A PLACEBO CONTROLLED, RANDOMIZED, PARALLEL COHORT, SAFETY AND TOLERABILITY STUDY OF TWO DOSE LEVELS OF LIPOSOMAL AMIKACIN FOR INHALATION (ARIKACE™) IN PATIENTS WITH BRONCHIECTASIS COMPLICATED BY CHRONIC INFECTION DUE TO *PSEUDOMONAS AERUGINOSA*

Protocol Number: TR02-107

Conflicts

Financial:
Grant support: Transave Inc

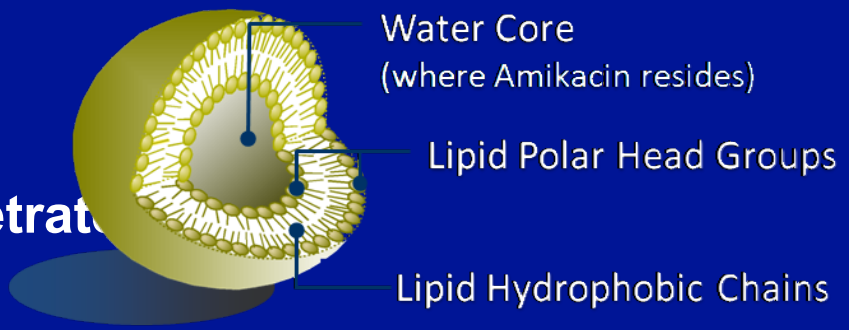
Unapproved indications:
Inhaled antibiotics for non-CF bronchiectasis

Other conflicts: Grant Support:
Bayer Inc
Gilead Inc
Pharmaxis Inc

Bronchiectasis: Background

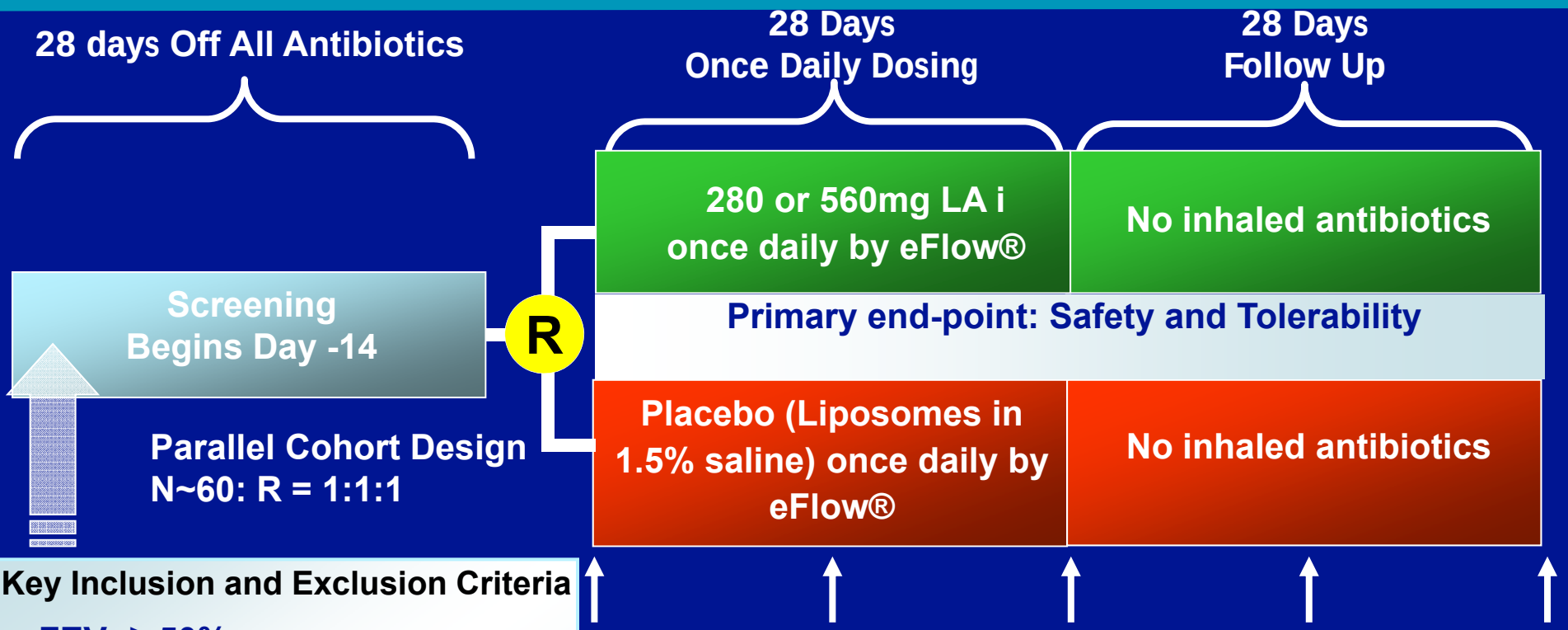
- No approved antibiotic for this indication
- Inhaled tobramycin: Phase 2 clinical studies
  - Evidence of microbiologic activity
  - Problems with tolerance
    - Increased cough, wheezing, dyspnea
  - Physician assessment of clinical benefit mixed
  - Used sparingly for some patients with frequent exacerbations
  - No Phase 3 studies underway
- Change in FEV1: May not be prognostic indicator: benefit/decline
- End-point showing clinical benefit (PSSS/SGRQ/Exacerbations/Rescue Antibiotic Use)

Liposomal Amikacin for Inhalation (Arikace™)



- Liposomes (~0.3 μm) shown to penetrat
  CF physical barriers
  - Diffusion through CF sputum
  - Biofilm penetration and retention confirmed at Center for Biofilm Engineering at Montana State University
- Sustained release of drug in the lung
  - Longer t½ and improved AUC to MIC ratio
- Virulence factors (Rhamnolipids & Phospholipase C) secreted by Pseudomonas facilitate further release of amikacin from Arikace™
- In vitro and in-vivo anti-pseudomonas activity demonstrated
- Liposomes provide high degree of biocompatibility
  - Natural lipids: DPPC and Cholesterol
- 3 and 6 month daily dosing toxicology studies in mice, rats and dogs support long-term dosing clinical studies

Phase II Study: TR02-107 : Liposomal Amikacin (LA inhaled) Chronic Pseudomonas Infection in Non-CF Bronchiectasis



Key Inclusion and Exclusion Criteria

- $FEV_1 \geq 50\%$
- Age ≥ 18 years
- Chronic Infection with *Pa*
- HRCT confirmed Bronchiectasis in >2 segments
- History of at least 1 exacerbation, and <3
- Exclude patients with Malignancy, active TB & NTM

Bi-weekly Safety and Efficacy Evaluation Assessments of Change in Frequency of Cough with Expectoration, PSSS, SGRQ, CFU, Anti-pseudomonal Rescue antibiotic Treatment, Exacerbations, and Hospitalization. PK in sub-group of patients

TR02-107 Liposomal amikacin inhaled

CLINICAL SITES DISTRIBUTION

Total countries = 7

Total initiated clinical sites = 25 (13-Europe), (12-India), 1 USA

Active Sites= 16 (10- Europe), (6- India)

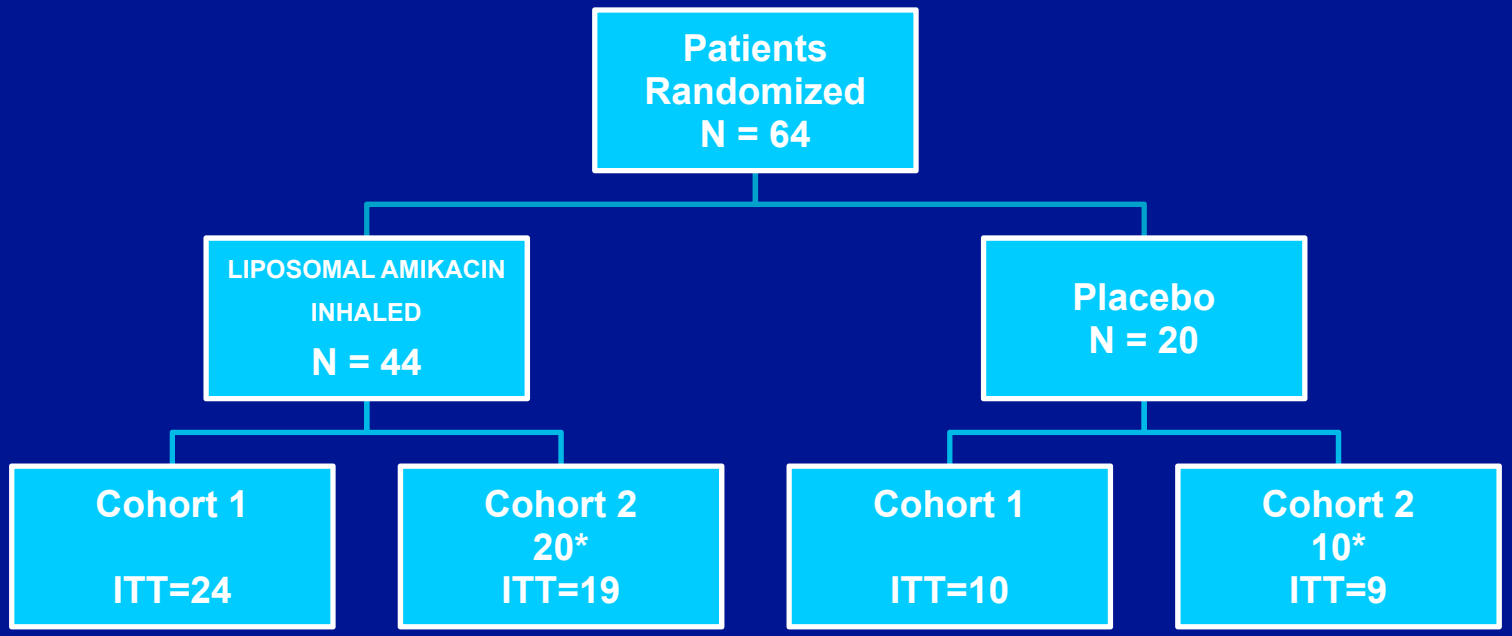
Country	# Active Sites	Total Patients
Bulgaria	3	16
Greece	1	3
Hungary	1	1
India	6	23
Serbia	2	6
Ukraine	3	15
Total	16	64

Patient Disposition

Demographics
&
Characteristics

TR02-107 Liposomal amikacin inhaled

PATIENT DISTRIBUTION



*1 Withdrew prior to Study Drug

Table 6.3.2

TR02-107 Liposomal amikacin- Patient Characteristics

		280mg LAi (N=24)	560mg LAi (N=19)	Placebo (N=19)
Age (yrs)	Mean (SD)	49.929 (21.129)	58.537 (16.000)	49.395 (13.250)
Gender	Male	14 (58.3%)	8 (42.1%)	10 (52.6%)
	Female	10 (41.7%)	11 (57.9%)	9 (47.4%)
FEV_1	Mean (SD)	1.917 (0.793)	1.939 (0.515)	1.802 (0.580)
FEV_1 (% Pred)	Mean (SD)	64.500 (20.680)	71.368 (23.898)	62.579 (15.696)
FVC (L)	Mean (SD)	2.639 (0.933)	2.504 (0.653)	2.565 (0.758)
BMI (kg/m^2)	Mean (SD)	22.475 (4.750)	24.942 (6.105)	21.774 (3.649)
Baseline Pa density (log cfu)	N	17	15	17
	Mean (SD)	6.662 (0.908)	7.022 (1.115)	6.973 (1.099)
	Median	6.380	7.079	6.903
	Min, Max	5.30, 8.04	4.62, 8.64	5.30, 8.93

(RUN 15JUN2009) RUN 29JUL2009

Table 6.4.1

TR02-107 Liposomal amikacin - Patient Characteristics

		280mg LAi (N=24)	560mg LAi (N=19)	Placebo (N=19)
SGRQ Total Score	N	21	19	18
	Mean (SD)	57.022 (18.757)	57.184 (17.583)	55.847 (20.776)
	Median	61.530	58.020	58.775
	Min, Max	13.86, 88.08	20.75, 78.74	11.47, 82.72
PSSS Total Score	N	24	19	19
	Mean (SD)	7.542 (3.526)	8.263 (3.664)	6.316 (2.405)
	Median	7.000	7.000	7.000
	Min, Max	2.00, 16.00	4.00, 18.00	3.00, 11.00

(RUN 15JUN2009) RUN 29JUL2009

Table 6.4.1

Safety

OVERVIEW OF ADVERSE EVENTS (ITT)

Overview of Adverse Events by Treatment Group

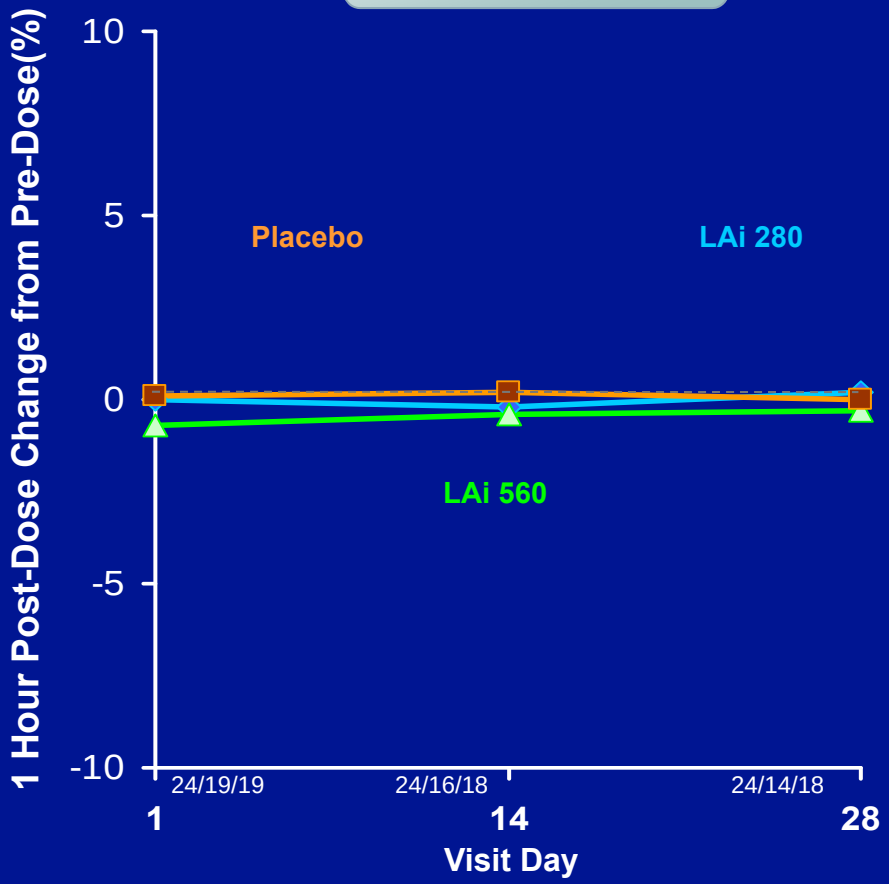
	LA i 280 mg (N=24)	LA i 560 mg (N=19)	Placebo (N=19)
Number of Adverse Events	24	39	71
Patients with Adverse Events	11 (45.8%)	11 (57.9%)	11 (57.9%)
Number of Treatment-Related Adverse Events (Probably or Possibly Related)	4	15	26
Patients with Treatment-Related Adverse Events	2 (8.3%)	5 (26.3%)	4(21.1%)
Deaths	0 (0.0%)	0 (0.0%)	0
Patients with Serious Adverse Events	1 (4.2%)	1 (5.3%)	1(5.3%)
Patients Permanently Discontinuing Therapy Due to Adverse Events	0 (0.0%)	1 (5.3%)	0

RUN 27JUL2009

Table 6.6.27

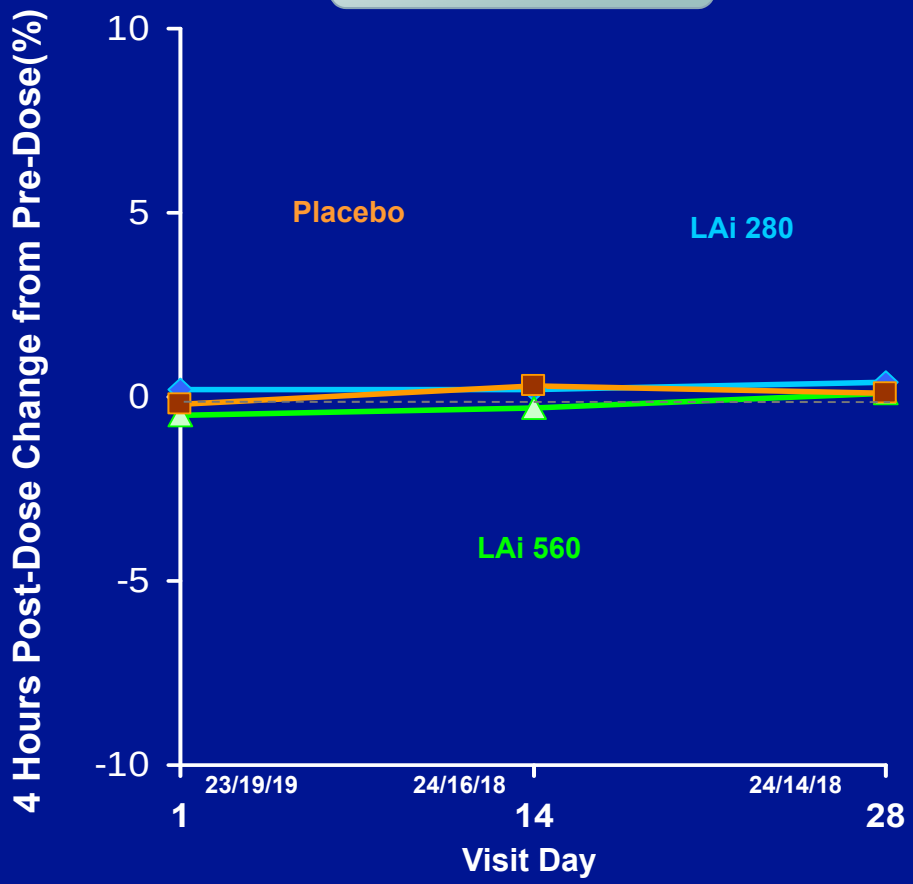
Arikace ™ - TR02-107 - CHANGE IN OXYGEN SATURATION

1 Hour Post-Dose Change from Pre-Dose



LA i 280 mg *	-0.0 (1.5)	-0.2 (1.3)	0.2 (1.2)
LA i 560 mg *	-0.7 (2.2)	-0.4 (1.5)	-0.3 (1.4)
Pooled Placebo *	0.1 (1.1)	0.2 (1.2)	0.0 (0.7)

4 Hours Post-Dose Change from Pre-Dose

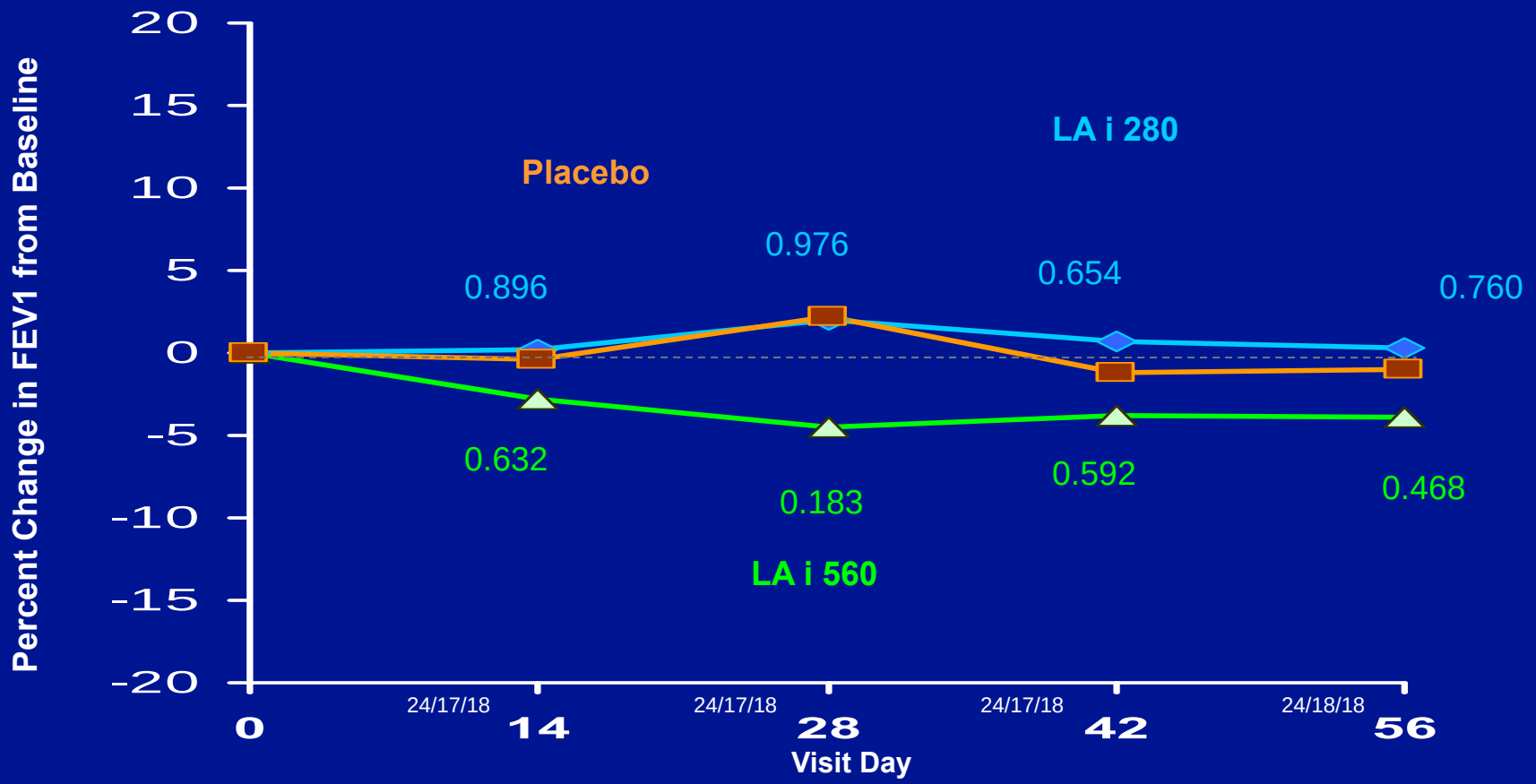


LA i 280 mg *	0.2 (1.7)	0.2 (1.3)	0.4 (1.4)
LAi 560 mg *	-0.5 (1.9)	-0.3 (1.2)	0.1 (0.7)
Pooled Placebo *	-0.2 (1.7)	0.3 (0.8)	0.1 (0.9)

* Mean (SD) (RUN 16JUN2009) RUN 29JUL2009

Table 6.6.16

Arikace ™ - TR02-107 - FEV_1 Relative Change - ITT



LA i 280 *	0.17% (14.14)	2.05% (13.94)	0.74% (14.99)	0.29% (15.58)
LA i 560 *	-2.81% (18.54)	-4.47% (18.08)	-3.80% (16.57)	-3.92% (13.31)
Placebo *	-0.36% (10.74)	2.17% (9.88)	-1.19% (11.73)	-1.01% (10.31)

* Mean (SD) (RUN 15JUN2009) RUN 29JUL2009

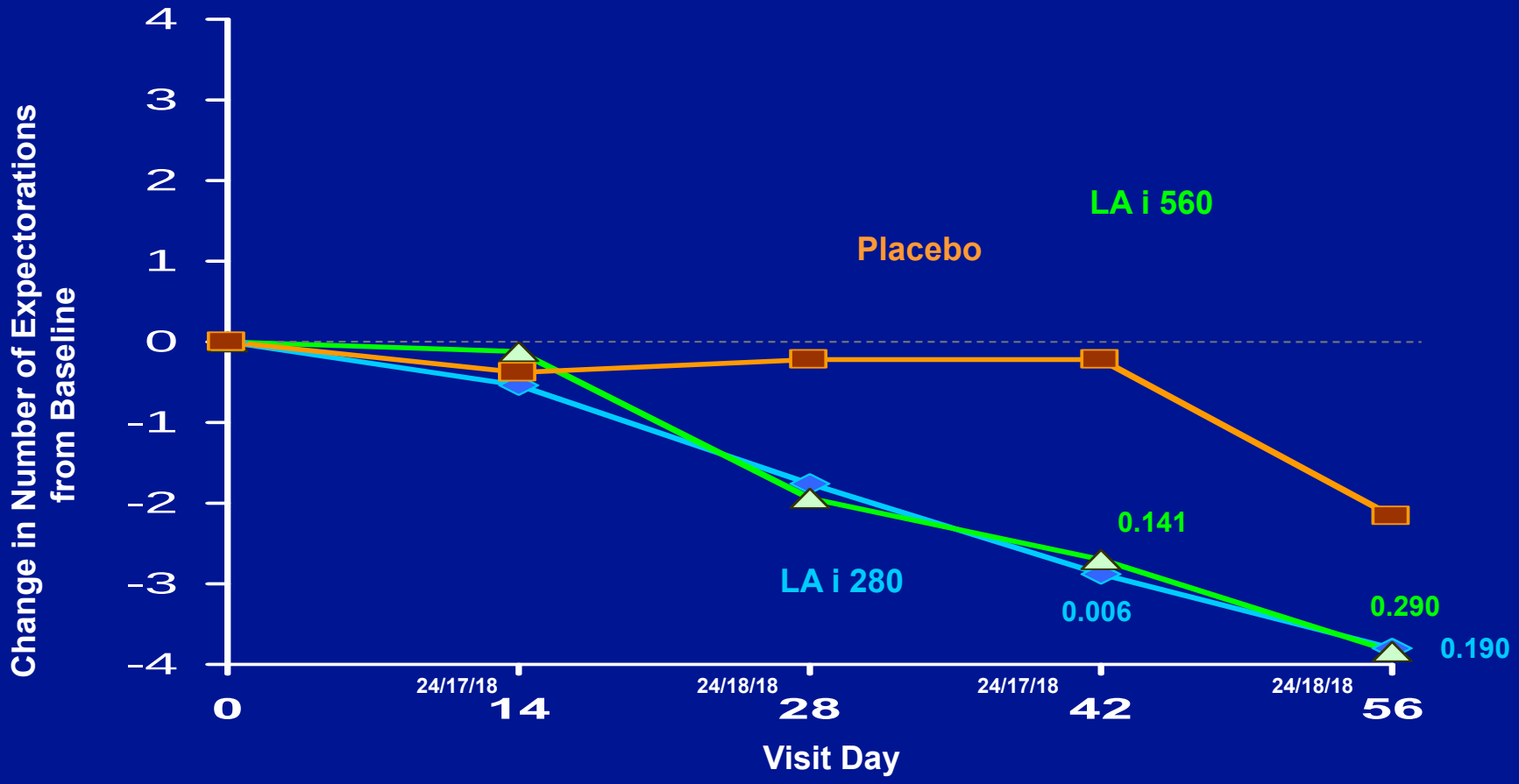
Table 6.6.5

Arikace ™ - TR02-107 SAFETY: >15% Decline in FEV_1

	LA i 280mg	LA i 560 mg	Placebo
Patients	6/24 (25.0%)	4/19 (21.0%)	4/19 (21.1%)

Efficacy

Arikace ™ - TR02-107 - Frequency of Cough with Expectoration-ITT

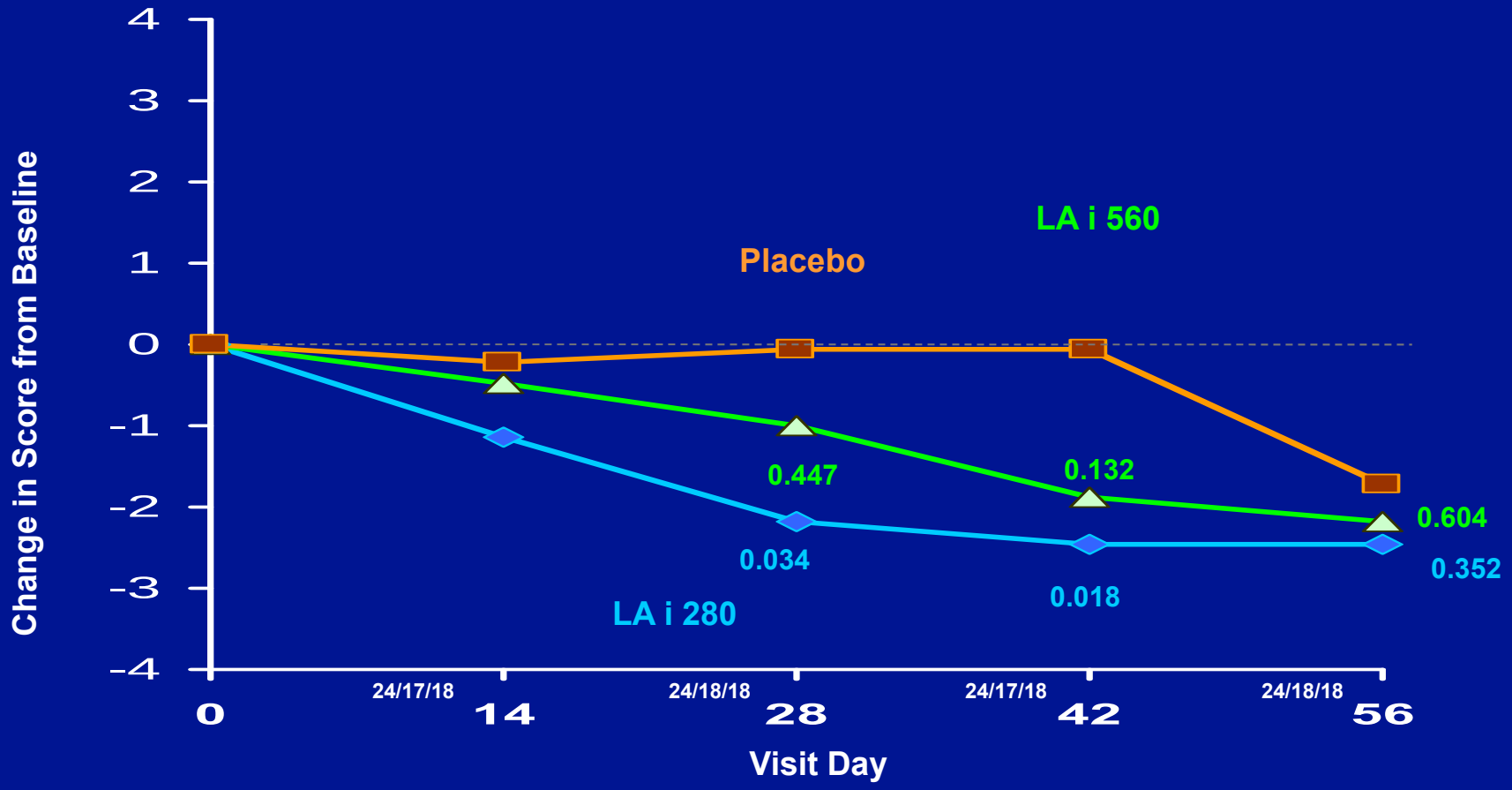


LA i 280 *	-0.542 (2.766)	-1.750 (3.274)	-2.875 (2.455)	-3.792 (3.349)
LA i 560 *	-0.118 (5.797)	-1.944 (3.489)	-2.706 (6.039)	-3.833 (4.743)
Placebo *	-0.389 (3.534)	-0.222 (4.387)	-0.222 (3.422)	-2.167 (4.554)

* Mean (SD) (RUN 30JUN2009) RUN 27JUL2009

Table 6.7.17

Arikace ™ - TR02-107 - SUMMARY OF PSSS TOTAL SCORE - ITT

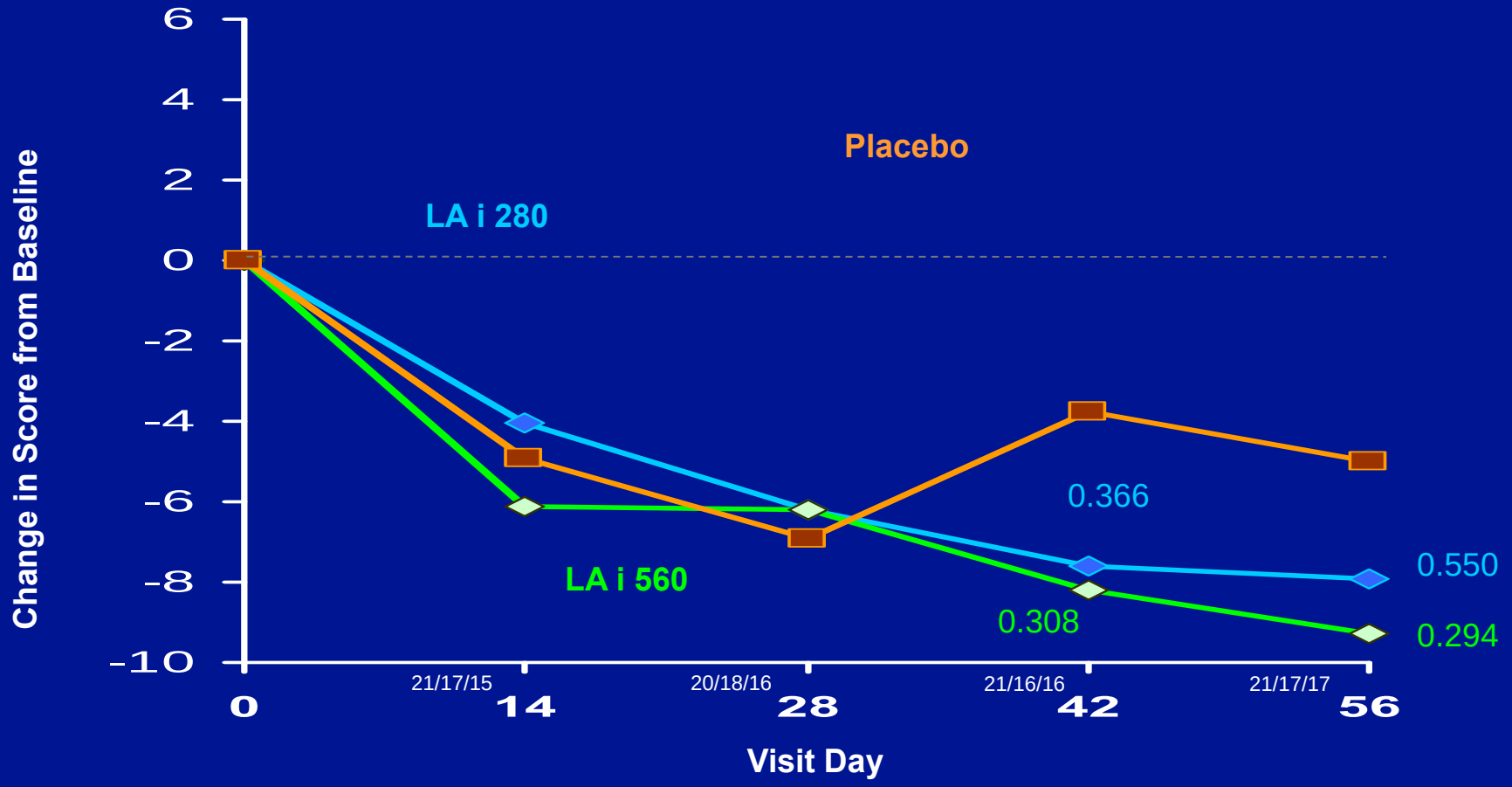


LA i 280 *	-1.125 (2.213)	-2.167 (2.988)	-2.458 (3.476)	-2.458 (2.874)
LA i 560 *	-0.471 (2.035)	-1.000 (4.087)	-1.882 (4.285)	-2.167 (3.053)
Pooled Placebo *	-0.222 (1.734)	-0.056 (3.226)	-0.056 (2.532)	-1.722 (1.904)

* Mean (SD) (RUN 30JUN2009) RUN 27JUL2009

Table 6.7.17

Arikace ™ - TR02-107 - SUMMARY OF SGRQ TOTAL SCORE (ITT)



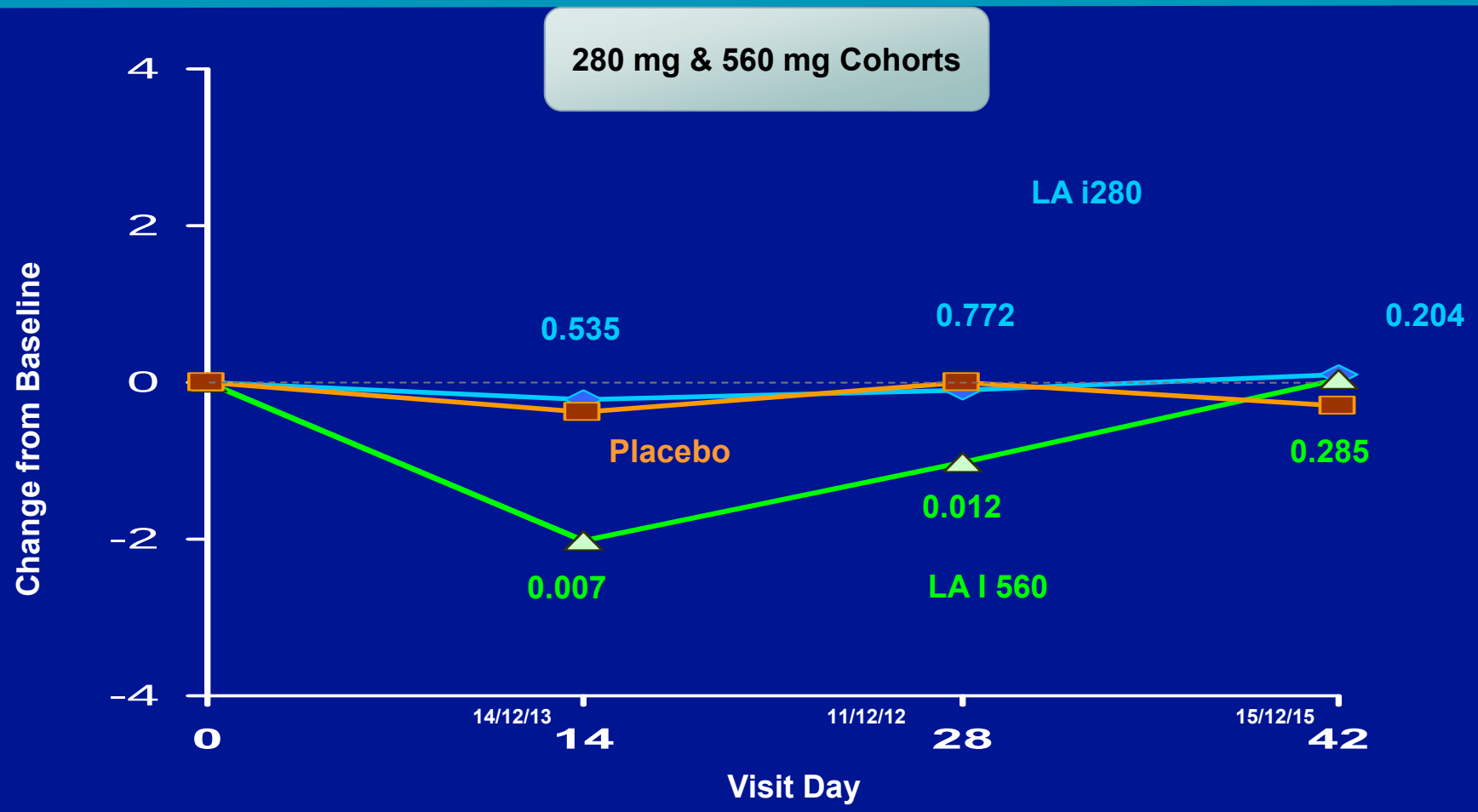
LA i 280 *	-4.024 (8.558)	-6.205 (13.661)	-7.611 (13.274)	-7.937 (16.281)
LA I 560 *	-6.101 (12.164)	-6.200 (11.855)	-8.196 (12.332)	-9.282 (10.302)
Pld Placebo *	-4.933 (8.114)	-6.903 (12.102)	-3.741 (11.985)	-5.010 (12.888)

* Mean (SD) (RUN 30JUN2009) RUN 27JUL2009

Table 6.7.9

QUANTITATIVE MICROBIOLOGY

Arikace ™ - TR02-107 - CHANGE IN LOG_{10} CFU (ITT-m)



LA i 280 *	-0.227 (0.805)	-0.094 (0.975)	0.101 (0.788)
LA i 560 *	-2.016 (1.942)	-1.013 (1.099)	0.046 (0.705)
Pooled Placebo *	-0.387 (0.459)	0.006 (0.661)	-0.291 (0.860)

* Mean (SD) (RUN 01JUL2009) RUN 27JUL2009

No Table #

Arikace ™ - TR02-107

Protocol Defined Pulmonary Exacerbations

	LA i	Placebo
Patients	1*/43 (2.3%)	2/19 (10.5%)

*2/43 (4.7%)
Any exacerbation

Arikace ™ - TR02-107: Anti-Pseudomonal Rescue Treatment

	LA inhaled	Placebo
Patients	**0/43 (0%)**	**3*/19 (15.7%)**

* 1 Received IV antibiotics

Arikace ™ - TR02-107: Conclusions

SAFETY

- Liposomal amikacin inhaled 280 mg and 560 mg, administered once daily for 28 days is safe and well tolerated
- AEs were consistent with underlying chronic lung disease in bronchiectasis patients
- No evidence of renal or ototoxicity
- Patients in the 560mg cohort appear to have a slightly higher frequency of dry cough post administration than in the 280 mg cohort. Cough was of short duration, and self-limiting. One patient discontinued due to dysphonia and cough.

TR02-107 Conclusions, continued

EFFICACY:

- Statistically significant reduction in *Pseudomonas aeruginosa* density was observed in the 560 mg arm vs placebo .
- Patients receiving LA inhaled experienced fewer pulmonary exacerbations (4.7%) vs those receiving Placebo (10.5%)
- No patients in the LA inhaled group required anti-pseudomonal rescue treatment while 3 patients in the placebo group required treatment.
- Greater frequency of any cause Hospitalization was noted in the placebo group (5.3%) vs active treated group (2.3%) .
- Patients receiving active drug demonstrated sustained superior clinical benefit vs patients receiving placebo as measured by improvement in Patient Respiratory Symptoms and Quality of Life assessment.

Arikace ™ - TR02-107: Conclusions, continued

- Arikace™ technology provides high levels of sustained release of antibiotic in the lung, with drug concentrations well above the MICs for *Pseudomonas aeruginosa* during the dosing interval, and biofilm penetration. These features likely contribute to clinical efficacy.

- We believe, this Phase 2 placebo controlled study has demonstrated safety, tolerability and clinically meaningful efficacy of lipsomal amikacin inhaled in the treatment of chronic *Pseudomonas aeruginosa* infection in non-CF patients with bronchiectasis that warrants confirmation in a Phase 3 trial.

Arikace ™ - TR02-107 - Acknowledgements

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