Abstract 57335
2014 International Conference of the American Thoracic Society
May 16–21, 2014
San Diego, CA

Interim Analysis of a Long-term, Open-label Safety, Tolerability, and Efficacy Study of Liposomal Amikacin for Inhalation in Cystic Fibrosis Patients With Chronic Infection Due to *Pseudomonas aeruginosa*

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Faculty Disclosures
ATS 2014 San Diego

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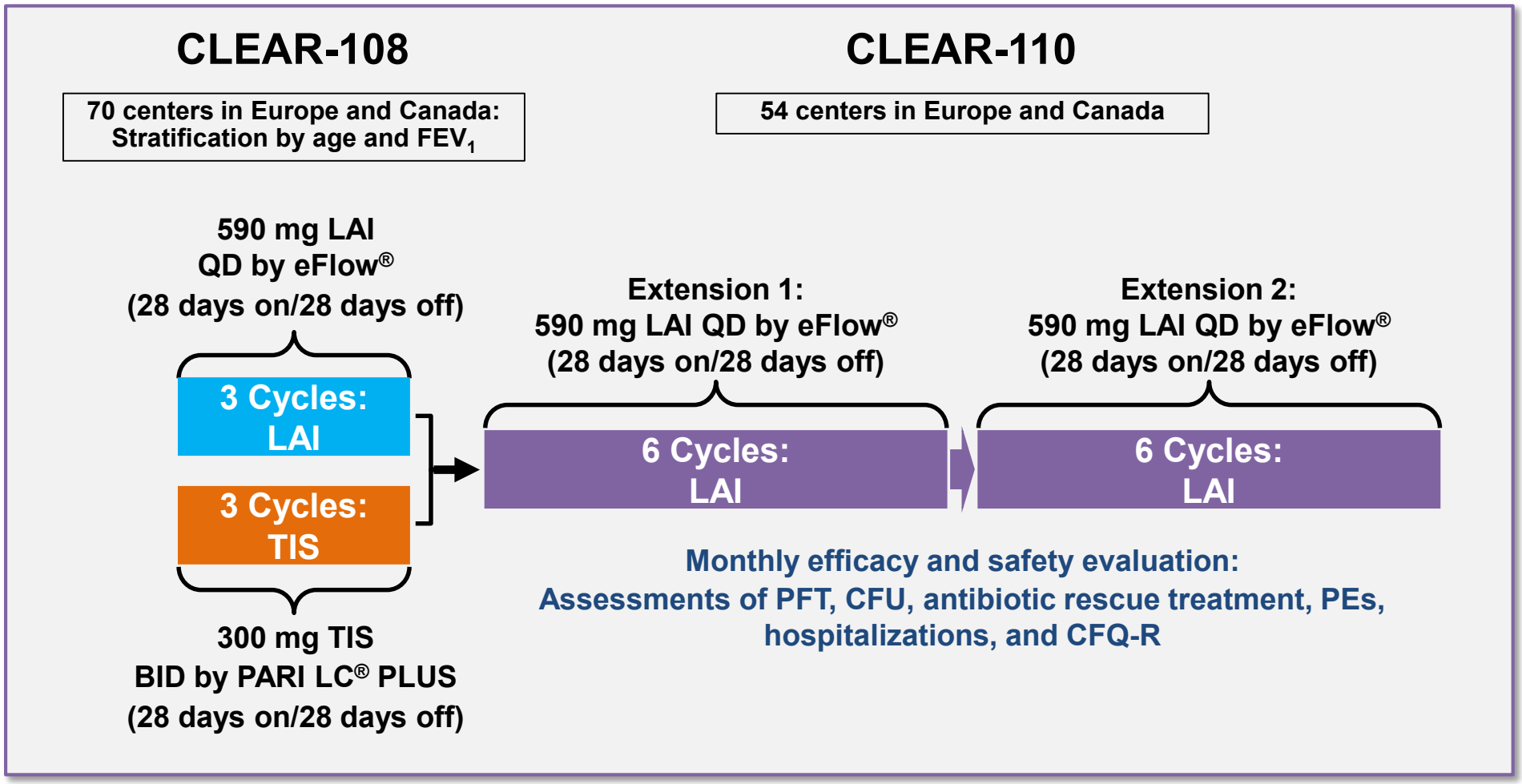
- Relevant financial relationships with a commercial interest:
  - Insmed Incorporated: Research Award, Now
  - Aradigm Corporation: Research Award, Expected
  - Gilead Sciences: Advisory Committee, Previously
  - Novartis Pharmaceuticals Corporation: Advisory Committee, Previously
  - Pharmaxis Ltd: Advisory Committee, Previously

Introduction

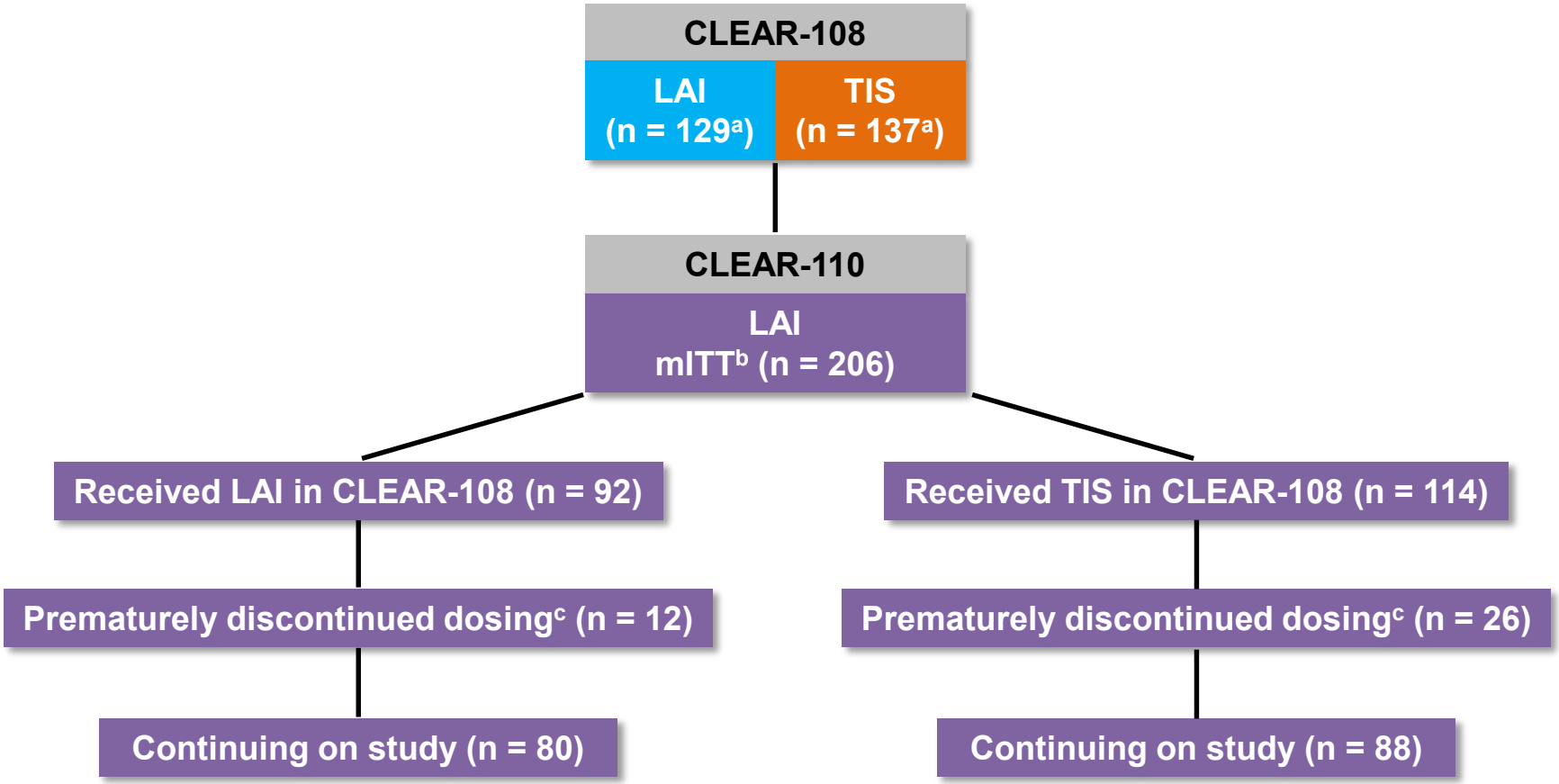
- Liposomal amikacin for inhalation (LAI) is a novel formulation of amikacin that is being developed for lung infections due to *Pseudomonas aeruginosa* (*Pa*) and nontuberculous mycobacteria (NTM)
- Charge neutral highly biocompatible liposomes (~0.3 μm) encapsulate amikacin and penetrate the biofilm to achieve a high drug concentration at the site of infection
- In CLEAR-108, once-daily LAI was noninferior to twice-daily tobramycin inhalation solution (TIS) with respect to the relative change from baseline to end of study (168 days) in forced expiratory volume in 1 second (FEV_1)
- Eligible patients who completed CLEAR-108 were enrolled in CLEAR-110, a phase 3, open-label study; all patients received LAI
- Primary objective of CLEAR-110 was to examine the long-term efficacy, safety, and tolerability of LAI

Study Design



BID, twice daily; CFQ-R, Cystic Fibrosis Questionnaire-Revised; CFU, colony-forming units; PEs, pulmonary exacerbations; PFT, pulmonary function testing; QD, once daily.

Patient Disposition



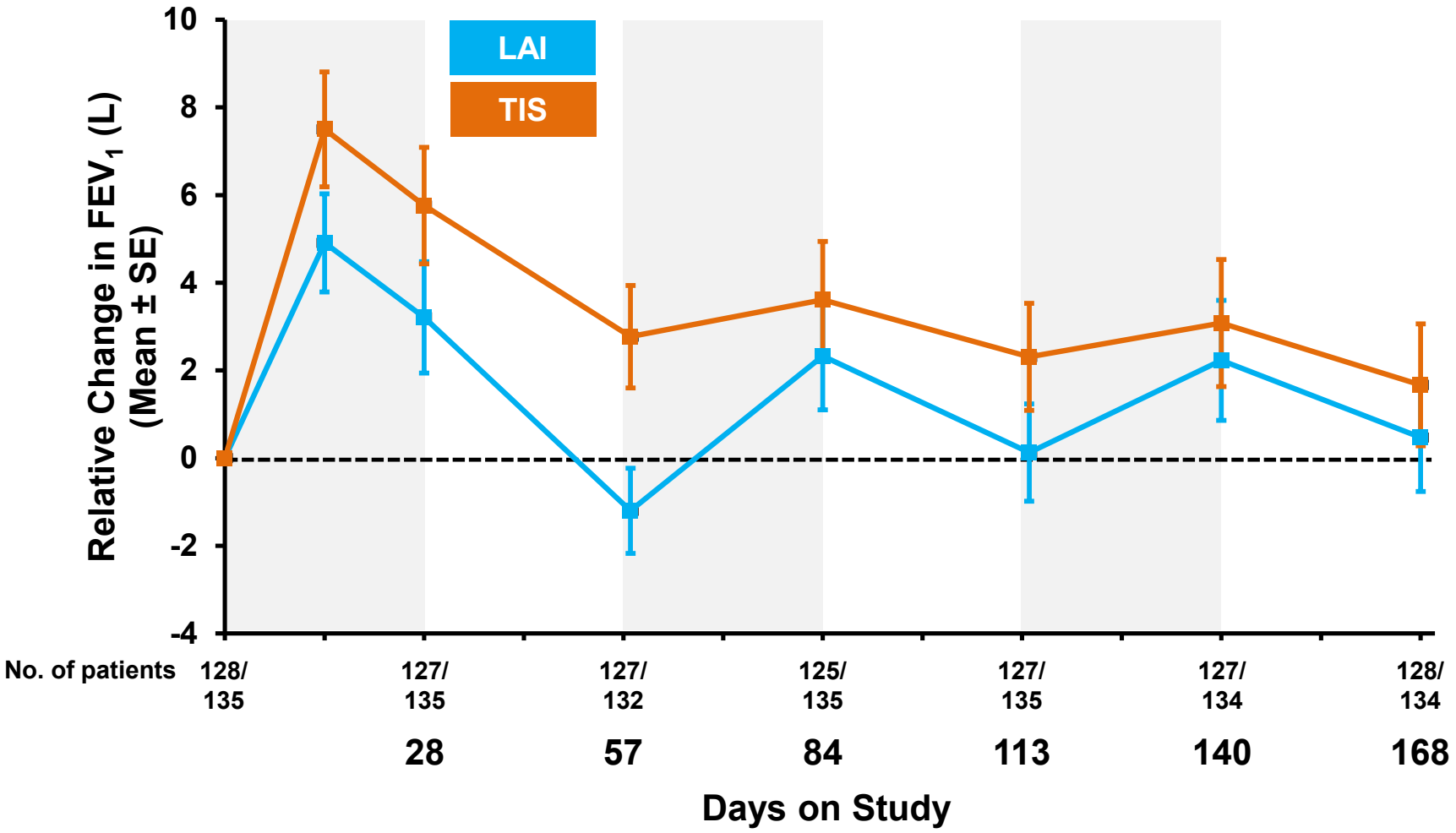
[a]Patients who completed dosing in CLEAR-108.
[b]All patients who received ≥1 dose of LAI in CLEAR-110. Data subject to analysis include those collected up to the December 31, 2013, cutoff, at which time 98 patients had completed 6 cycles of LAI in CLEAR-110.
[c]As of December 31, 2013.
mITT, modified intent-to-treat.

Demographics and Baseline Characteristics in CLEAR-110: By Prior Treatment Arm and Overall (Safety Population[a])

Variable	LAI[b] (n = 92)	TIS[b] (n = 114)	Overall (n = 206)
Race/ethnicity, n (%)			
White (not of Hispanic origin)	89 (96.7)	111 (97.4)	200 (97.1)
Hispanic	2 (2.2)	3 (2.6)	5 (2.4)
Asian	1 (1.1)	0	1 (0.5)
Sex, n (%)			
Male	47 (51.1)	56 (49.1)	103 (50.0)
Female	45 (48.9)	58 (50.9)	103 (50.0)
Age (years), mean (SD)	20.8 (10.09)	21.2 (9.47)	21.0 (9.73)
FEV_1 % predicted, mean (SD)	65.5 (23.44)	63.5 (22.94)	64.4 (22.07)

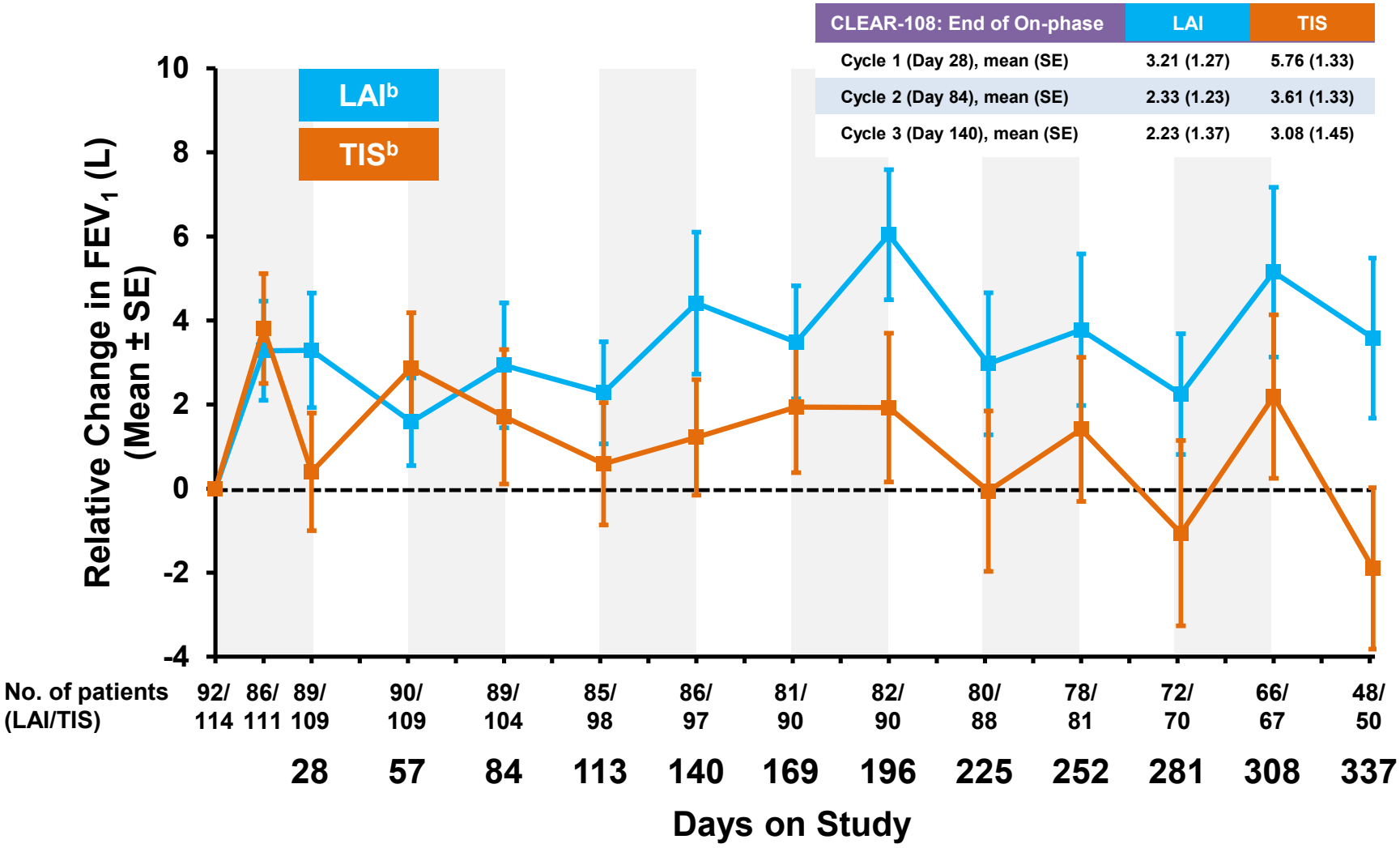
[a]All patients who received ≥1 dose of LAI in CLEAR-110.
[b]Per treatment arm in CLEAR-108. All patients in CLEAR-110 received LAI.
SD, standard deviation.

Relative Change in FEV_1 Over 3 Cycles in CLEAR-108 (Per-Protocol Population)



NOTE: Shaded regions represent 28 days on-treatment; dashed line represents baseline.
L, liter; SE, standard error.

Relative Change in FEV_1 Over 6 Cycles in CLEAR-110: By Prior Treatment Arm (mITT Population[a])

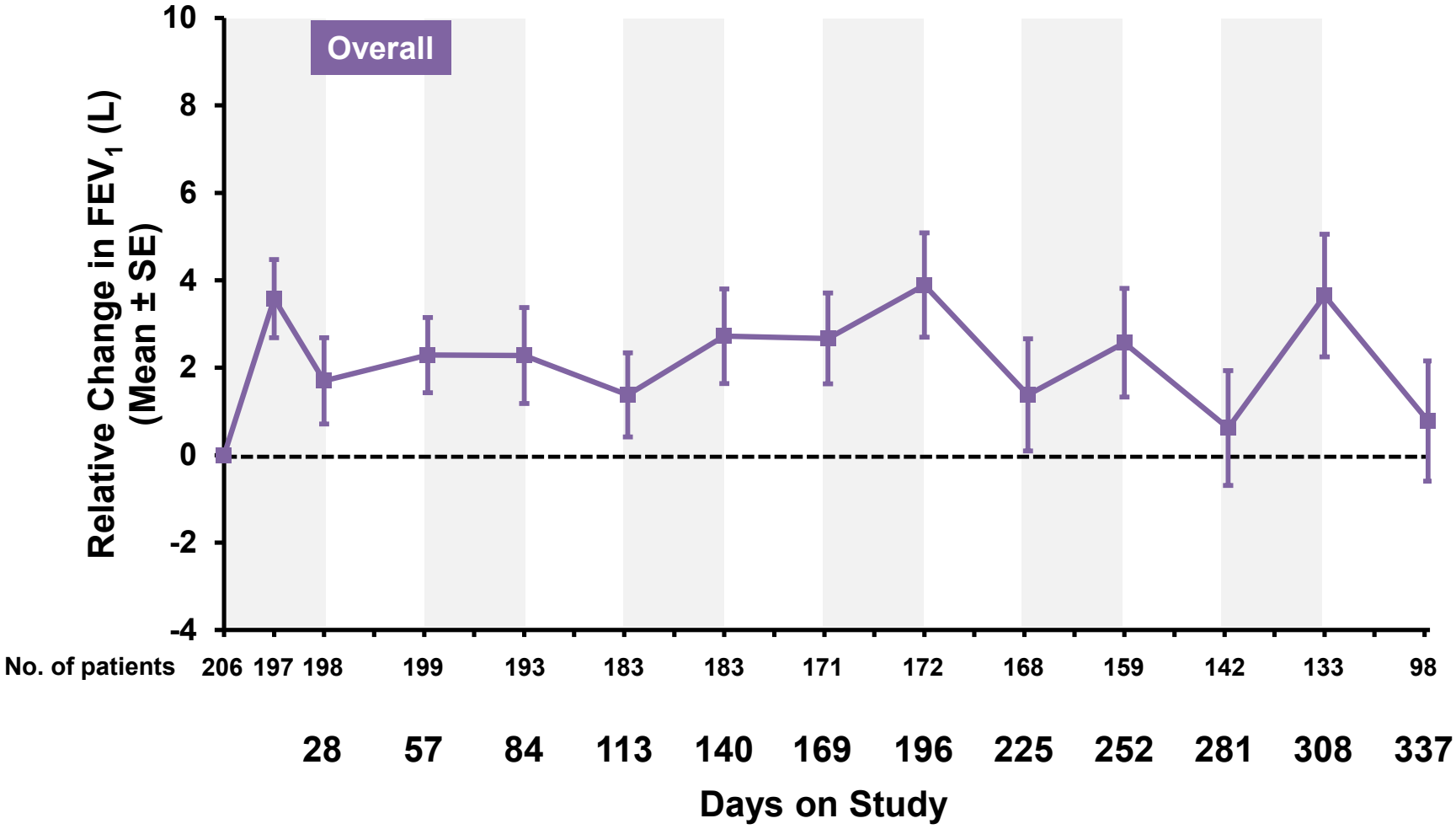


NOTE: Shaded regions represent 28 days on-treatment; dashed line represents baseline.

[a]All patients who received ≥1 dose of LAI in CLEAR-110.

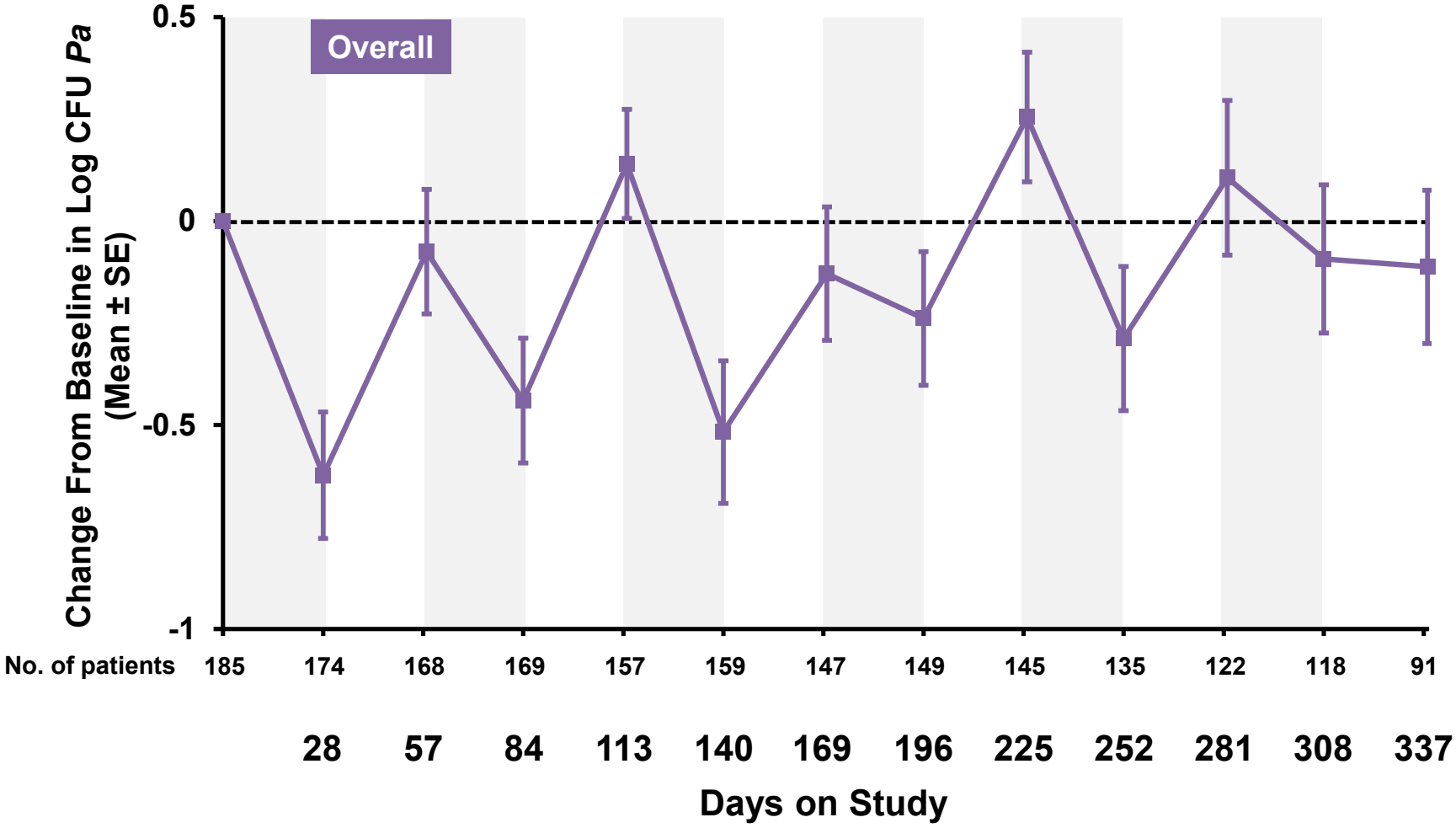
[b]Per treatment arm in CLEAR-108. All patients in CLEAR-110 received LAI.

Relative Change in FEV_1 Over 6 Cycles in CLEAR-110: Overall (mITT Population[a])



NOTE: Shaded regions represent 28 days on-treatment; dashed line represents baseline.
[a]All patients who received ≥1 dose of LAI in CLEAR-110.

Change in *Pa* Sputum Density From Baseline in CLEAR-110: Overall (mITT Population[a])



NOTE: Shaded regions represent 28 days on-treatment; dashed line represents baseline.
[a]All patients who received ≥1 dose of LAI in CLEAR-110.

Efficacy Summary

- FEV_1 was improved at the end of the on-phase of all 6 treatment cycles with LAI
- Patients who previously received LAI in CLEAR-108 appear to have a sustained improvement in FEV_1 with longer term exposure
- Overall, *Pa* sputum density reductions were similar between patients regardless of prior treatment assignment
- As the study was ongoing during this data cut, the number of subjects at Day 337 do not represent the complete dataset; therefore, although trends may be observed, conclusions cannot be drawn at this time

Overview of AEs in CLEAR-110: By Prior Treatment Arm and Overall (Safety Population[a])

Patients With:	LAI[b] (n = 92)	TIS[b] (n = 114)	Overall (n = 206)
TEAEs, n (%)	72 (78.3)	96 (84.2)	168 (81.6)
TEAEs by strongest relationship to study drug, n (%)			
Related	19 (20.7)	30 (26.3)	49 (23.8)
Not related	53 (57.6)	66 (57.9)	119 (57.8)
TEAEs by maximum severity, n (%)			
Grade 1: mild	26 (28.3)	27 (23.7)	53 (25.7)
Grade 2: moderate	39 (42.4)	55 (48.2)	94 (45.6)
Grade 3: severe	6 (6.5)	13 (11.4)	19 (9.2)
Grade 4: life-threatening or disabling	1 (1.1)	1 (0.9)	2 (1.0)
TEAEs by seriousness, n (%)			
Serious	21 (22.8)	37 (32.5)	58 (28.2)
Not serious	51 (55.4)	59 (51.8)	110 (53.4)
Treatment-emergent SAEs by strongest relationship to study drug, n (%)			
Related	1 (1.1)	3 (2.6)	4 (1.9)
Not related	20 (21.7)	34 (29.8)	54 (26.2)
TEAEs leading to study drug discontinuation, n (%)	0	14 (12.3)	14 (6.8)

[a]All patients who received ≥1 dose of LAI in CLEAR-110.
[b]Per treatment arm in CLEAR-108. All patients in CLEAR-110 received LAI.
AEs, adverse events; SAEs, serious AEs; TEAEs, treatment-emergent AEs.

TEAEs Reported by ≥10.0% of Patients in CLEAR-110: By Prior Treatment Arm and Overall (Safety Population[a])

System Organ Class Preferred Term	LAI[b] (n = 92)	TIS[b] (n = 114)	Overall (n = 206)
Infections and infestations, n (%)	70 (76.1)	83 (72.8)	153 (74.3)
Infective PE of CF, n (%)	48 (52.2)	70 (61.4)	118 (57.3)
Nasopharyngitis, n (%)	17 (18.5)	19 (16.7)	36 (17.5)
Upper respiratory tract infection, n (%)	13 (14.1)	14 (12.3)	27 (13.1)
Respiratory, thoracic, and mediastinal disorders, n (%)	34 (37.0)	44 (38.6)	78 (37.9)
Hemoptysis, n (%)	14 (15.2)	11 (9.6)	25 (12.1)
Cough, n (%)	12 (13.0)	12 (10.5)	24 (11.7)
Dysphonia, n (%)	8 (8.7)	15 (13.2)	23 (11.2)

[a]All patients who received ≥1 dose of LAI in CLEAR-110.
[b]Per treatment arm in CLEAR-108. All patients in CLEAR-110 received LAI.
CF, cystic fibrosis.

Safety Summary

- LAI administered once daily was generally safe and well tolerated in CF patients with chronic bronchopulmonary infection due to *Pa*
- In CLEAR-110, the majority of patients experienced ≥1 TEAE to LAI (81.6%); most were mild or moderate. As in CLEAR-108, there were no unexpected AEs, and the TEAEs were consistent with underlying CF disease
- SAEs were experienced by 28.2% of patients. These were primarily hospitalizations for the treatment of PEs; in 4 patients the events were considered related to study drug

Conclusions

- Based on the available data included in this analysis:
  - LAI may provide long-term improvement in pulmonary function in CF patients with bronchopulmonary infection caused by *Pa*
  - LAI is safe and well tolerated with prolonged exposure

Acknowledgments

- LAI Study Group
- Principal Investigator: Diana Bilton, MD, FRCP
- Arikace Steering Committee Members
- Accelsiors CRO & Consultancy Services
- Chiltern International Ltd
- ICON Central Laboratories
- PARI Pharma GmbH
- Vitalograph Ltd
- Xerimis Inc
- Cystic Fibrosis Foundation Therapeutics, Inc
- European Cystic Fibrosis Society−Clinical Trials Network
- Seattle Children's Hospital
- Patients