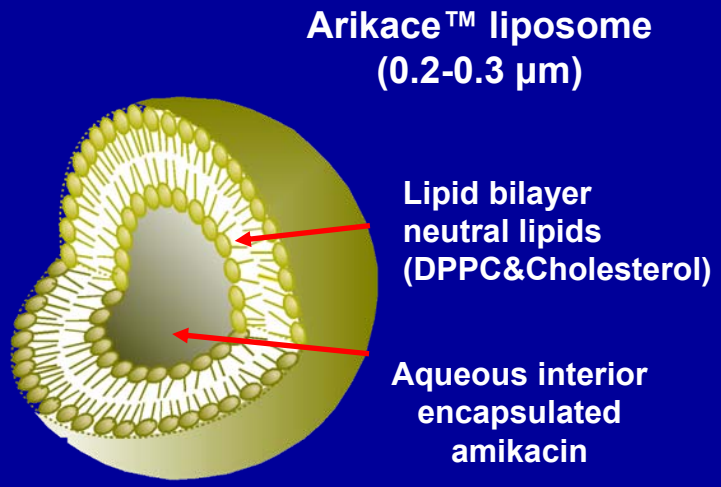
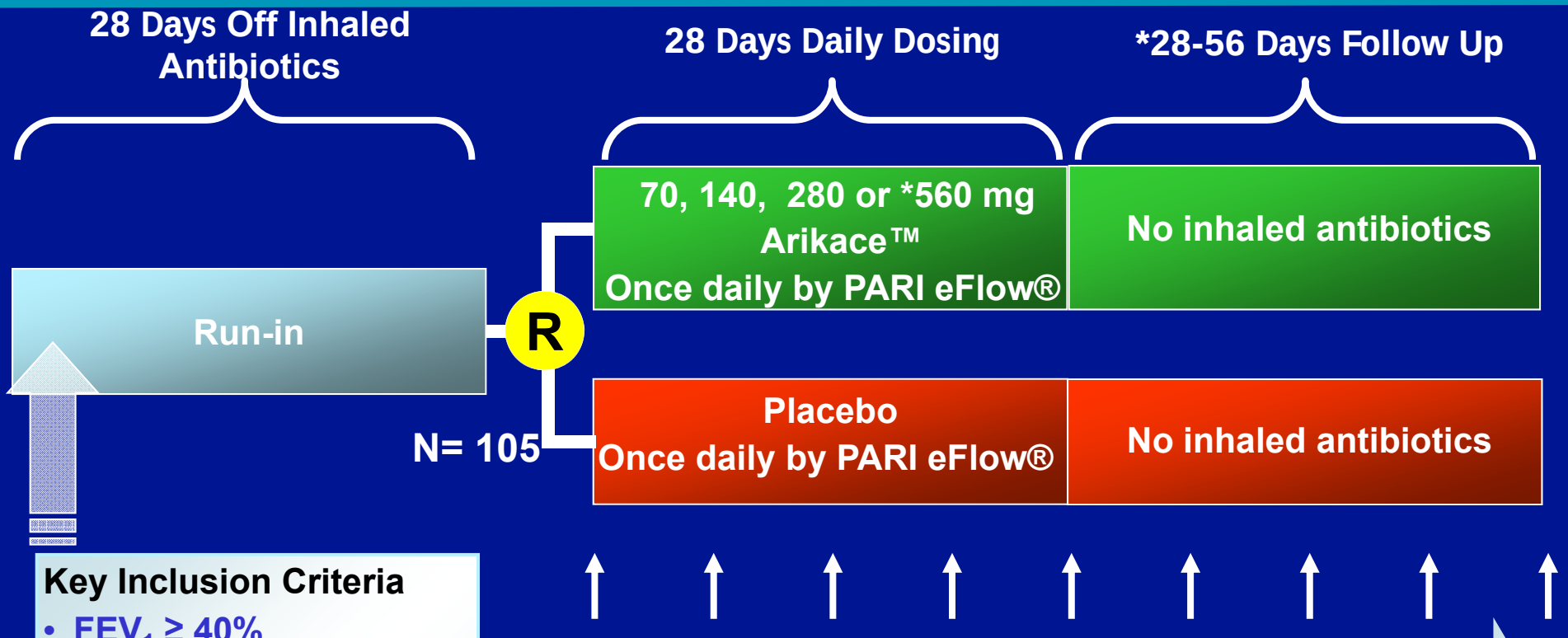
Arikace™-Liposomal Amikacin: Preclinical Summary

- 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

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

Baseline Characteristics- CF Phase II Studies

		US Study:TR02-106		Pooled Data from US & Europe TR02-105 & TR02-106	
		Arikace ™ 560 mg (N=15)	Placebo (N=7)	Arikace ™ 560 mg (N=36)	Pooled Placebo (N=36)
Age (yrs)	Mean (SD)	31.5 (14.5)	26.3 (6.7)	23.0 (12.6)	20.3 (7.7)
Gender	Male	10 (66.7%)	4 (57.1%)	21 (58.3%)	16 (44.4%)
	Female	5 (33.3%)	3 (42.9%)	15 (41.7%)	20 (55.6%)
FEV_1 (L)	Mean (SD)	2.409 (0.780)	2.347 (0.884)	2.190 (0.873)	2.133 (0.702)
FEV_1 (% Predicted)	Mean (SD)	68.800 (17.026)	66.143 (12.020)	66.389 (17.443)	67.861 (19.357)
BMI (kg/m^2)	Mean (SD)	22.452 (3.405)	22.817 (2.737)	20.379 (4.064)	19.900 (3.458)
Sweat Chloride (mmol/L)	Mean (SD)	105.769 (20.384)	108.800 (5.263)	104.719 (21.745)	110.367 (26.848)
Oxygen Saturation (SaO_2)	Mean (SD)	95.533 (2.295)	97.571 (1.902)	95.889 (2.011)	96.444 (2.197)

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

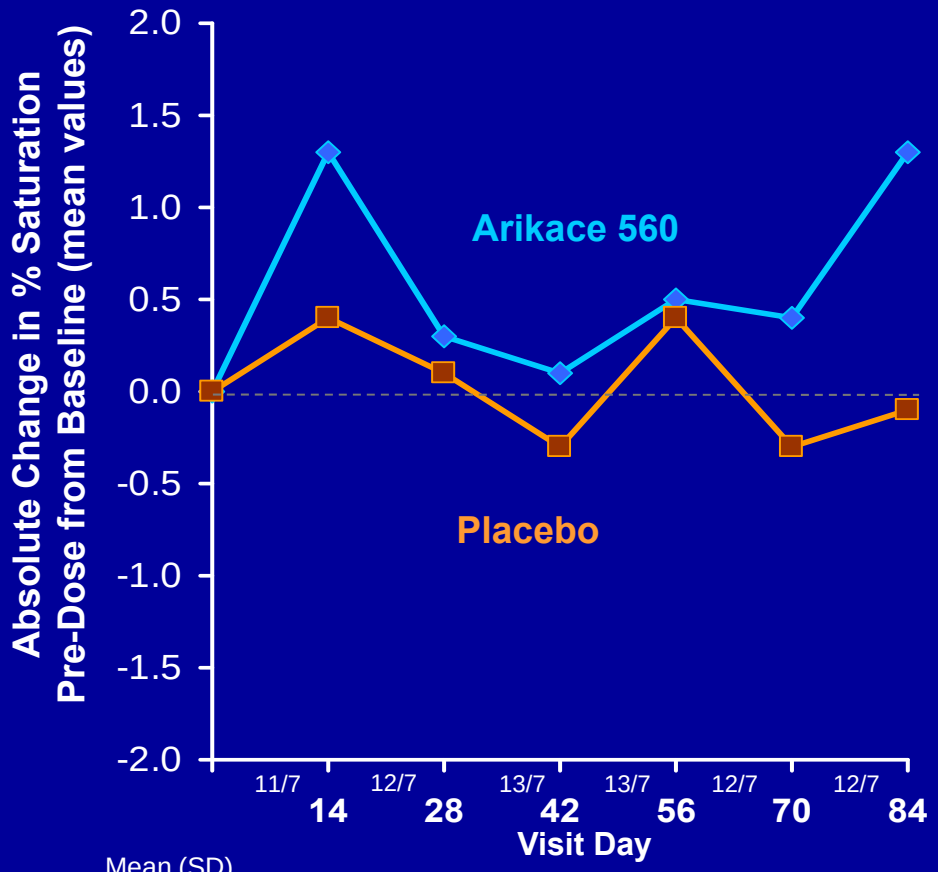
Demographics: European and US Phase 2 Studies

- **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
    - Prolonged 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%

Arikace ™ - TR02-106 – Safety and Tolerability

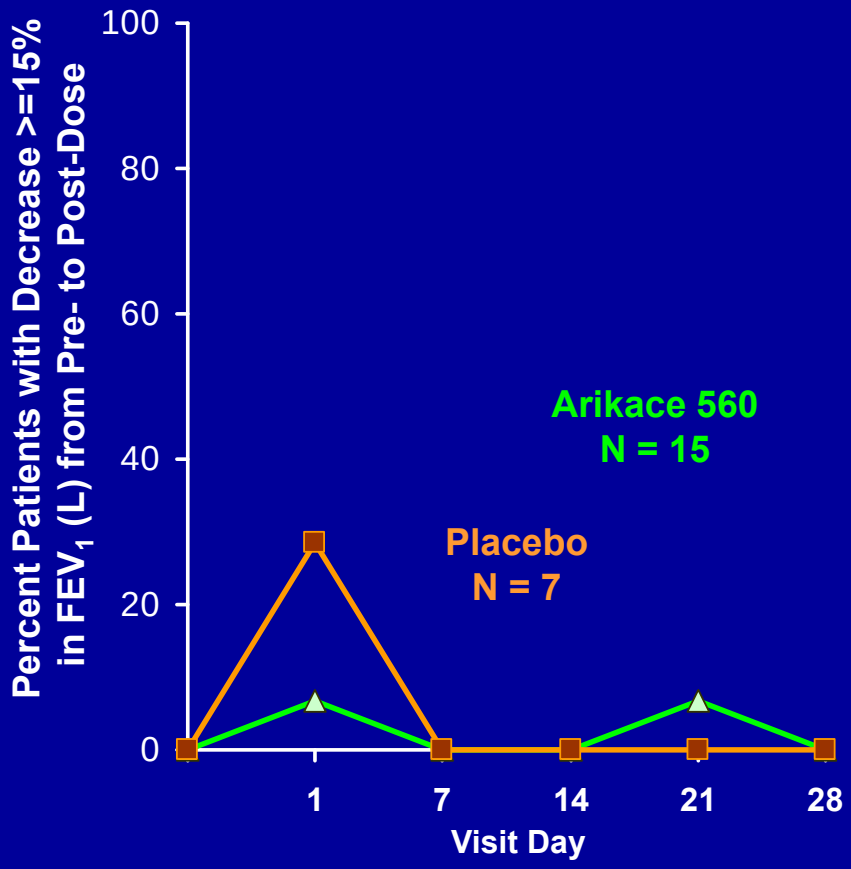
Cohort III – 560 mg



Mean (SD)

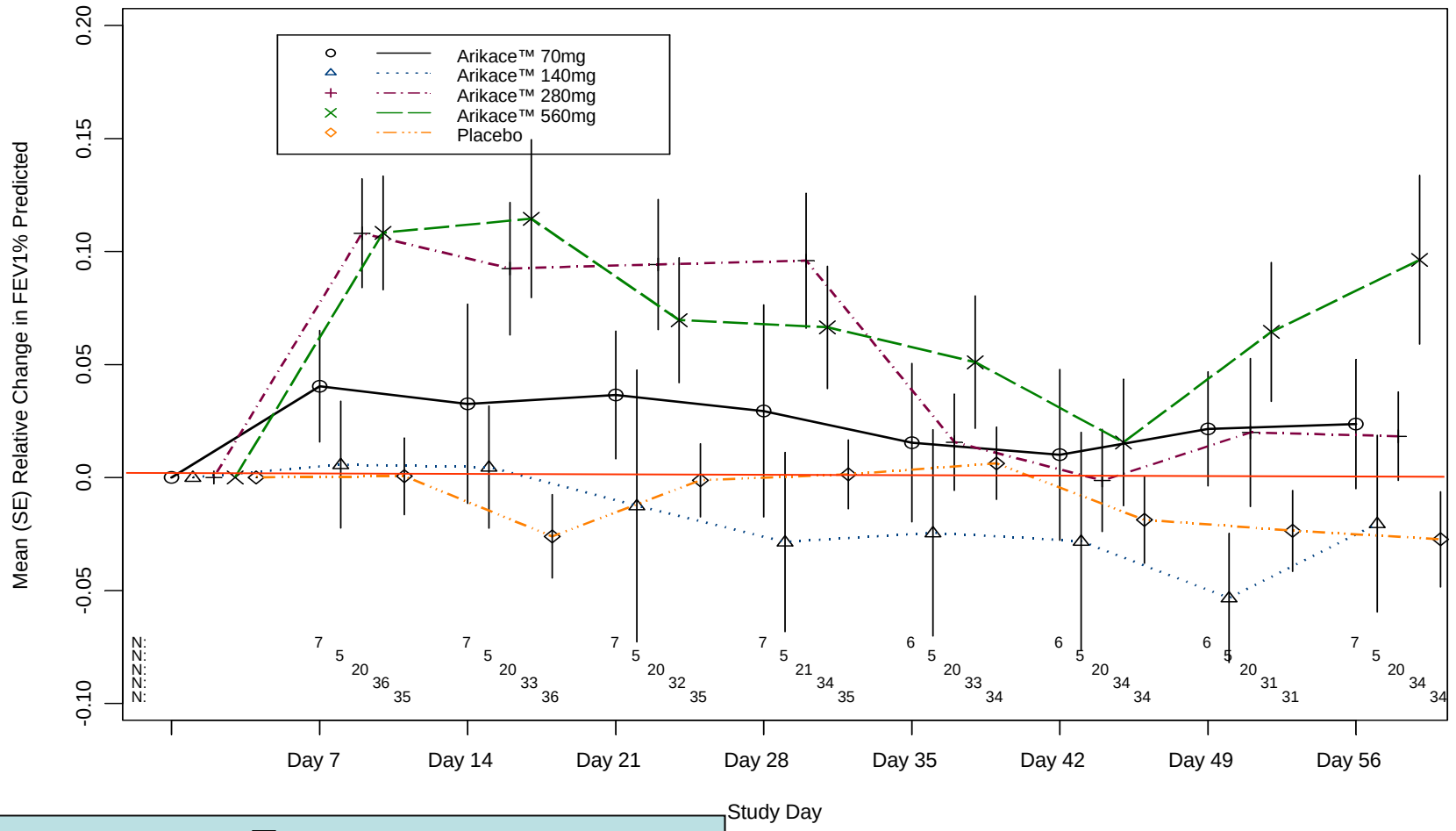
Arikace 560	1.3 (2.6)	0.3 (1.6)	0.1 (1.7)	0.5 (2.2)	0.4 (2.2)	1.3 (1.9)
Placebo	0.4 (1.0)	0.1 (1.1)	-0.3 (2.1)	0.4 (1.3)	-0.3 (1.6)	-0.1 (1.3)

Cohort III – 560 mg
Decrease of >=15% in FEV_1 (L)

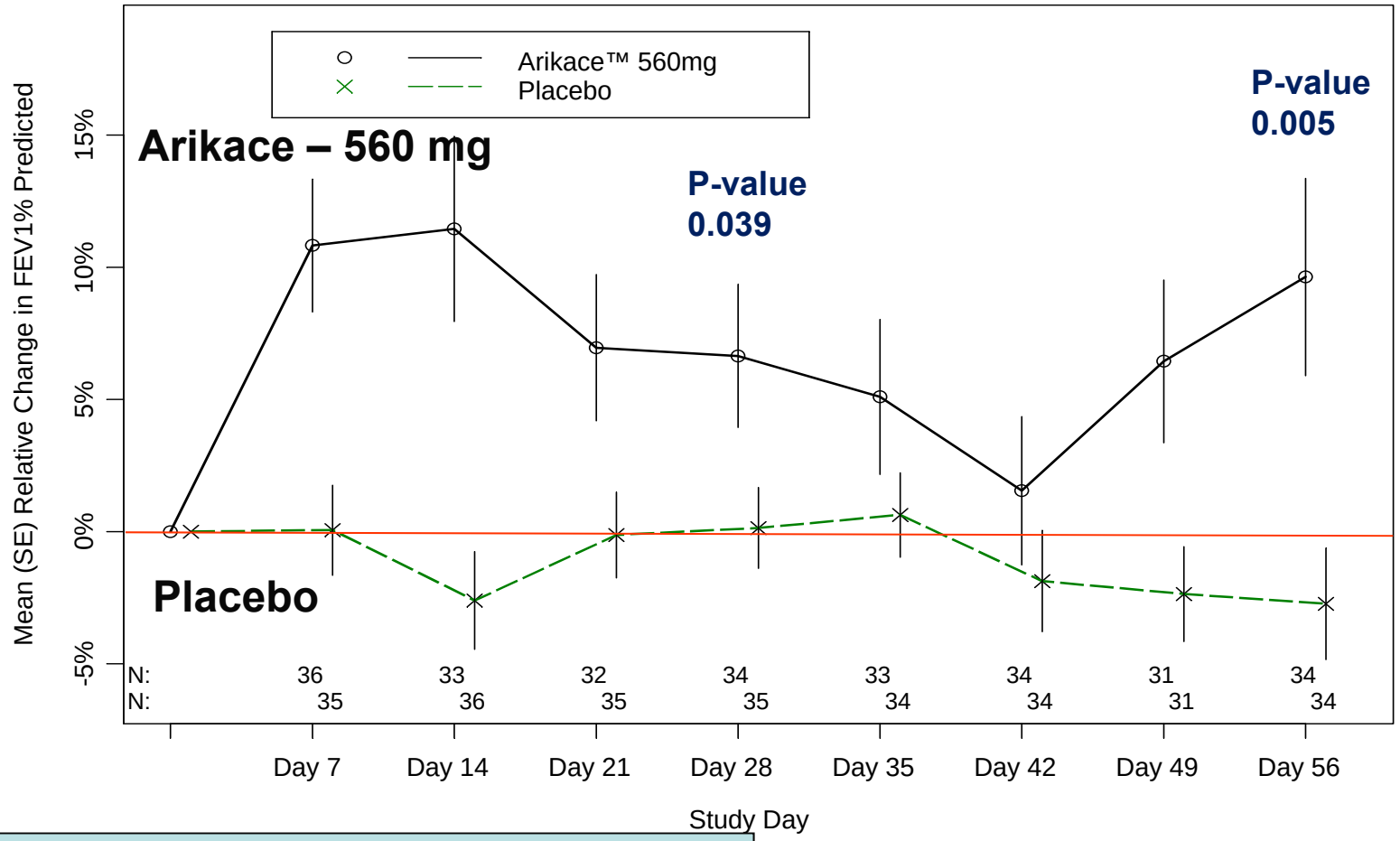


Arikace 560	6.7%	0%	0%	6.7%	0%
Placebo	28.6%	0%	0%	0%	0%

Arikace™- Relative Change in FEV_1 % Predicted: All Cohorts in European and US Phase II Studies: TR2-105 and106

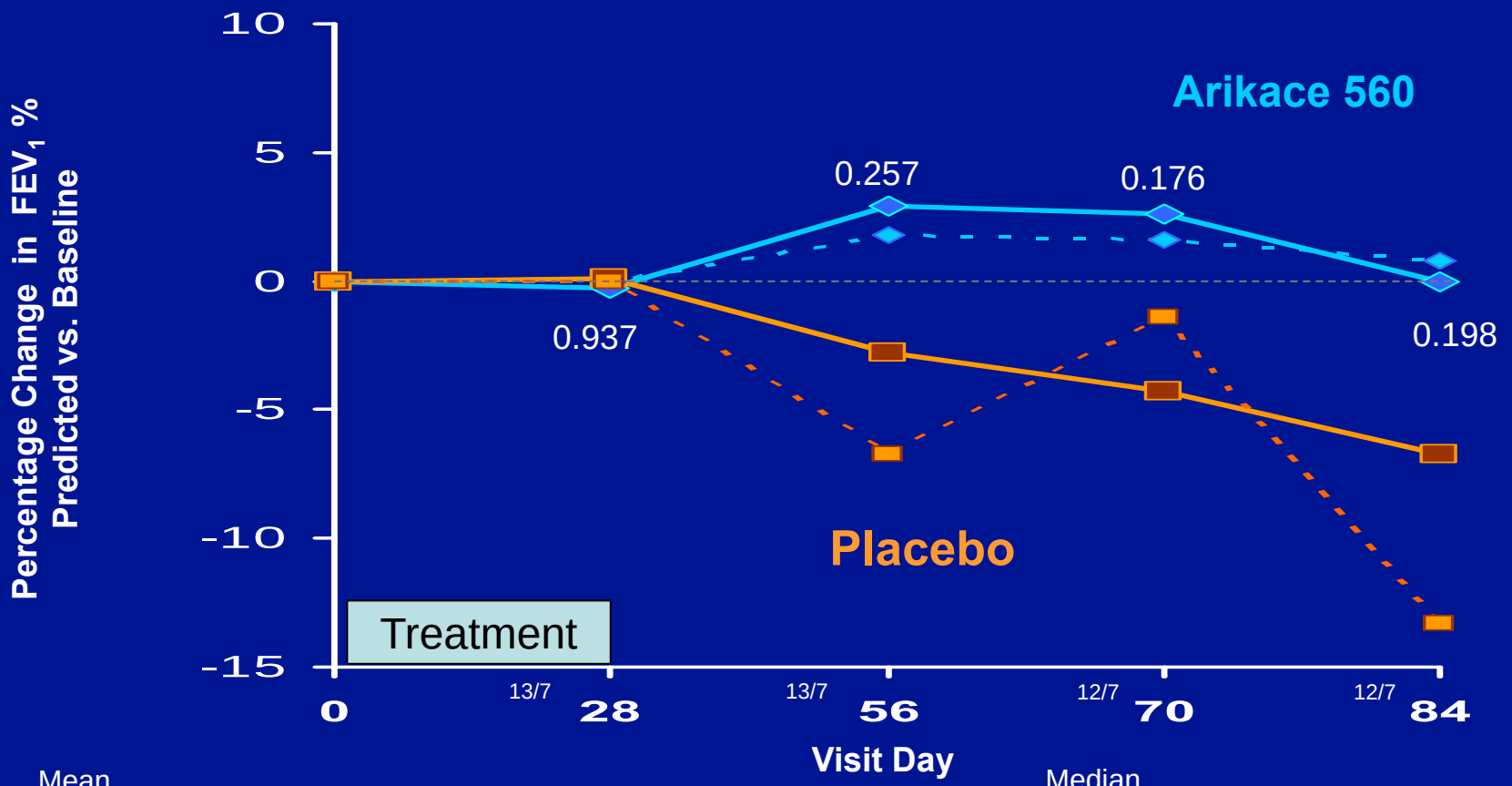


Arikace™ -Relative Change in FEV_1% Predicted: Pooled Data TR02-105 and TR02-106



Treatment

Arikace™ - Relative Change in FEV_1 % Predicted: TR02-106



Mean

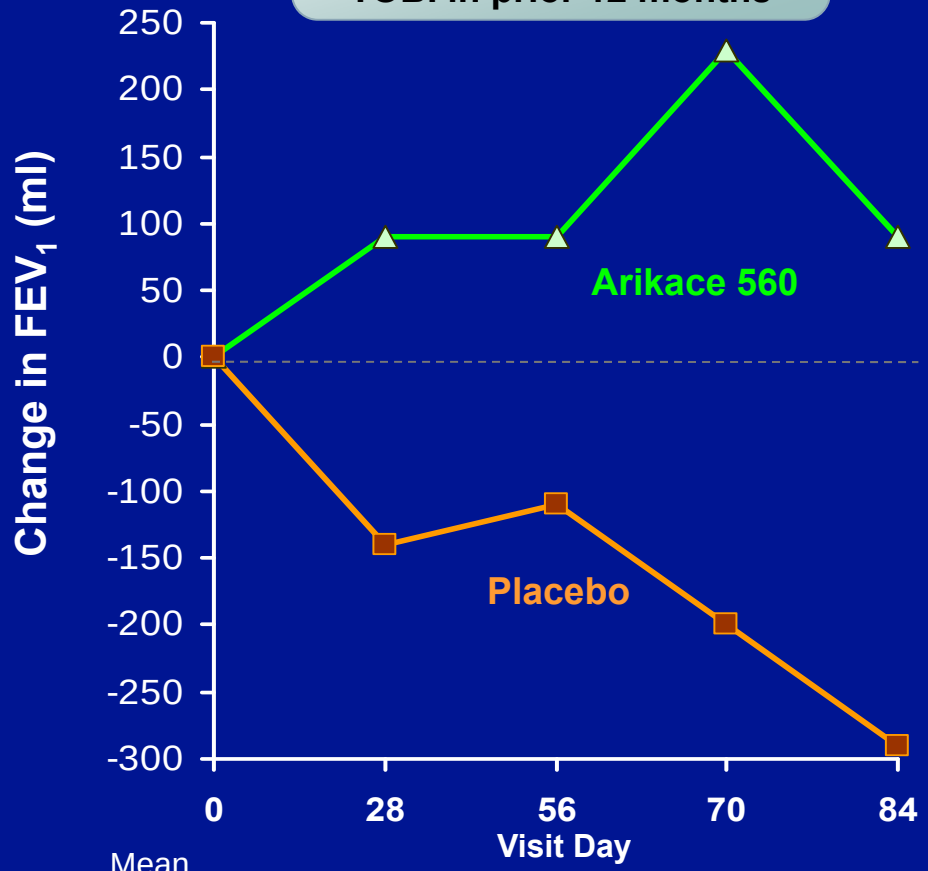
Arikace 560 ——	-0.3% (12.4)	2.9% (9.2)	2.6% (10.7)	0% (7.8)
Placebo ——	0.1% (7.5)	-2.8% (12.9)	-4.3% (9.7)	-6.7% (14.5)

Median

Arikace 560 - - -	0	1.8	1.6	0.8
Placebo - - -	0	-6.7	-1.4	-13.3

Arikace™ - Efficacy in Patients with Prior Tobramycin Use: TR02-106

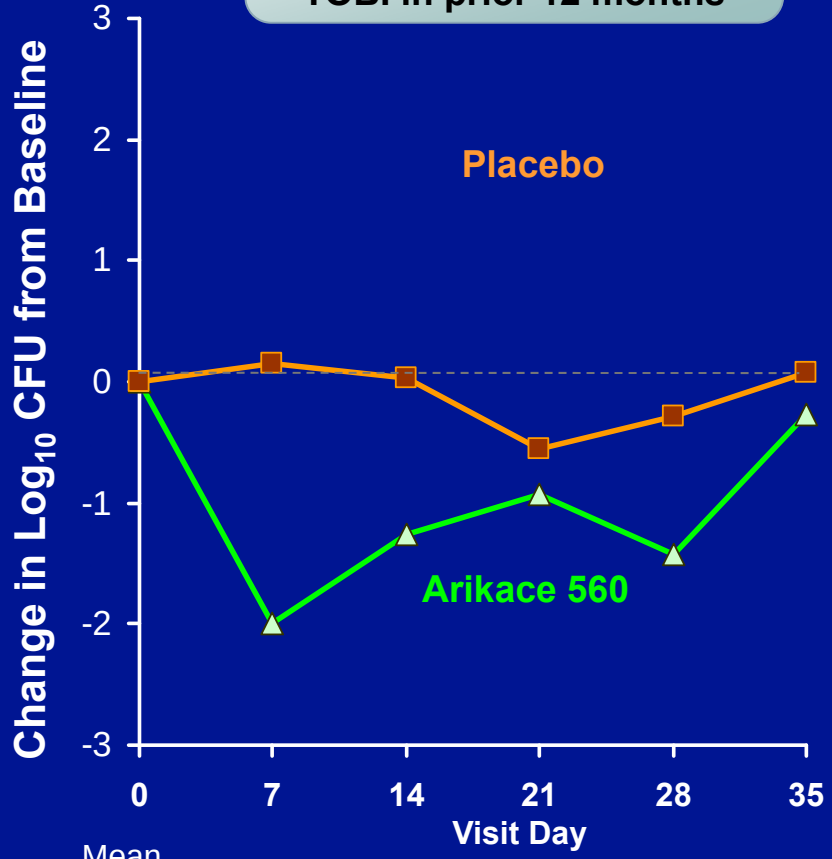
Change in FEV_1 (ml)
Subjects with 5-6 Cycles of TOBI in prior 12 months



Mean

Arikace 560	90 (220)	90 (30)	230 (60)	90 (90)
Placebo	-140 (210)	-110 (350)	-200 (20)	-290 (10)

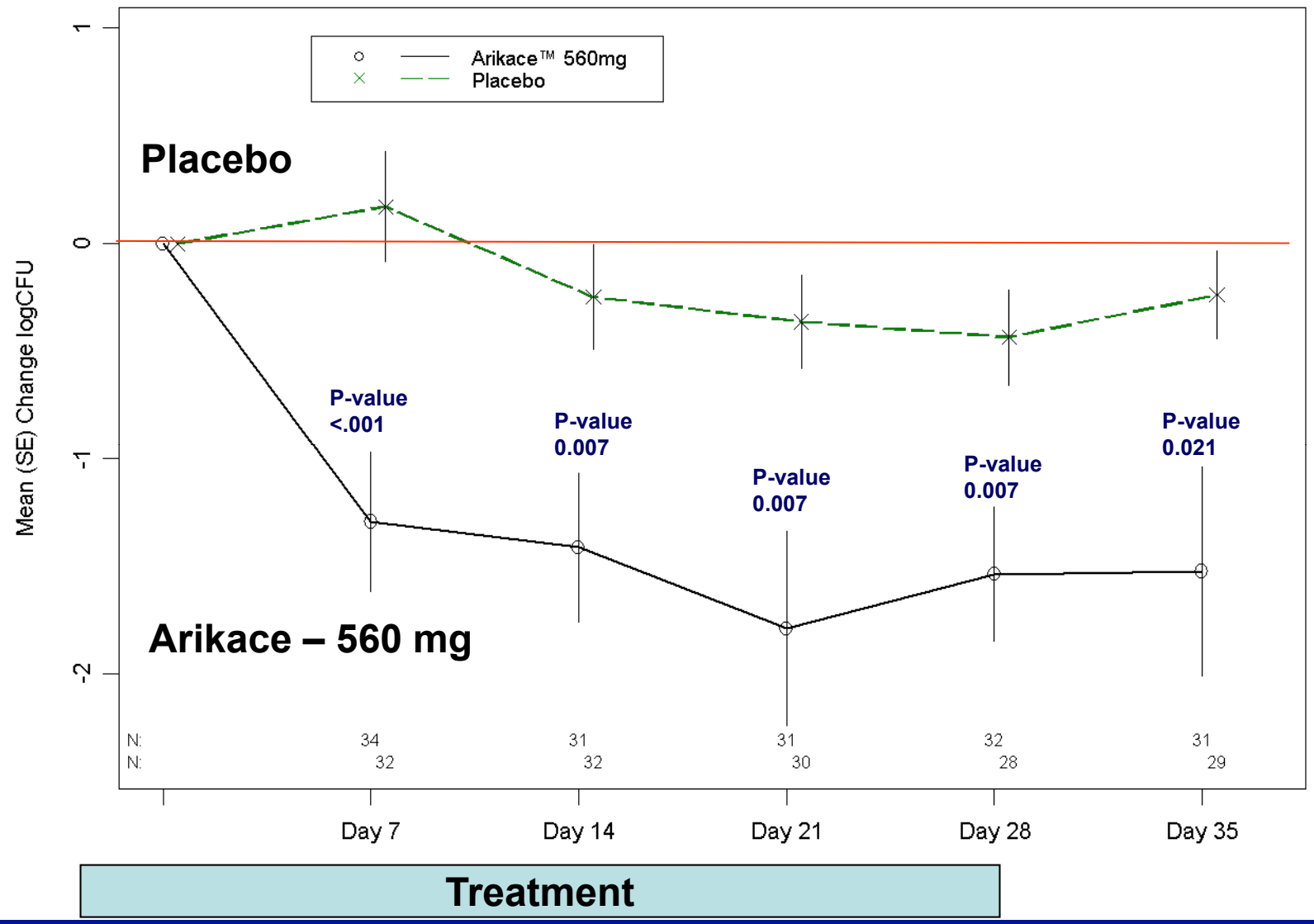
Change in Log_{10} CFU
Subjects with 5-6 Cycles of TOBI in prior 12 months



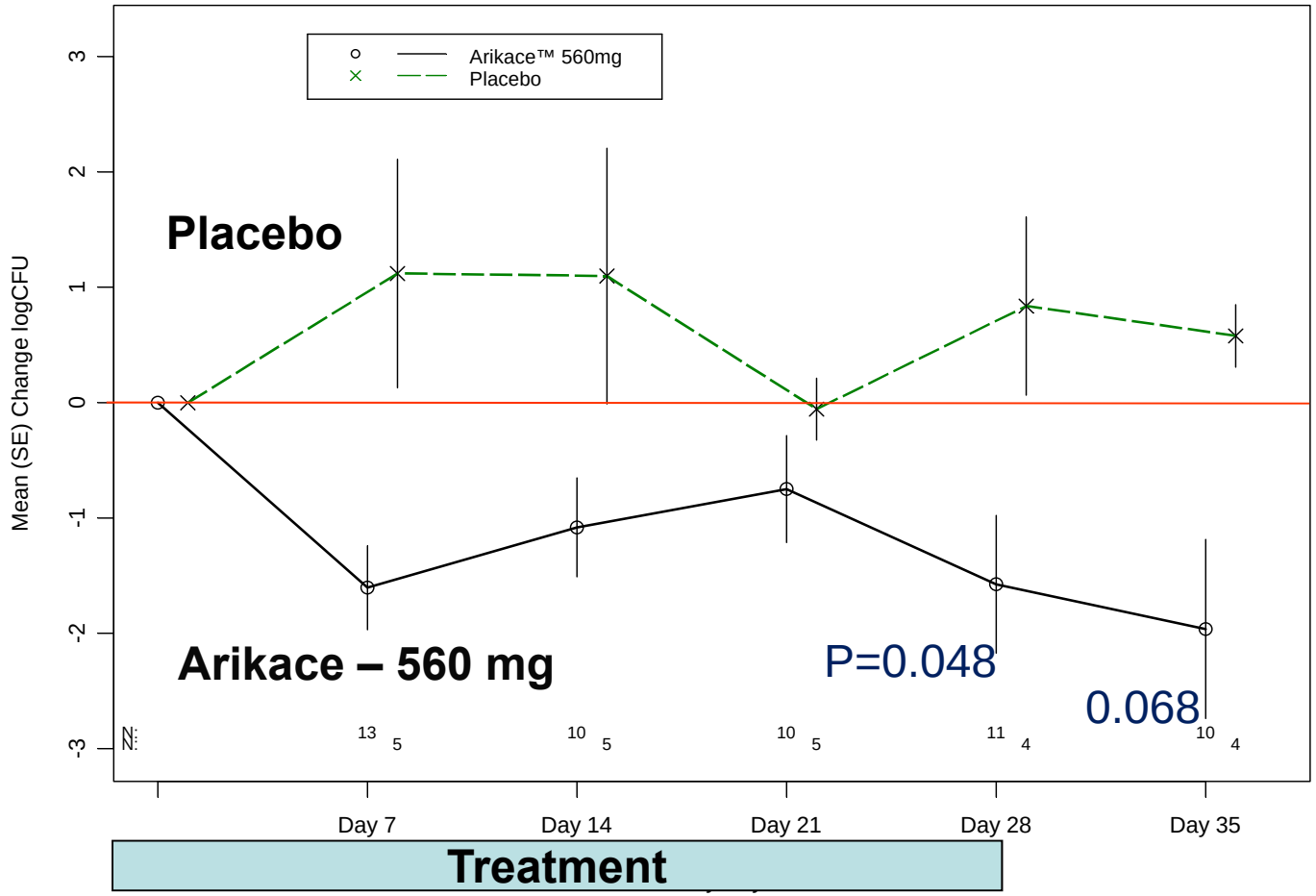
Mean

Arikace 560	-1.99 (0.70)	-1.26 (0.86)	-0.93 (1.19)	-1.43 (0.89)	-0.27 (0.44)
Placebo	0.15	0.03	-0.55	-0.29	0.08

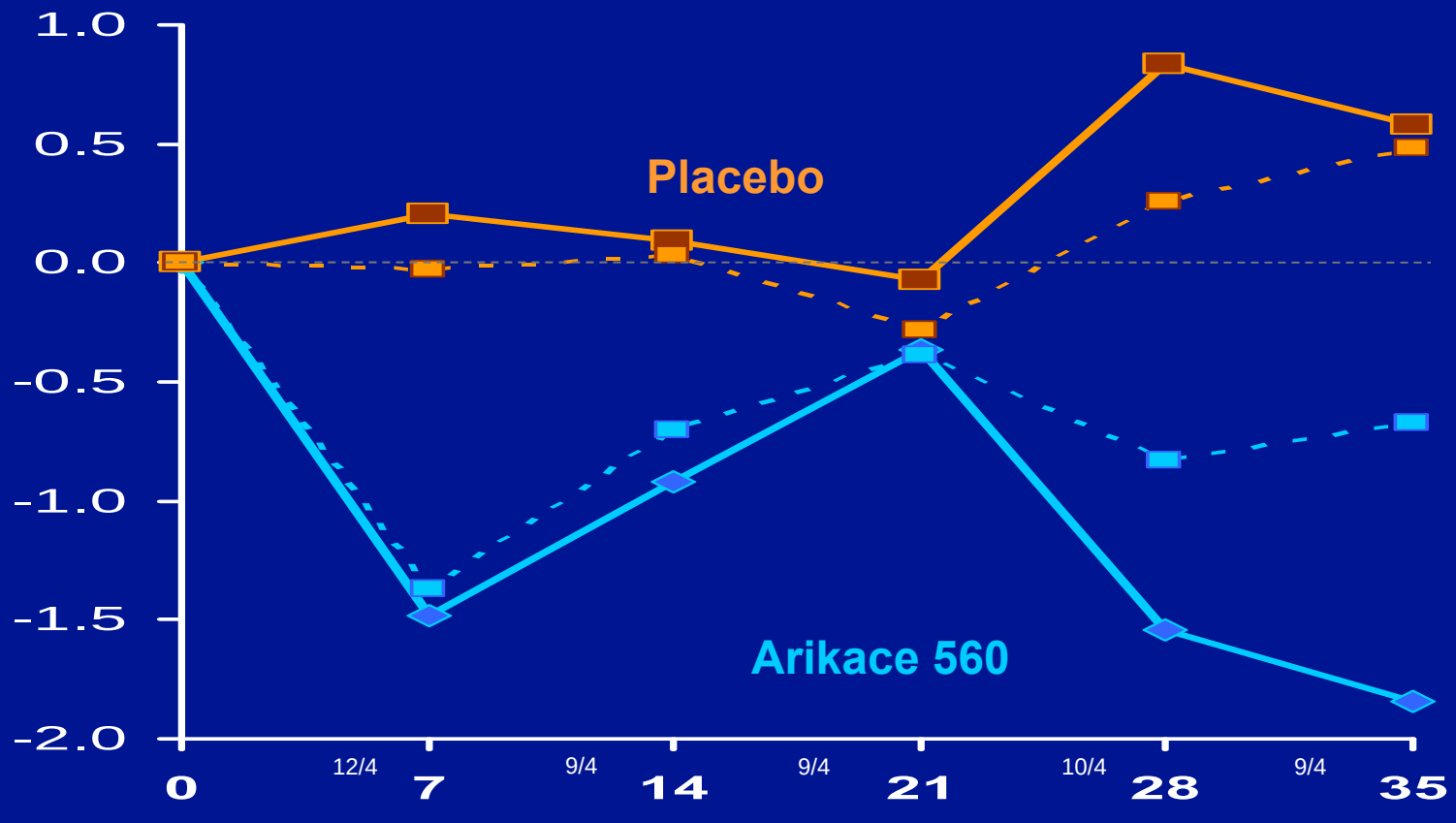
Arikace™ - Change in LOG_{10} CFU: Pooled Data TR02-105 & TR02-106



Arikace™ - Change in Log_{10} CFU: TR02-106



Arikace™ - Change in LOG_{10} CFU- Mucoid Strains: TR02-106

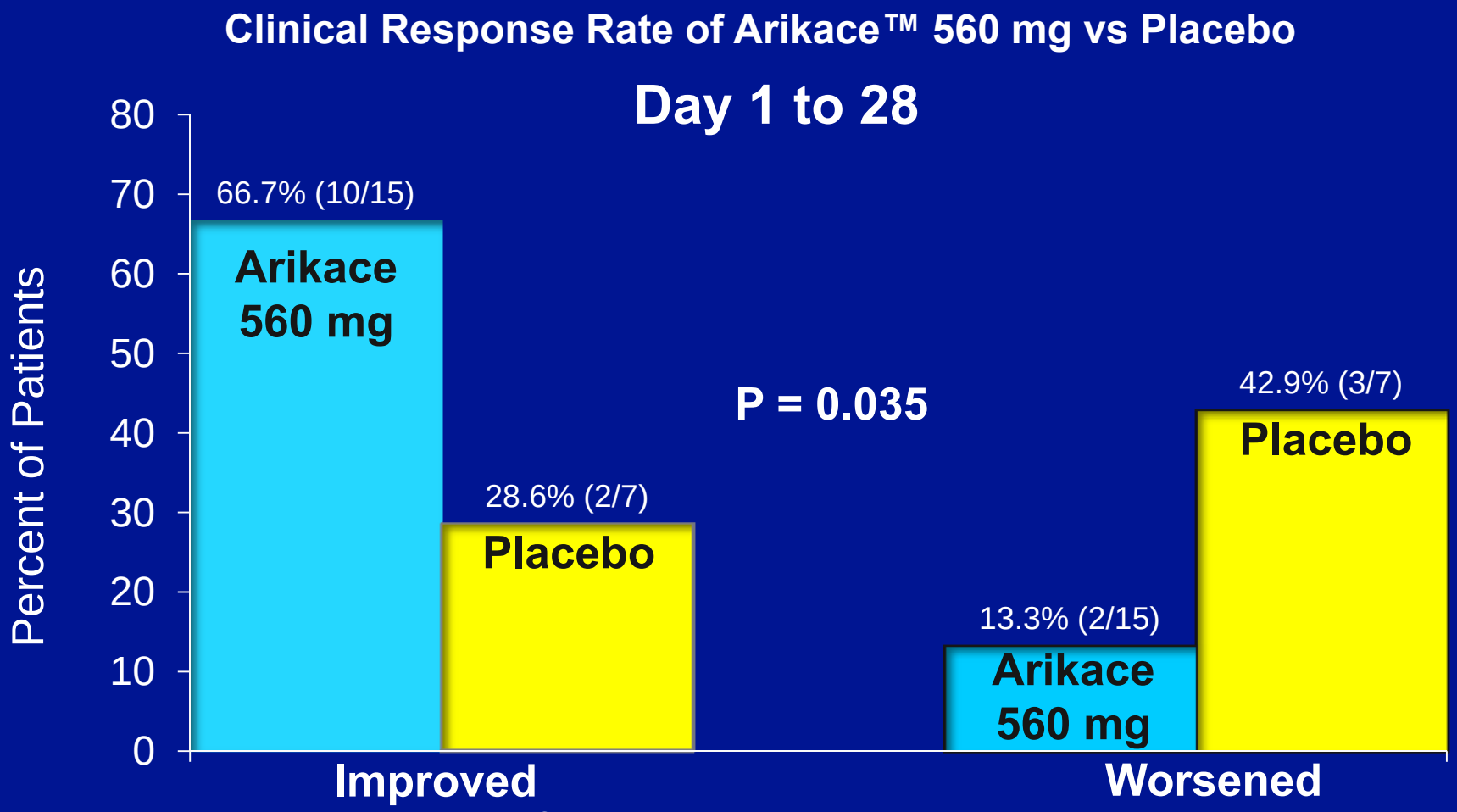


Mean (SD)

Arikace 560	-1.482 (1.286)	-0.923 (1.334)	-0.366 (0.870)	-1.545 (2.084)	-1.844 (2.574)
Placebo	0.207 (1.000)	0.096 (1.218)	-0.071 (0.692)	0.836 (1.544)	0.578 (0.539)

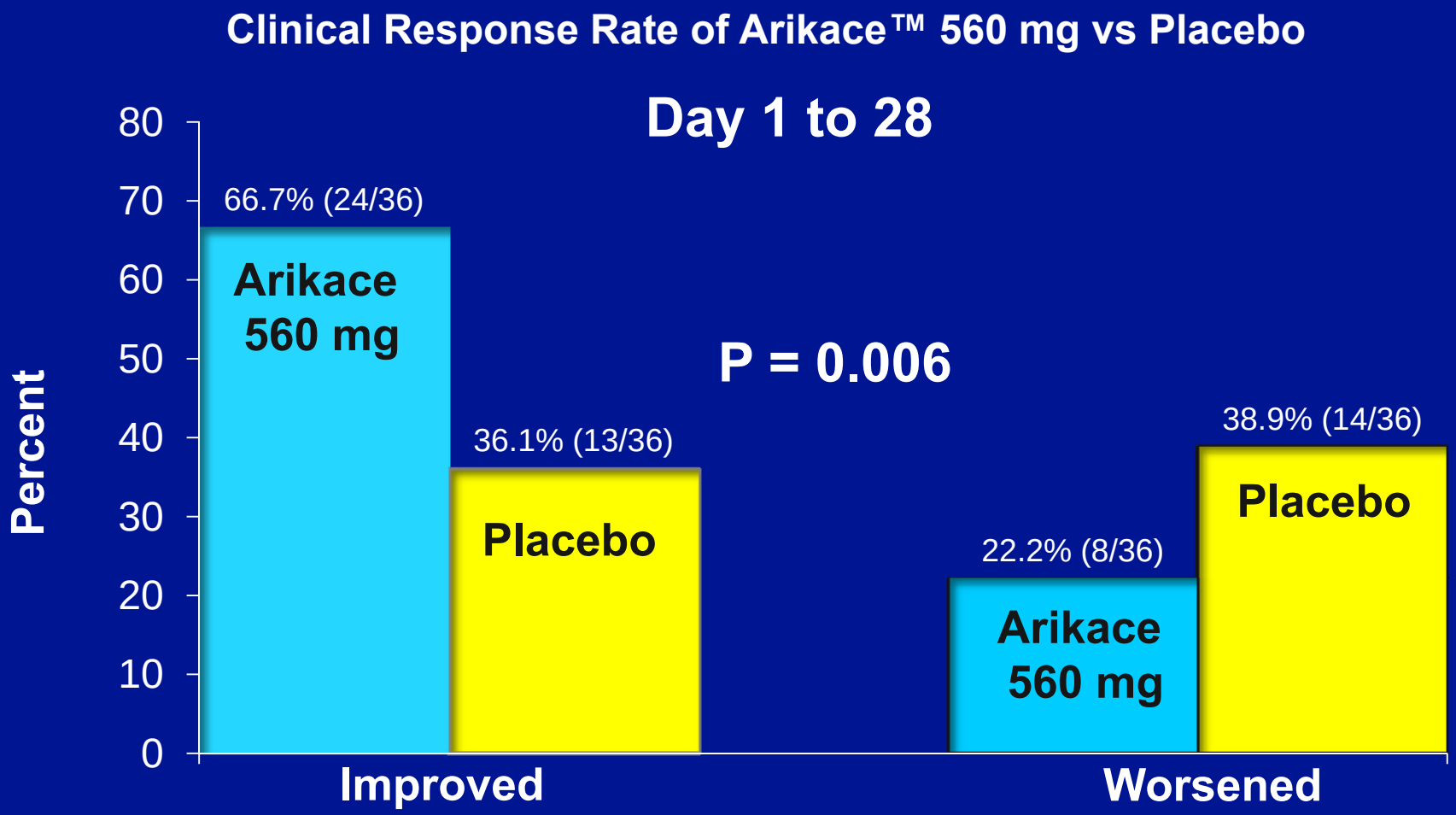
Arikace and Placebo Median - - -

Arikace™ - CFQR – Respiratory Scale Clinical Response Rate: TR02-106



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: CFQR - Respiratory Scale - Clinical Response Rate: Pooled Data



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

Arikace™- CF Phase 2 Summary Observations: Safety

- Overall, Arikace™ 70 mg, 140 mg, 280 mg and 560 mg, administered once daily for 28 days is 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 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

Arikace™- 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 treatment effect of FEV_1% predicted of 14.0% was observed at two months after discontinuing study drug.
- Patients receiving Arikace™ had prolonged time to exacerbation (Mean = 45.3 days) as compared to placebo (Mean = 20.5 days)

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 shift in MICs
- Although sample size per cohort is small, the Arikace™ arms vs placebo group demonstrate dose related effect, with 560 mg dose showing significant improvement in clinical symptoms, and microbiologic activity, and sustained improvement in lung function for up to two months after discontinuation of study drug
- These data warrant confirmation of safety and efficacy of Arikace™ in Phase 3 trials

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
- Increased microbiologic activity, including against mucoid and resistant isolates: significantly superior to placebo
- Reduction in inflammation
- Improvement in respiratory symptoms, and lung function: significantly superior to placebo
- Prolonged time to exacerbation
- Sustained clinical benefit up to two months after discontinuing dosing of 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
Dr. Nasr
Dr. Nick
Dr. Rubenstein
Dr. Sannuti
Dr. Sawicki
Dr. Taylor-Cousar
Dr. Trapnell
Dr. Wallace
Dr. Woo

European Investigators
Co-PIs
Prof. Dupont
Prof. Minic

Co-PIs
Study Coordinators

Cystic Fibrosis Foundation Therapeutics
- CFFT Protocol Review Committee
  Preston Campbell III, MD
  Diana Wetmore, PhD
- CF Therapeutics Development Network
  Consulting Services Group
- Drug Safety Monitoring Board

University of Washington
Bonnie Ramsey, MD
Jane Burns, MD
Prof. Donald Patrick
Nicole Hamblett, PhD
Jim Lymp, PhD

University of Miami
Alexandra Quittner, PhD

Univ. of Edinburgh
Prof. John Govan

PARI Pharma GmbH

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