Poster #: 212

Long-Term Study of Liposomal Amikacin for Inhalation in Patients With Cystic Fibrosis and Chronic *Pseudomonas aeruginosa* Infection

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INTRODUCTION

- Liposomal amikacin for inhalation (LAI) is a novel formulation of amikacin currently in development for the treatment of patients with CF who have chronic lung infections caused by *Pseudomonas aeruginosa* and nontuberculous mycobacteria (NTM).[1,2]
- The Clinical Evaluation of ARIKAYCE™ (CLEAR)-108 study compared the efficacy, safety, and tolerability of 3 cycles of LAI once daily (QD) with tobramycin inhalation solution (TIS) twice daily (BID) in patients with CF and chronic bronchopulmonary infections due to *P. aeruginosa*.[3]
- In CLEAR-108[3]:
  - LAI given QD was noninferior to TIS given BID regarding the relative change from baseline to end of study (168 days) in forced expiratory volume in 1 second (FEV_1) (liters).
  - LAI was generally safe and well tolerated, with no unexpected adverse events.
- Eligible patients who completed CLEAR-108 were enrolled in CLEAR-110, a 2-year open-label extension study, in which all patients received LAI.[3,4]

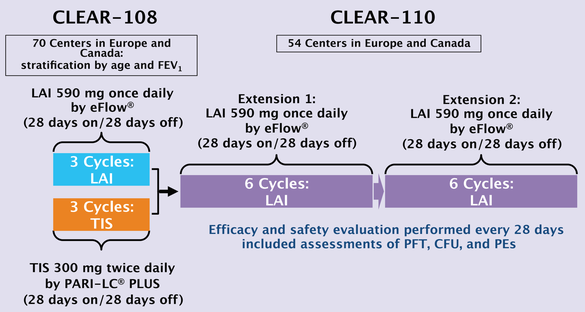
STUDY OBJECTIVE

- To determine the long-term safety, tolerability, and efficacy of LAI in patients with CF and chronic *P. aeruginosa* infection previously treated with LAI or TIS

METHODS

- **Figure 1** shows the CLEAR-108/110 study design.
- CLEAR-108 was a phase 3, multicycle, multicenter study.[3]
- CLEAR-110 was the phase 3, multicycle, multicenter extension study of CLEAR-108.
- Key eligibility criteria for CLEAR-108 included a confirmed diagnosis of CF; chronic infection with *P. aeruginosa*; age ≥6 years; FEV_1 ≥25 percent predicted; off inhaled antibiotics for 28 days before screening; tolerance to TIS.
- Eligible patients in CLEAR-108 were randomized 1:1 to 3 treatment cycles (28 days on/28 days off) of LAI 590 mg QD via a customized investigational eFlow® technology nebulizer (PARI Pharma GmbH) or TIS 300 mg BID via PARI-LC PLUS® nebulizer system, and stratified by age and FEV_1 percent predicted.[3]
- Patients who completed CLEAR-108 on study medication could consent to enroll in CLEAR-110 to receive up to 12 additional treatment cycles (one cycle is 28 days on/28 days off) of LAI 590 mg QD.
- Monthly efficacy and safety evaluations included pulmonary function tests, *P. aeruginosa* colony-forming unit (CFU) sputum assays, and adverse event (AE) assessments.

Figure 1. Study designs of CLEAR-108 and CLEAR-110

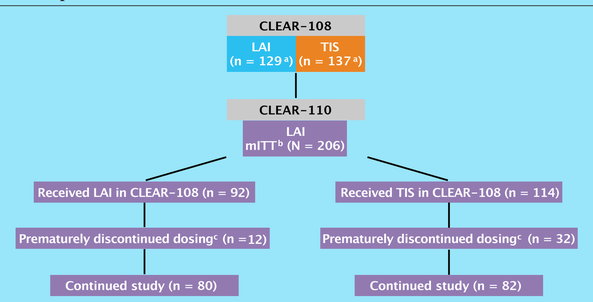


CFU, colony-forming units; CLEAR, Clinical Evaluation of ARIKAYCE study; FEV_1 forced expiratory volume in 1 second; LAI, liposomal amikacin for inhalation; PEs, pulmonary exacerbations; PFT, pulmonary function testing; TIS, tobramycin inhalation solution.

RESULTS

- Results are presented for patients who received at least one dose of LAI and completed up to 12 cycles of LAI treatment.
- Of 206 patients overall **(Figure 2)**, 134 completed through Year 2: 66 of 92 patients in the CLEAR-108 LAI group (prior LAI), and 68 of 114 patients in the CLEAR-108 TIS group (prior TIS).

Figure 2. Patient disposition[5]



CLEAR, Clinical Evaluation of ARIKAYCE study; LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat; TIS, tobramycin inhalation solution.
[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 March 17, 2014, data cut, at which time 147 patients had completed 6 cycles of treatment with LAI in CLEAR-110.
[c]As of March 17 2014.

Table 1. Demographics and Baseline Characteristics in CLEAR-110: By Prior Treatment Arm and Overall (mITT Population[a])

	Prior LAI[b] (n = 92)	Prior TIS[b] (n = 114)	Overall (N = 206)
Race/ethnicity, n (%)			
Caucasian (not of Hispanic origin)	89 (96.7)	111 (97.4)	200 (97.1)
Hispanic	2 (2.2)	3 (2.6)	5 (2.4)
African	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, mean (SD), y	20.8 (10.09)	21.2 (9.47)	21.0 (9.73)
FEV_1 (L), mean (SD)	2.1 (0.91)	2.1 (0.83)	2.1 (0.87)
FEV_1 percent predicted, mean (SD)	65.5 (23.44)	63.3 (20.83)	64.3 (22.01)

CLEAR, Clinical Evaluation of ARIKAYCE study; FEV_1, forced expiratory volume in 1 second; LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat; SD, standard deviation; TIS, tobramycin inhalation solution.
[a]All patients who received ≥1 dose of LAI in CLEAR-110. Baseline is defined as the measurement at the most recent time point prior to the administration of the first dose of LAI in CLEAR-110.
[b]Per treatment arm in CLEAR-108. All patients in CLEAR-110 received LAI.

Safety Summary

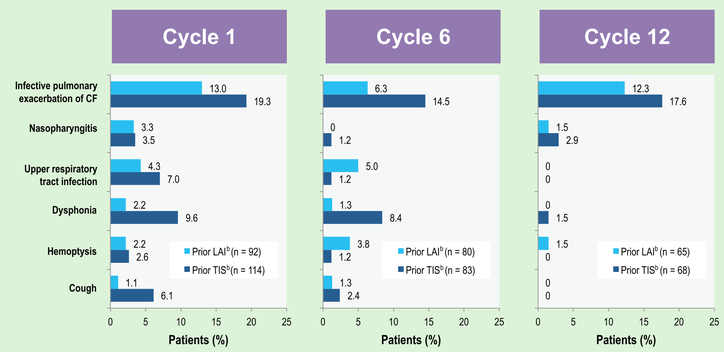
- The majority (84.5%) of patients in CLEAR-110 had ≥1 treatment-emergent AE and, as in CLEAR-108, most AEs were respiratory in nature.
- Reported AEs in both CLEAR-108 and CLEAR-110 were consistent with those expected in a population of patients with CF.
- In both treatment groups, similar trends in treatment-emergent adverse events (TEAEs) were observed in CLEAR-108 and CLEAR-110 **(Table 2)**.
- Upper respiratory tract infection, dysphonia, hemoptysis, and cough decreased from Cycle 1 to Cycle 12 in both treatment groups **(Figure 3)**.
- Most TEAEs were mild or moderate in severity.
- 20 of 92 (21.7%) patients in the prior LAI group and 32 of 114 (28.1%) in the prior TIS group had TEAEs related to the study drug.
- 4 (4.3%) patients in the prior LAI group and 17 (14.9%) in the prior TIS group discontinued study drug because of an AE.
- 62 (67.4%) patients in the prior LAI group and 87 (76.3%) in the prior TIS group had a TEAE requiring treatment for a pulmonary exacerbation.
- 1 (1.1%) patient in the prior LAI group and 4 (3.5%) in the prior TIS group had ≥1 serious TEAE related to the study drug.
- 1 patient in the LAI group who was on-study for 1 year died; this death was due to renal failure and infective pulmonary exacerbation of CF, and was not considered related to the study drug.

Table 2. Overview of the Most Frequently Reported TEAEs in CLEAR-108 and CLEAR-110 (On-Treatment, Safety Population[a])

	CLEAR-108		CLEAR-110 (Cycle 6)			CLEAR-110 (Cycle 12)		
System Organ Class Preferred Term	LAI (n = 148)	TIS (n = 146)	Prior LAI[b] (n = 92)	Prior TIS[b] (n = 114)	Overall (N = 206)	Prior LAI[b] (n = 92)	Prior TIS[b] (n = 114)	Overall (N = 206)
Patients with ≥1 TEAE, n (%)	125 (84.5)	115 (78.8)	75 (81.5)	99 (86.8)	174 (84.5)	79 (85.9)	104 (91.2)	183 (88.8)
Infections and infestations, n (%)	112 (75.7)	104 (71.2)	74 (80.4)	90 (78.9)	164 (79.6)	78 (84.8)	97 (85.1)	175 (85.0)
Infective pulmonary exacerbation of CF	82 (55.4)	71 (48.6)	52 (56.5)	74 (64.9)	126 (61.2)	63 (68.5)	86 (75.4)	149 (72.3)
Nasopharyngitis	24 (16.2)	33 (22.6)	21 (22.8)	23 (20.2)	44 (21.4)	24 (26.1)	28 (24.6)	52 (25.2)
Upper respiratory tract infection	15 (10.1)	9 (6.2)	14 (15.2)	14 (12.3)	28 (13.6)	15 (16.3)	17 (14.9)	32 (15.5)
Rhinitis	9 (6.1)	9 (6.2)	7 (7.6)	5 (4.4)	12 (5.8)	9 (9.8)	7 (6.1)	16 (7.8)
Pharyngitis	0 (0.0)	3 (2.1)	7 (7.6)	5 (4.4)	12 (5.8)	8 (8.7)	10 (8.8)	18 (8.7)
Sinusitis	7 (4.7)	5 (3.4)	8 (8.7)	3 (2.6)	11 (5.3)	9 (9.8)	6 (5.3)	15 (7.3)
Viral infection (clinical diagnosis)	4 (2.7)	4 (2.7)	6 (6.5)	5 (4.4)	11 (5.3)	8 (8.7)	7 (6.1)	15 (7.3)
Respiratory, thoracic, and mediastinal disorders, n (%)	59 (39.9)	42 (28.8)	36 (39.1)	46 (40.4)	82 (39.8)	40 (43.5)	52 (45.6)	92 (44.7)
Hemoptysis	24 (16.2)	10 (6.8)	16 (17.4)	12 (10.5)	28 (13.6)	19 (20.7)	13 (11.4)	32 (15.5)
Dysphonia	18 (12.2)	8 (5.5)	8 (8.7)	16 (14.0)	24 (11.7)	9 (9.8)	16 (14.0)	25 (12.1)
Cough	18 (12.2)	11 (7.5)	10 (10.9)	12 (10.5)	22 (10.7)	11 (12.0)	16 (14.0)	27 (13.1)
Oropharyngeal pain	11 (7.4)	6 (4.1)	5 (5.4)	7 (6.1)	12 (5.8)	7 (7.6)	9 (7.9)	16 (7.8)

CF, cystic fibrosis; CLEAR, Clinical Evaluation of ARIKAYCE study; LAI, liposomal amikacin for inhalation; TEAE, treatment-emergent adverse event; TIS, tobramycin inhalation solution.
[a]All patients who received ≥1 dose of LAI in CLEAR-108 and CLEAR-110.
[b]Per treatment arm in CLEAR-108. All patients in CLEAR-110 received LAI.

Figure 3. Most frequently reported TEAEs in CLEAR-110: by treatment cycle (on-treatment, safety population[a])

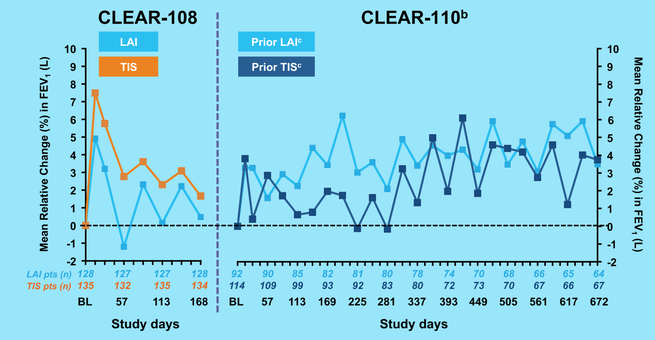


CF, cystic fibrosis; CLEAR, Clinical Evaluation of ARIKAYCE study; LAI, liposomal amikacin for inhalation; TEAE,treatment-emergent adverse event; TIS, tobramycin inhalation solution.
[a]All patients who received ≥1 dose of LAI in CLEAR-110.
[b]Per treatment arm in CLEAR-108. All patients in CLEAR-110 received LAI.

Efficacy Summary

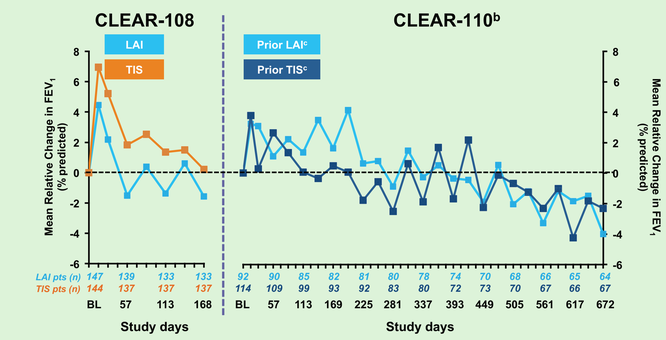
- Both treatment groups in CLEAR-110 showed improvements in the mean relative change in FEV_1 (L) from baseline to the end of the study **(Figure 4)**.
  - At the end of the twelfth off-treatment cycle in CLEAR-110 (Day 672), FEV_1 (L) continued to show improvements from baseline values, with a mean relative change of 3.49% and 3.74% for patients previously treated with LAI and TIS, respectively.
- Both treatment groups in CLEAR-110 showed small decreases in the mean relative change in FEV_1 percent predicted **(Figure 5)**.
- Reductions in *P. aeruginosa* sputum density were similar at the end of 12 cycles of LAI between those who previously received LAI and TIS **(Figure 6)**.
- In CLEAR-110, LAI maintained *P. aeruginosa* sputum densities at levels that were similar to CLEAR-108 baseline levels.
- Changes from baseline in *P. aeruginosa* sputum density were comparable between groups regardless of prior treatment, with a mean (SD) change of 0.020 (2.56) log CFU/g for all patients between the beginning of Cycle 1 and the end of Cycle 12.

Figure 4. Mean relative change (%) in FEV_1 (L) from baseline to end of study over 3 cycles in CLEAR-108 and over 12 cycles in CLEAR-110 (mITT population[a])



BL, baseline; CLEAR, Clinical Evaluation of ARIKAYCE study; FEV_1, forced expiratory volume in 1 second; LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat; pts, patients; TIS, tobramycin inhalation solution.
[a]All patients who received ≥1 dose of LAI in CLEAR-110. Baseline was defined as the measurement at the most recent time point prior to the administration of the first dose of LAI in CLEAR-110.
[b]All patients in CLEAR-110 received LAI.
[c]Per treatment arm in CLEAR-108.

Figure 5. Mean relative change in FEV_1 percent predicted from baseline to the end of the study (mITT population[a])



BL, baseline; CLEAR, Clinical Evaluation of ARIKAYCE study; FEV_1, forced expiratory volume in 1 second; LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat; pts, patients; TIS, tobramycin inhalation solution.
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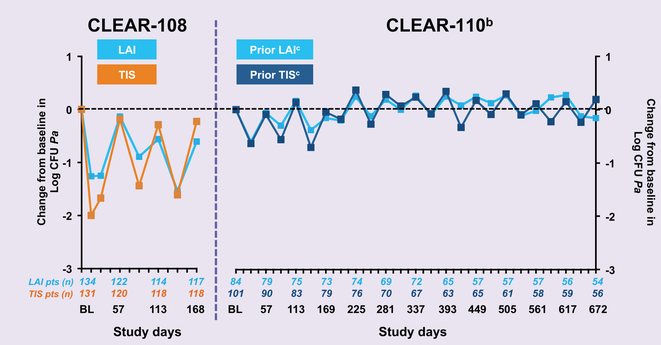
[b]All patients in CLEAR-110 received LAI.
[c]Per treatment arm in CLEAR-108.

Figure 6. Mean change from baseline in *Pseudomonas aeruginosa* sputum density in CLEAR-108 and CLEAR-110 (mITT population[a])



BL, baseline; CFU, colony forming unit; CLEAR, Clinical Evaluation of ARIKAYCE study; FEV_1, forced expiratory volume in 1 second; LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat; *Pa*, *Pseudomonas aeruginosa*; pts, patients; TIS, tobramycin inhalation solution.
[a]All patients who received ≥1 dose of LAI in CLEAR-110. Baseline was defined as the measurement at the most recent time point prior to the administration of the first dose of LAI in CLEAR-110.
[b]All patients in CLEAR-110 received LAI.
[c]Per treatment arm in CLEAR-108.

CONCLUSIONS

- LAI was generally safe and well tolerated, with no unexpected adverse events.
- Patients with CF and chronic *P. aeruginosa* infection who continued treatment with LAI for 12 cycles or who switched from TIS to LAI for 12 cycles had similar changes in FEV_1 (L) and FEV_1 percent predicted, regardless of the prior treatment.
- Changes from baseline in *P. aeruginosa* sputum density were similar, regardless of prior treatment.

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3. Bilton D, Pressler T, Fajac I, et al. Poster presented at: the 2013 North American Cystic Fibrosis Conference (NACFC); October 17-19, 2013; Salt Lake City, UT. Poster 235.
4. Bilton D, Pressler T, Fajac I, et al. Oral presentation presented at: the European Respiratory Society (ERS) International Congress; September 6-10, 2014; Munich, Germany. Abstract 3445.
5. Bilton D, Pressler T, Fajac I, et al. Poster presented at: the 2014 North American Cystic Fibrosis Conference (NACFC); October 9-11, 2014; Atlanta, GA. Poster 284.

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DISCLOSURES

Michael Konstan, MD, has served on the Arikayce Clinical Program Steering Committee and has served on advisory boards for Genentech, Gilead, Novartis, Savara, and Vertex. Isabelle Fajac, MD, PhD, has received research contract support from Insmed Incorporated, has received a research grant from Actelion, and has served on advisory boards for Gilead and Vertex. John P. Clancy, MD, has served on the Arikayce Clinical Program Steering Committee. Tacjana Pressler, Dorota Sands, Predrag Minic, Ivanka Galeva, and Marco Cipolli have received research contract support from Insmed Incorporated. Amparo Solé, MD, PhD, has served on the advisory board for Gilead Sciences and Vertex. Rebecca Monroe, John P. McGinnis II, and Gina Eagle are employees of Insmed Incorporated, Bridgewater, NJ, USA. Diana Bilton, MD, FRCP, has received a research award from Insmed Incorporated and has served on the Advisory Committees for Gilead Sciences, Novartis, and Pharmaxis Ltd.

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