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

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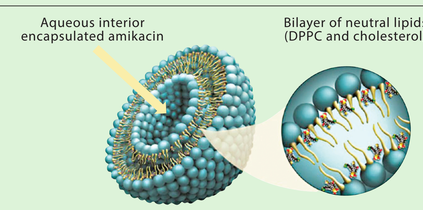
Poster # 284

INTRODUCTION

- Liposomal amikacin for inhalation (LAI) is a novel formulation of amikacin currently in development for the treatment of patients with lung infections caused by *Pseudomonas aeruginosa* and nontuberculous mycobacteria (NTM).[1,2]
- LAI is composed of charge-neutral, highly biocompatible liposomes (~0.3 μm) that encapsulate amikacin and penetrate the biofilm to achieve a high drug concentration at the site of infection (**Figure 1**).[1,2]
- Key features of LAI include[1]:
  - High lung concentration (C_{max}) and area under the curve (AUC), as well as longer half-life ($t_{½}$), which result in improved AUC: minimum inhibitory concentration (MIC) ratio that enables once-daily dosing
  - Potent *P aeruginosa* killing, including resistant isolates
  - Additional release of amikacin from LAI when virulence factors are secreted by *P aeruginosa*
  - Potent in vitro and in vivo NTM killing that is superior to amikacin solution
- In preclinical studies, the lung level of LAI administered once daily (QD) was approximately 5 times greater than the level of an equivalent amount of tobramycin inhalation solution (TIS), USP, given twice daily (BID).[1]

Figure 1. Schematic diagram of LAI liposome encapsulating amikacin



LAI, liposomal amikacin for inhalation; DPPC, dipalmitoylphosphatidylcholine.

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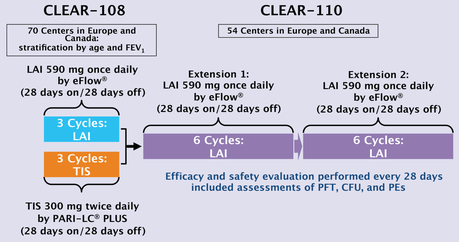
- The Clinical Evaluation of ARIKAYCE (CLEAR)-108 study compared the efficacy, safety, and tolerability of 3 cycles of LAI QD with TIS BID in patients with cystic fibrosis (CF) and chronic bronchopulmonary infections due to *P aeruginosa*.[3,4]
- In CLEAR-108[3]:
  - LAI given QD was noninferior to TIS given BID with respect to the relative change from baseline to end of study (168 days) in forced expiratory volume in 1 second (FEV_1).
  - LAI was generally safe and well tolerated, and no unexpected adverse events were observed.
- Eligible patients who completed CLEAR-108 were enrolled in CLEAR-110, a currently ongoing, phase 3, open-label study, in which all patients received LAI.
- The primary goal of this interim analysis was to evaluate the long-term efficacy, safety, and tolerability of up to 6 cycles (alternating 28 days on / 28 days off) of LAI treatment in patients previously treated with LAI and TIS.

METHODS

- The CLEAR-108/110 study design is presented in **Figure 2**.
- CLEAR-108/110 were phase 3, open-label, multicycle, multicenter studies conducted at 70 centers and 18 countries in Europe and Canada.
- In CLEAR-108, key eligibility criteria included:
  - Confirmed diagnosis of CF
  - FEV_1 ≥25%
  - Age ≥6 years
  - Chronic *P aeruginosa* infection
  - Off inhaled antibiotics for 28 days prior to screening
  - Tolerant of TIS
- Eligible patients in CLEAR-108 were randomized 1:1 to receive 3 treatment cycles (alternating 28 days on / 28 days off) of LAI 590 mg QD via eFlow® nebulizer system (PARI Pharma GmbH) or TIS 300 mg BID via PARI LC PLUS® nebulizer.
  - Patients were stratified by age and FEV_1 percent predicted.

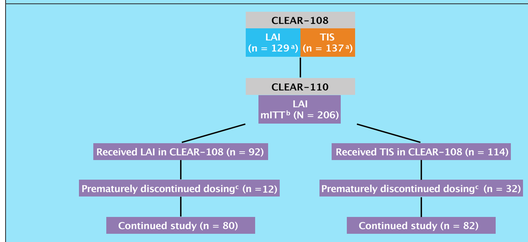
Figure 2. CLEAR-108 and CLEAR-110 study designs



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.

- Patients who completed CLEAR-108 on study medication were eligible to enroll in the CLEAR-110 study to receive up to an additional 12 treatment cycles of LAI 590 mg QD.
- Efficacy and safety evaluations performed during study visits every 28 days included:
  - Pulmonary function testing
  - Colony-forming unit assays
  - Adverse event assessments

Figure 3. Patient disposition



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 % 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.

RESULTS

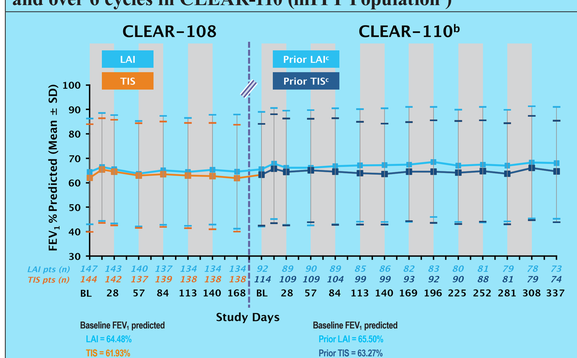
Efficacy Summary

- Patients in both treatment groups entered CLEAR-110 with a higher baseline FEV_1 than their respective baseline values in CLEAR-108 (**Figures 4** and **5**).
  - At the end of the sixth off-treatment cycle in CLEAR-110, FEV_1 showed sustained improvement above baseline values, with a relative mean change of 3.39% and 1.11% for patients previously treated with LAI and TIS, respectively.
  - Patients who previously received LAI in CLEAR-108 appear to have a sustained improvement in FEV_1 with longer-term exposure.
- Overall, reductions in *P aeruginosa* sputum density were similar in all patients regardless of prior treatment (**Figure 6**).
  - In CLEAR-110, LAI continues to show the ability to manage *P aeruginosa* colonies, as demonstrated by the maintained reductions in *P aeruginosa* sputum density at levels that were below CLEAR-108 baseline levels.
- Because the study was ongoing at the time of the data cut of March 17, 2014, the number of patients at day 337 does not represent the complete dataset. Therefore, although trends may be observed, conclusions cannot be drawn at the present time.

Safety and Tolerability Summary

- In CLEAR-108, the number of patients who experienced ≥1 treatment-emergent adverse event (TEAE) decreased from 77 (52.0%) in Cycle 1 to 53 (39.6%) in Cycle 3 on LAI; the proportion of patients who experienced ≥1 TEAE on TIS was similar between Cycle 1 (52 [35.6%]) and Cycle 3 (47 [34.6%]) (**Table 2**, **Figures 7** and **8**).
- A similar trend was observed in CLEAR-110, with continued reductions in TEAEs from Cycle 1 to Cycle 6 for both treatment groups (**Table 2**, **Figures 7** and **8**).
- The majority of adverse events were respiratory in nature, with the highest frequency occurring in Cycle 1 for patients entering CLEAR-110 from the TIS arm (21.1% vs 8.6% for Cycles 1 and 6, respectively). For patients entering from the LAI arm, respiratory adverse events were 7.6% vs 8.9% for Cycles 1 and 6, respectively (**Table 2**, **Figures 7** and **8**).

Figure 4. Mean FEV_1 percent predicted over 3 cycles in CLEAR-108 and over 6 cycles in CLEAR-110 (mITT Population[a])



Note. Shaded regions represent 28 days on treatment.

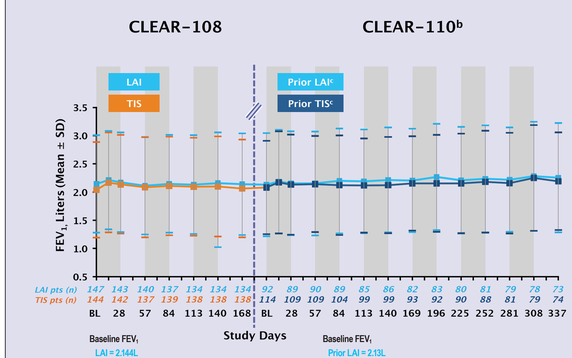
BL, baseline; CLEAR, Clinical Evaluation of ARIKAYCE study; FEV_1, forced expiratory volume in 1 second; LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat; pts, patients; SD, standard deviation; TIS, tobramycin inhalation solution.

[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 FEV_1 over 3 cycles in CLEAR-108 and over 6 cycles in CLEAR-110 (mITT population[a])



Note. Shaded regions represent 28 days on treatment.

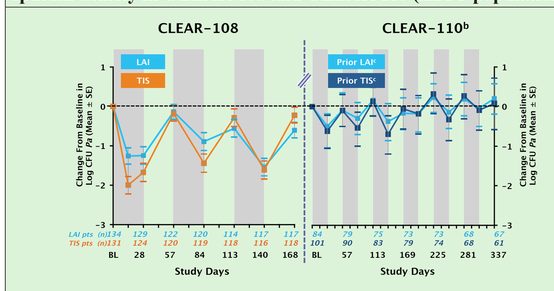
BL, baseline; CLEAR, Clinical Evaluation of ARIKAYCE study; FEV_1, forced expiratory volume in 1 second; LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat; pts, patients; SD, standard deviation; TIS, tobramycin inhalation solution.

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



CFU, colony-forming units; CLEAR, Clinical Evaluation of ARIKAYCE study; FEV_1, forced expiratory volume in 1 second; LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat; SE, standard error; *Pa*, *Pseudomonas aeruginosa*; 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-1.

[b]All patients in CLEAR-110 received LAI.

[c]Per treatment arm in CLEAR-108.

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

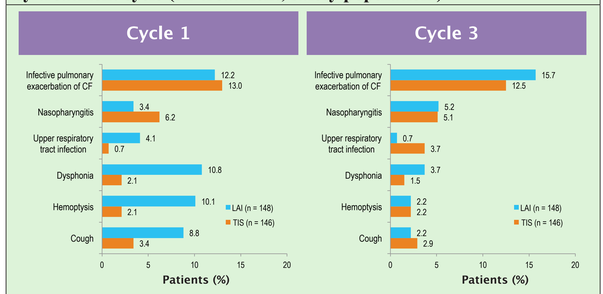
	CLEAR-108			CLEAR-110		
System Organ Class Preferred Term	**LAI (n = 148)**	**TIS (n = 146)**	**Overall (N = 294)**	**Prior LAI[b] (n = 92)**	**Prior TIS[b] (n = 114)**	**Overall (N = 206)**
Patients with ≥1 TEAE, n (%)	125 (84.5)	115 (78.8)	240 (81.6)	75 (81.5)	99 (86.8)	174 (84.5)
Infections and infestations, n (%)	112 (75.7)	104 (71.2)	216 (73.5)	74 (80.4)	90 (78.9)	164 (79.6)
Infective pulmonary exacerbation of CF	82 (55.4)	71 (48.6)	153 (52.0)	52 (56.5)	74 (64.9)	126 (61.2)
Nasopharyngitis	24 (16.2)	33 (22.6)	57 (19.4)	21 (22.8)	23 (20.2)	44 (21.4)
Upper respiratory tract infection	15 (10.1)	9 (6.2)	24 (8.2)	14 (15.2)	14 (12.3)	28 (13.6)
Rhinitis	9 (6.1)	9 (6.2)	18 (6.1)	7 (7.6)	5 (4.4)	12 (5.8)
Pharyngitis	0 (0.0)	3 (2.1)	3 (1.0)	7 (7.6)	5 (4.4)	12 (5.8)
Sinusitis	7 (4.7)	5 (3.4)	12 (4.1)	8 (8.7)	3 (2.6)	11 (5.3)
Viral infection (clinical diagnosis)	4 (2.7)	4 (2.7)	8 (2.7)	6 (6.5)	5 (4.4)	11 (5.3)
Respiratory, thoracic, and mediastinal disorders, n (%)	59 (39.9)	42 (28.8)	101 (34.4)	36 (39.1)	46 (40.4)	82 (39.8)
Hemoptysis	24 (16.2)	10 (6.8)	34 (11.6)	16 (17.4)	12 (10.5)	28 (13.6)
Dysphonia	18 (12.2)	8 (5.5)	26 (8.8)	8 (8.7)	16 (14.0)	24 (11.7)
Cough	18 (12.2)	11 (7.5)	29 (9.9)	10 (10.9)	12 (10.5)	22 (10.7)
Oropharyngeal pain	11 (7.4)	6 (4.1)	17 (5.8)	5 (5.4)	7 (6.1)	12 (5.8)

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.

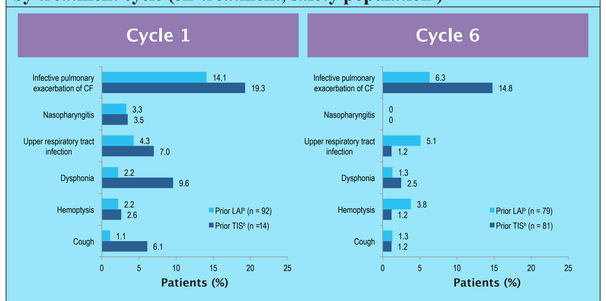
Figure 7. Most frequently reported TEAEs by patients in CLEAR-108: by treatment cycle (on-treatment, safety population[a])



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-108.

Figure 8. Most frequently reported TEAEs by patients 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.

CONCLUSIONS

- Based on the available data included in this analysis:
  - LAI provides sustained improvement in pulmonary function in patients with CF who have bronchopulmonary infection caused by *P aeruginosa*.
  - LAI has a favorable tolerability profile with prolonged exposure, with most adverse events being respiratory in nature.
  - Bacterial load and sputum density were maintained at baseline levels.
- Data from ongoing data analyses will provide further understanding of factors that may have an impact on patient response.
- Additional studies are warranted in patients for whom LAI may afford additional benefit.

References

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Amparo Solé, MD, PhD has served on the Advisory board for Gilead Sciences and Vertex.

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