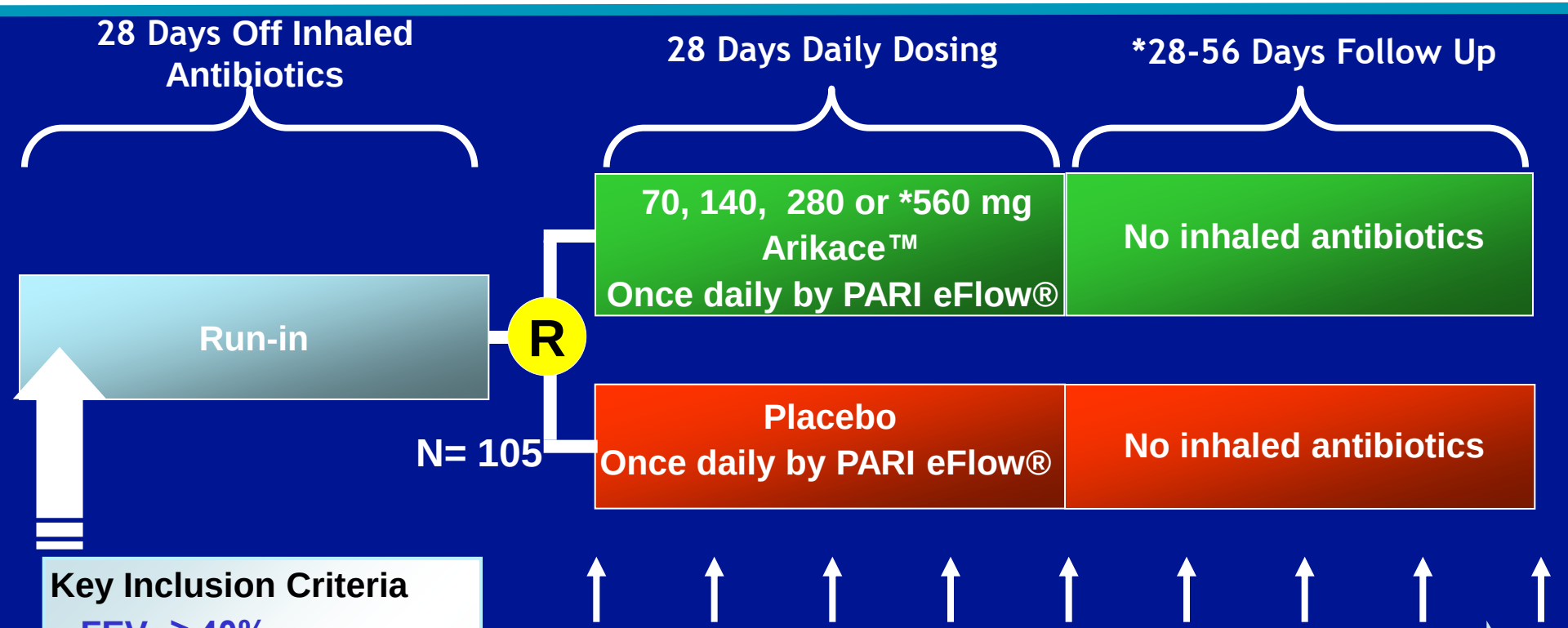
Arikace™ liposome (0.2-0.3 µm)



~3 µm nebulized droplet (>300 liposomes/drop)

- Charge neutral highly biocompatible liposomes packed with amikacin
- Potent *PsA* killing, including resistant isolates
- High lung Cmax, T½, and AUC
- Low sputum binding
- Penetration of drug into biofilms
- Amikacin release by *PsA* byproducts
- Retained BAL macrophage killing
- Toxicology in dogs and rats (6 mos) supports long-term clinical studies

Phase 2 Arikace™ Studies TR02-105 – TR02-106



Key Inclusion Criteria

- $FEV_1 \geq 40\%$
- Age ≥ 6 years
- Chronic Pa Infection
- 28 Days Off Inhalation Antibiotics
- Continued Azithromycin, DNAse, Hypertonic saline, Bronchodilators

Weekly Safety Evaluation
Assessments of PFT, CFU, Exacerbations, Time to Rescue Antibiotics, Hospitalizations, CFSD, CFQ-R and PK

***DSMB and FDA Evaluation of Interim Safety Data from 106; and Safety and Efficacy data from 105: Amended Study 106 to add 560 mg Cohort; Pediatric patients; and 56 days off treatment for durability of response**

Arikace™ Phase 2 Study Features: Europe and US

Study	Sites	Subjects	Doses	Duration	Outcome
TR02-105 (Europe)	15	N =66 Age: 16.5 yr (6.0) FEV1: 65.7% (20.2)	560mg 280mg placebo	28 days on 28 day f/u	Safety PK/PD efficacy
TR02-106 (US)	18	N=19 Age: 30.5 yr (8.3) FEV1: 65.3% (19.0)	140mg 70mg placebo	28 days on 28 day f/u	Safety PK/PD efficacy
TR02-106 (US)	18	N=22 Age: 29.4 yr (11.9) FEV1: 67.4% (15.2)	560mg placebo	28 days on 56 day f/u	Safety PK/PD efficacy

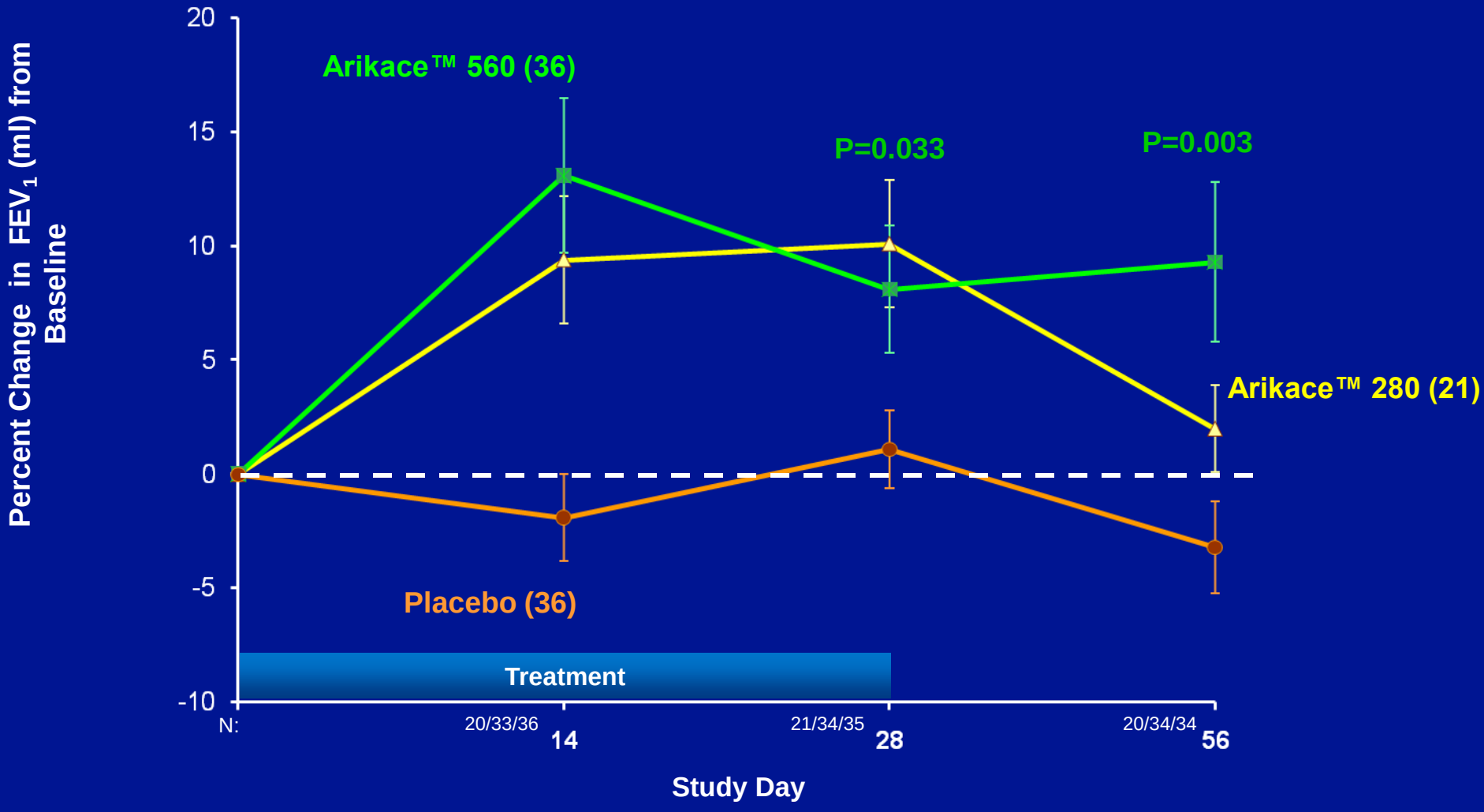
Summary: *33* *105*

- **Mucoid *PsA***: 85% (TR02-105); 89% (TR02-106)
- **TOBI® use**: 19% (TR02-105); 35% (TR02-06)

Safety and Tolerability

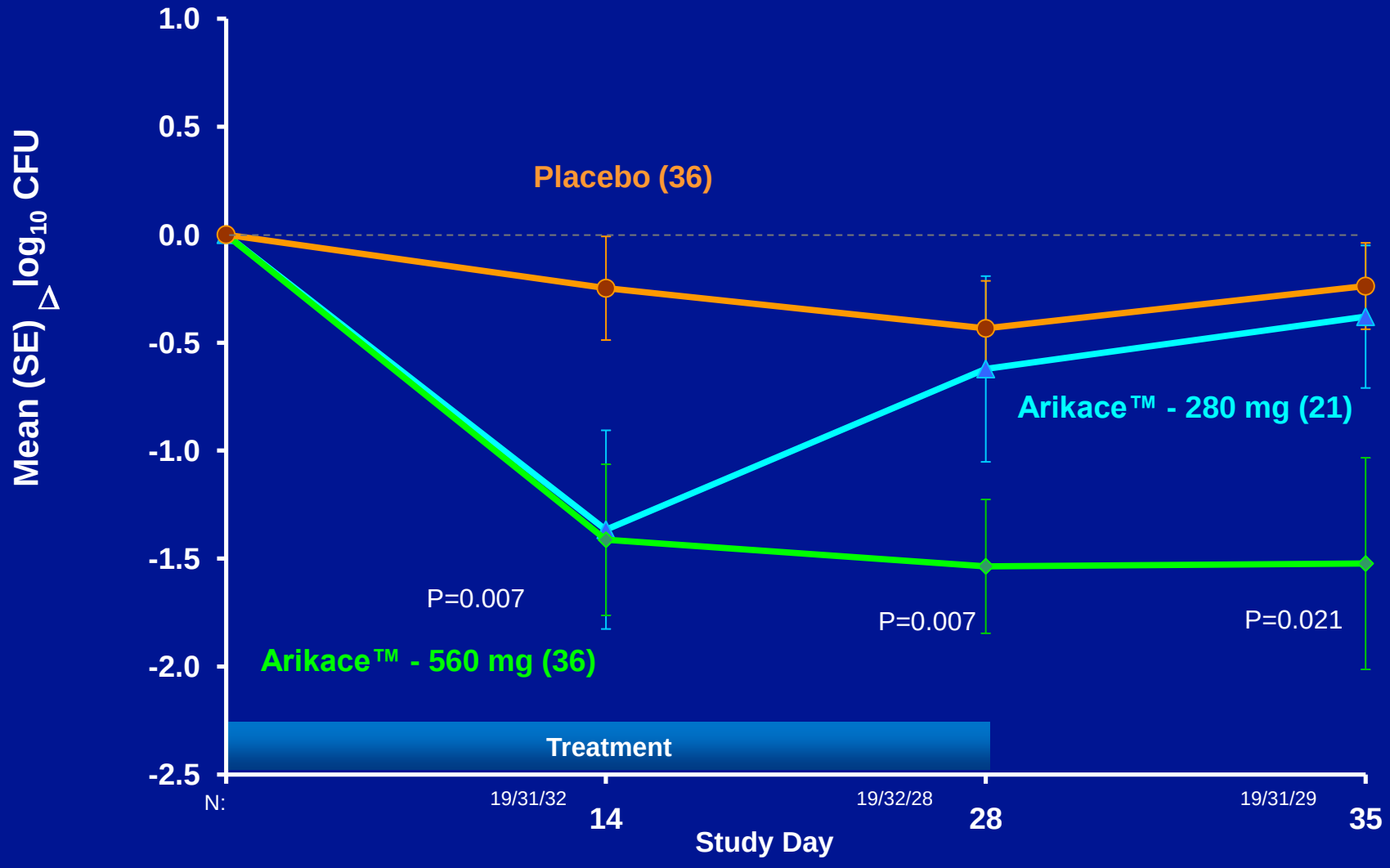
- AEs were consistent with underlying CF disease although a trend towards mild to moderate dysphonia (8%) in the higher dose Arikace™ group
- Acute Tolerability: Percent Patients with >/= 15% decline in FEV_1
  - Arikace™: 2.8%
  - Placebo: 11.1%
- Discontinuations
  - Arikace™: four subjects (70 mg, 560 mg) – respiratory, laryngitis, tinnitis, dysphonia, (one of each)
  - One in placebo group (respiratory)
- Distribution of adverse events similar across Arikace™ and placebo groups
  - Ear/labyrinth disorder
  - Audiology
- AEs (relatedness)
  - Arikace™ (560 mg, n=36): 22% of subjects-possibly related
  - Placebo (n=36): 17% of subjects-possibly/probably related
- CTC grade 3: AEs Not related (pyrexia, laryngitis, tooth abscess, low wbc, arthralgia, exacerbation)
  - Arikace™ (560 mg, n=36): 11% of subjects
  - Placebo (n=36): 8%

Arikace™ TR02-105 and TR02-106: ΔFEV_1



Mean (SE)

Arikace™ TR02-105 and TR02-106: Δlog_{10} CFU

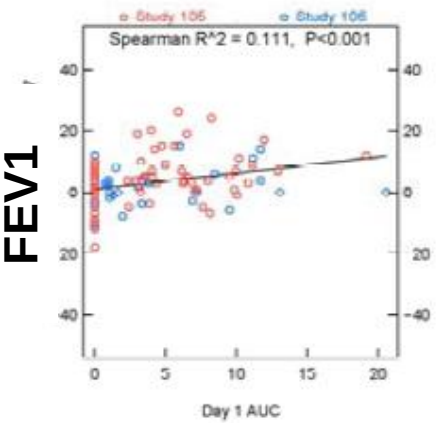


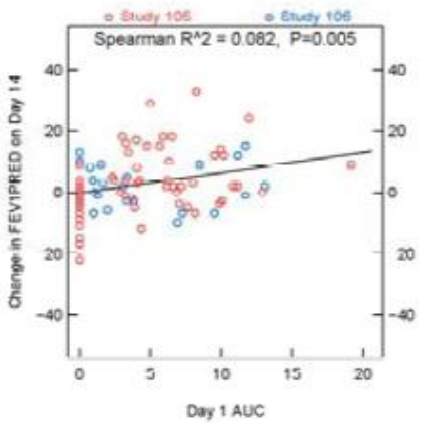
Mean (SE)

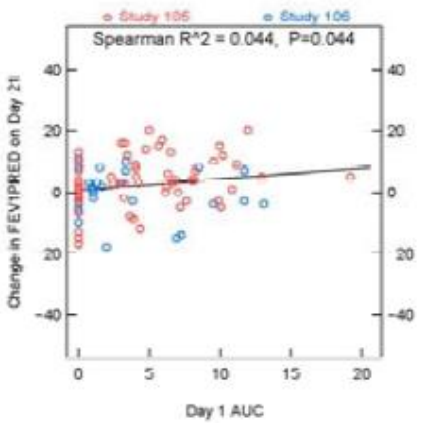
PK and PD Relationships: ΔFEV_1 and CFU vs AUC

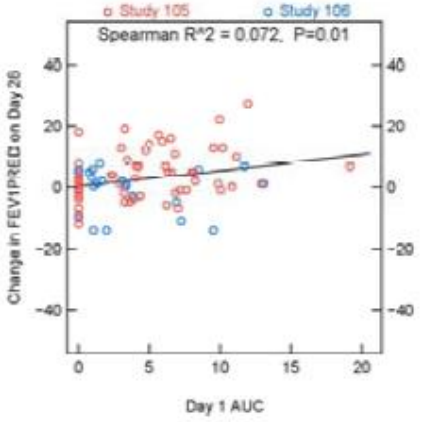
***p<0.05 each treatment day vs pre**

FEV1

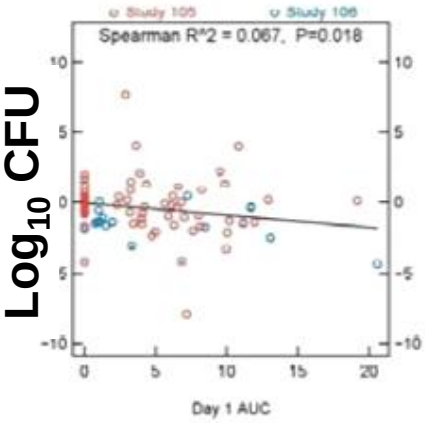


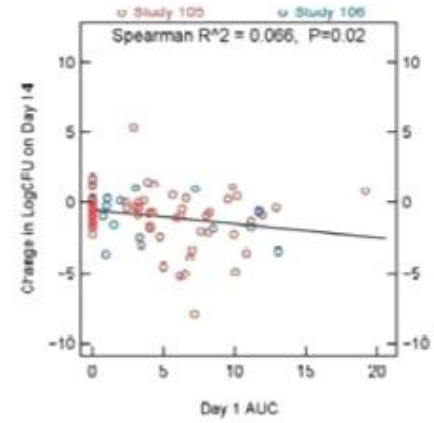


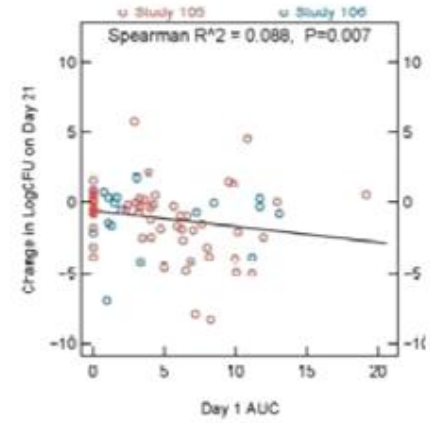


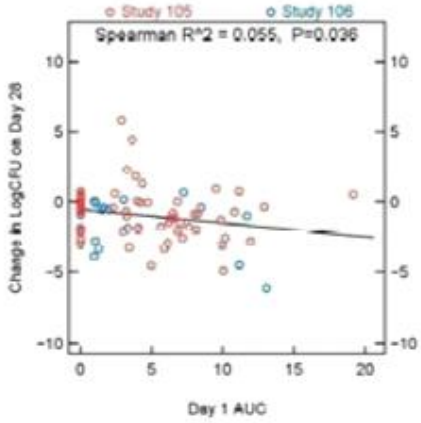


Log_{10} CFU



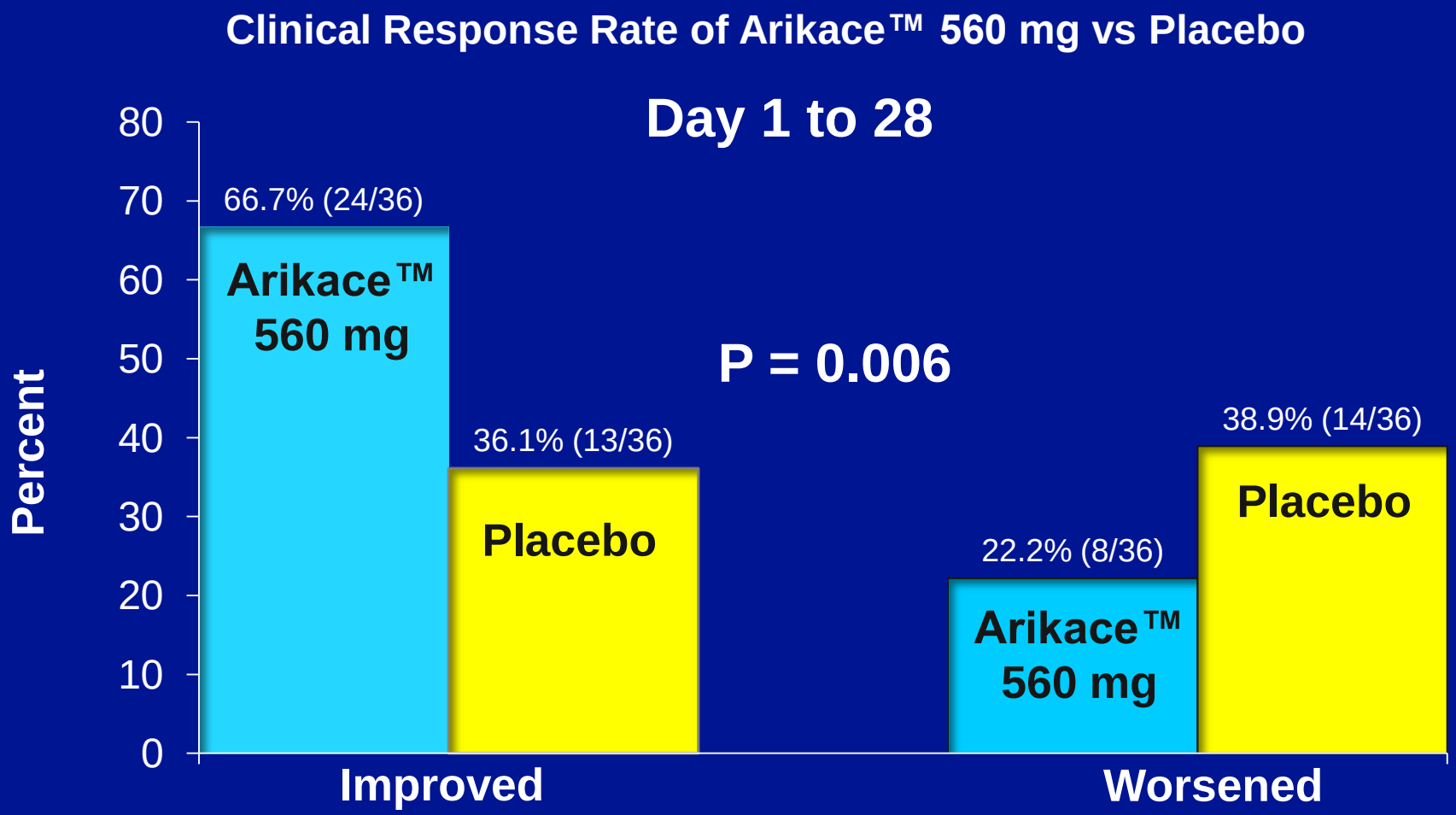






Day 7 | **Day 14** | **Day 21** | **Day 28**

Arikace™ - TR02-105 & 106
CFQR - Respiratory Scale - Clinical Response Rate



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

Arikace™- TR02-105 & 106
Correlation-FEV_1 & CFQ-R- Respiratory Scores

Correlation Between Change in CFQ-R Respiratory Domain Scores and FEV_1

	Day 15 N = 61	Day 28 N = 63	Day 42 N = 58
FEV_1 % Predicted Day 28	***r = 0.26** p = 0.0435	***r = 0.42** p = 0.0006	***r = 0.34** p = 0.0093

* Pearson Correlation Coefficients

Summary of Arikace™ Safety & PK/PD Data

- 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

- PK and PD data support mechanism of action *in vivo*
  - High sputum Cmax, and AUC with low serum concentrations
  - Prolonged t½: once daily dosing
  - Dose proportional and statistically significant correlation between AUC; increasing FEV_1 and decreasing CFU
  - No shift in MICs

Summary of Arikace™ Phase 2 Efficacy Data

- Patients receiving 560 mg of Arikace™ demonstrated improvement in lung function over baseline while patients on placebo declined over time. A treatment effect of relative change in FEV_1 of 12.5% was observed at one month after discontinuing study drug (p=0.003).
- Patients receiving Arikace™ demonstrated superior clinical benefit vs patients receiving placebo
  - Significant Improvement in patient reported respiratory symptoms (67% on Arikace™ improving versus 36% on placebo; p=0.006).
  - Statistically significant correlation between respiratory symptom score and FEV_1 at end of treatment (p=0.0006)
  - Statistically significant reduction in *Pseudomonas aeruginosa* density, including mucoid strains (~1.7 log reduction; p=0.007)
  - Patients receiving Arikace™ had prolonged time to exacerbation as compared to placebo (Arikace™ arm: Mean = 45.3 days vs Placebo arm: Mean = 31.4 days)

Global CF Program Acknowledgements

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