Poster **235**

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Phase 3 Efficacy and Safety Data from Randomized, Multicenter Study of Liposomal Amikacin for Inhalation (Arikace®) Compared with TOBI® in Cystic Fibrosis Patients with Chronic Infection Due to *Pseudomonas aeruginosa*

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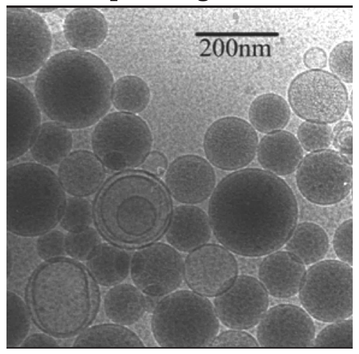
Introduction

Liposomal Amikacin for Inhalation (LAI): Nonclinical Summary

- LAI is a novel lipid formulation of amikacin (**Figure 1**) for inhalation that is being developed for lung infections due to *Pseudomonas aeruginosa (Pa)* and nontuberculous mycobacteria (NTM)
- **Key Features of LAI**
  - —Charge neutral highly biocompatible liposomes (~0.3 µm) encapsulating amikacin
  - —Penetration of drug into biofilm
  - —High lung concentration (C_{max}), area under the curve (AUC), and half-life ($t_{½}$)⇒ improved AUC:minimum inhibitory concentration (MIC) ratio
  - —Potent *Pa* killing, including resistant isolates
  - —Virulence factors secreted by *Pa* facilitate further release of amikacin from LAI
  - —Potent *in vitro* and *in vivo* NTM killing that is superior to amikacin solution

Figure 1. Cryo-Electron Microscopic Image of LAI



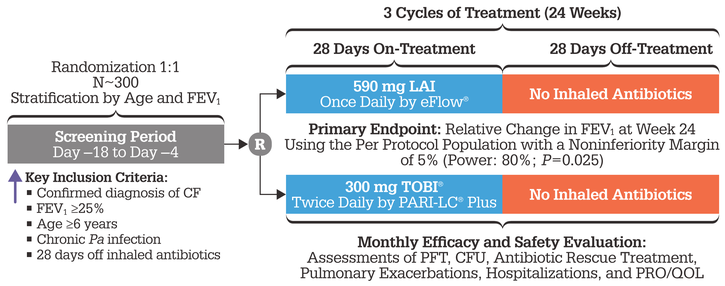
LAI, liposomal amikacin for inhalation.

CLEAR-108: Primary Objective

- To evaluate the efficacy, safety, and tolerability of 3 cycles of once-daily LAI in patients with cystic fibrosis (CF) with chronic bronchopulmonary infections due to *Pa*

Methods

Figure 2. CLEAR-108 Study Design



CF, cystic fibrosis; CFU, colony-forming units; FEV_1, forced expiratory volume in 1 second; LAI, liposomal amikacin for inhalation; *Pa*, *Pseudomonas aeruginosa*; PFT, pulmonary function testing; PRO, patient-reported outcome; QOL, quality of life; TOBI®, tobramycin inhalation solution.

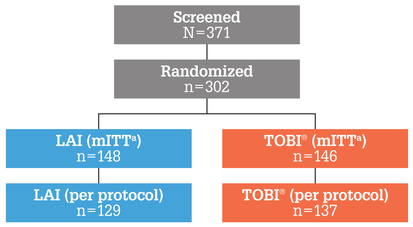
- A multicenter study was conducted in 73 sites in Europe and Canada
- Upon completion of CLEAR-108, eligible patients were rolled over to a multicycle (up to 2 years) study of LAI (CLEAR-110)

Results

CLEAR-108: Safety Summary

- LAI administered once daily was generally safe and well tolerated in patients with CF with chronic bronchopulmonary infection due to *Pa*
- The majority of patients in the LAI (84.5%) and tobramycin inhalation solution (TOBI®; 78.8%) treatment groups experienced ≥1 treatment-emergent adverse event (TEAE); most were mild or moderate. There were no unexpected adverse events, and the TEAEs were consistent with underlying CF disease
- Serious adverse events (SAEs), primarily hospitalizations for the treatment of pulmonary exacerbations, were experienced by 17.6% and 19.9% of LAI and TOBI® patients, respectively; SAEs were considered related to study drug in 1 patient given LAI (FEV_1 decreased) and 1 patient given TOBI® (infective pulmonary exacerbation of CF)

Figure 3. Patient Disposition



[a]All patients who received at least 1 dose of study drug.

LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat; TOBI®, tobramycin inhalation solution.

Table 1. Demographic and Baseline Characteristics (mITT Population)

Variable		LAI 590 mg Once Daily (n=148)	TOBI® 300 mg Twice Daily (n=146)	Total (n=294)
Race/ethnicity, n (%)				
White (not of Hispanic origin)		139 (93.9)	141 (96.6)	280 (95.2)
Hispanic		5 (3.4)	3 (2.1)	8 (2.7)
African		1 (0.7)	0	1 (0.3)
Asian		0	0	0
Other		3 (2.0)	1 (0.7)	4 (1.4)
Sex, n (%)	Male	79 (53.4)	76 (52.1)	155 (52.7)
	Female	69 (46.6)	70 (47.9)	139 (47.3)
Age	Mean (SD)	22.8 (10.2)	22.0 (10.0)	22.4 (10.1)
	6–12 years, n (%)	27 (18.2)	26 (17.8)	53 (18.0)
	13–18 years, n (%)	34 (23.0)	33 (22.6)	67 (22.8)
	>18 years, n (%)	87 (58.8)	87 (59.6)	174 (59.2)
Height (cm), mean (SD)		162.3 (15.0)	162.2 (15.6)	162.3 (15.2)
Weight (kg), mean (SD)		54.5 (17.2)	53.1 (15.9)	53.8 (16.5)
BMI (kg/m²), mean (SD)		20.1 (4.0)	19.7 (3.7)	19.9 (3.9)
CF genotype at screening, n (%)				
ΔF508 homozygous		72 (48.6)	70 (47.9)	142 (48.3)
ΔF508 heterozygous		40 (27.0)	43 (29.5)	83 (28.2)
Other		21 (14.2)	25 (17.1)	46 (15.6)
FEV_1 % predicted				
n		148	144	292
Mean (SD)		64.5 (21.5)	61.9 (22.0)	63.2 (21.7)
25%–50%, n (%)		42 (28.4)	44 (30.1)	86 (29.3)
>50%–75%, n (%)		54 (36.5)	55 (37.7)	109 (37.1)
>75%, n (%)		52 (35.1)	47 (32.2)	99 (33.7)
FEV_1 (L)	n	148	144	292
	Mean (SD)	2.142 (0.861)	2.037 (0.846)	2.090 (0.854)

BMI, body mass index; CF, cystic fibrosis; FEV_1, forced expiratory volume in 1 second; LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat; SD, standard deviation; TOBI®, tobramycin inhalation solution.

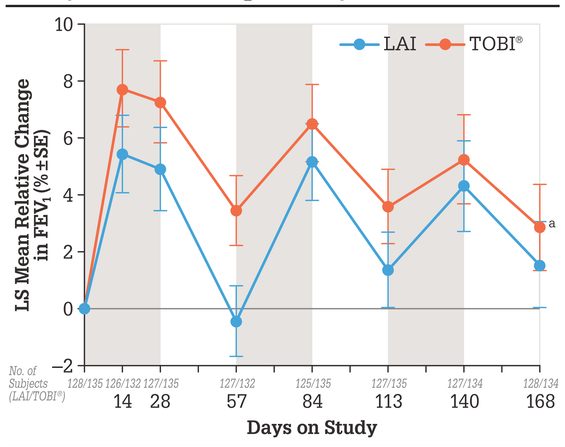
Table 2. Summary of AEs (Safety Population[a])

Variable	LAI 590 mg Once Daily (n=148)	TOBI® 300 mg Twice Daily (n=146)	Total (n=294)
Patients with TEAEs, n (%)	125 (84.5)	115 (78.8)	240 (81.6)
Patients with TEAEs by strongest relationship to study drug, n (%)			
Related	57 (38.5)	21 (14.4)	78 (26.5)
Not related	68 (45.9)	94 (64.4)	162 (55.1)
Patients with TEAEs by maximum severity, n (%)			
Grade 1: mild	52 (35.1)	50 (34.2)	102 (34.7)
Grade 2: moderate	62 (41.9)	59 (40.4)	121 (41.2)
Grade 3: severe	11 (7.4)	5 (3.4)	16 (5.4)
Grade 4: life-threatening or disabling	0	1 (0.7)	1 (0.3)
Patients with treatment-emergent SAEs, n (%)	26 (17.6)	29 (19.9)	55 (18.7)
Patients with treatment-emergent SAEs by strongest relationship to study drug, n (%)			
Related	1 (0.7)	1 (0.7)	2 (0.7)
Not related	25 (16.9)	28 (19.2)	53 (18.0)
Patients with AEs leading to study drug discontinuation, n (%)	15 (10.1)	7 (4.8)	22 (7.5)

[a]All patients who received at least 1 dose of study drug.

AEs, adverse events; LAI, liposomal amikacin for inhalation; SAEs, serious AEs; TEAEs, treatment-emergent AEs; TOBI®, tobramycin inhalation solution.

Figure 4. Primary Endpoint: Relative Change in FEV_1 (Per Protocol Population)



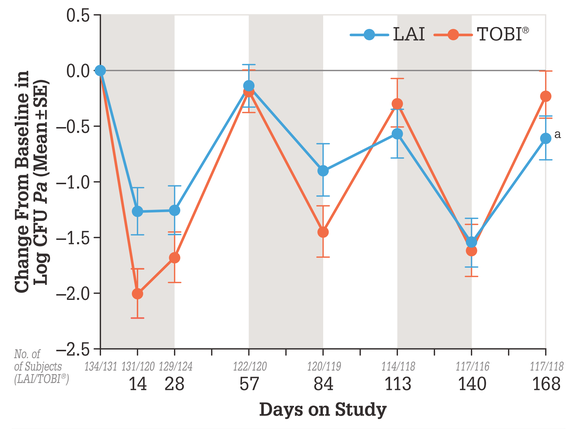
[a]LS mean difference (LAI–TOBI®) adjusted for treatment and randomization strata at Day 168 was −1.31% (95% CI, −4.95 to 2.34; P=0.4809). The lower bound of the 95% CI was above −5%, indicating noninferiority of LAI to TOBI®.

FEV_1, forced expiratory volume in 1 second; LAI, liposomal amikacin for inhalation; LS, least squares; SE, standard error; TOBI®, tobramycin inhalation solution.

CLEAR-108: Efficacy Summary

- The study achieved its primary endpoint by demonstrating that LAI administered once daily was noninferior to TOBI® administered twice daily with respect to the relative change in FEV_1 from baseline to end of study (Day 168)
- Relative change in FEV_1 observed at the end of the treatment period in Cycle 3 (Day 140) was similar to that observed at the end of the treatment period in Cycle 1 (Day 28), suggesting that the treatment effect was maintained over the course of 3 cycles

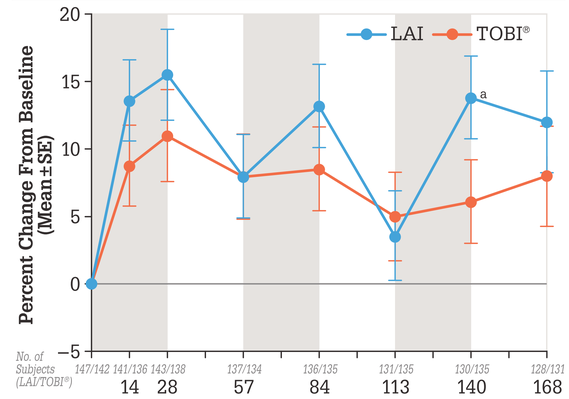
Figure 5. Change from Baseline in Sputum Density of *Pseudomonas aeruginosa* (mITT Population)



[a]LS mean difference (LAI–TOBI®) adjusted for treatment and randomization strata at Day 168 was not statistically significant (P=0.1285).

CFU, colony-forming units; LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat; *Pa*, *Pseudomonas aeruginosa*; SE, standard error; TOBI®, tobramycin inhalation solution.

Figure 6. CFQ-R: Percent Change in Respiratory Symptoms (mITT Population)

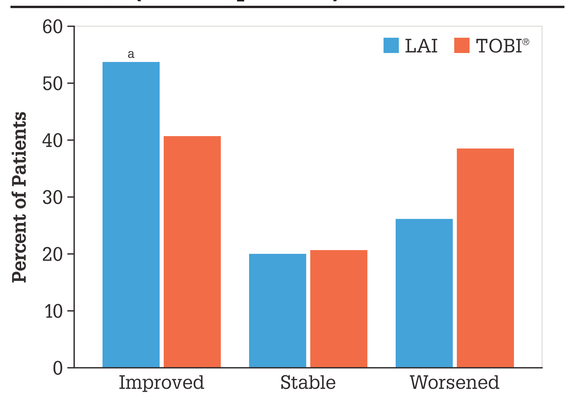


[a]LS mean difference (LAI–TOBI®) adjusted for treatment and randomization strata at Day 140 (end of treatment period) was 7.74% (95% CI, 0.43 to 15.06; P=0.0380).

CFQ-R, Cystic Fibrosis Questionnaire-Revised; LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat; SE, standard error; TOBI®, tobramycin inhalation solution.

- Mean reductions in *Pa* sputum density were comparable during the on-treatment periods in Cycles 1, 2, and 3
- Based on change from baseline assessment on the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Treatment Burden scale, mean improvement in treatment burden was observed at the end of treatment of Cycle 2 (Day 84) in the LAI group (least squares [LS] mean, 1.686), with worsening in the TOBI® group (LS mean, –2.586; P=0.0254). This trend was also observed at the end of treatment of Cycle 3 (Day 140: LAI=0.739, TOBI®=–2.826; P=0.0608)

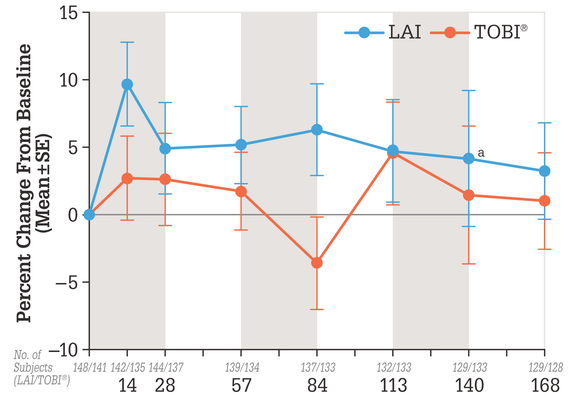
Figure 7. CFQ-R Respiratory Scale Response at Day 140, Based on Minimal Clinically Important Difference (mITT Population)



[a]Patients were categorized, based on the minimal clinically important difference, as improved (increase ≥4 points), worsened (decrease ≥4 points), or stable (change <4 points in either direction); at Day 140, a greater proportion of patients given LAI were improved (χ^2[1]=5.50, P=0.02).

CFQ-R, Cystic Fibrosis Questionnaire-Revised; LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat; TOBI®, tobramycin inhalation solution.

Figure 8. CFQ-R: Percent Change in Treatment Burden (mITT Population)



[a]LS mean difference (LAI–TOBI®) adjusted for treatment and randomization strata at Day 140 was 2.69% (95% CI, –9.40 to 14.77; P=0.6621).

CFQ-R, Cystic Fibrosis Questionnaire-Revised; LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat; SE, standard error; TOBI®, tobramycin inhalation solution.

- Mean increases on the CFQ-R Respiratory Symptoms scale adjusted for baseline assessment suggested clinically meaningful improvement (score ≥4 points) for both treatment groups at the end of Cycle 1 (LAI=5.23, TOBI®=5.85) and for the LAI group only at the end of Cycles 2 and 3 (Day 84: LAI=4.25, TOBI®=3.22; Day 140: LAI=4.94, TOBI®=2.13)
- Based on the categorical changes, higher proportions of patients given LAI vs TOBI® were improved at the end of Cycle 2 (Day 84); this difference reached statistical significance at the end of treatment of Cycle 3 (LAI=53.8%, TOBI®=40.7%; P=0.02)

Conclusions

- LAI was generally safe and well tolerated, and no unexpected adverse events were observed
- LAI administered once daily is comparable to TOBI® administered twice daily in improving lung function, the standard of care in patients with CF chronically infected with *Pa*
- Patients maintained on LAI reported significantly greater improvement in their respiratory symptoms compared with the TOBI® arm at the end of the treatment period of the study
- Patients also reported less treatment burden in the LAI arm, which is administered once daily
- LAI is an effective inhaled aminoglycoside antibiotic in the treatment of chronic *Pa* bronchopulmonary infection in patients with CF

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