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Clinical Benefit of Liposomal Amikacin for Inhalation as Assessed by the Cystic Fibrosis Questionnaire-Revised

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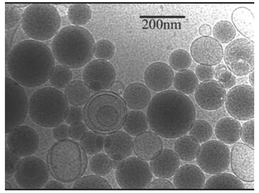
Introduction

- Liposomal amikacin for inhalation (LAI) is a novel lipid formulation of amikacin (**Figure 1**) 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 mm) encapsulating amikacin
  - —Penetration of drug into biofilm
  - —High lung concentration and area under the curve (AUC), and longer half-life ⇒ improved AUC:minimum inhibitory concentration ratio
  - —*Pa* suppression and killing, including resistant isolates in *in vitro* models
  - —Virulence factors from *Pa* facilitate amikacin release
  - —In *in vitro* and *in vivo* preclinical models, greater NTM suppression and killing when compared with amikacin solution

Figure 1. Cryo-Electron Microscopic Image of LAI



LAI, liposomal amikacin for inhalation.

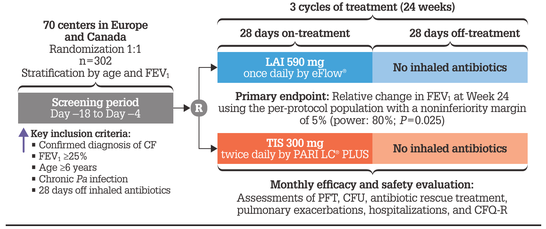
- Patient-reported outcomes (PROs), such as health-related quality of life (HRQoL), are important indicators of patient benefit in clinical trials[1]
- The Cystic Fibrosis Questionnaire-Revised (CFQ-R) is a validated HRQoL measure for cystic fibrosis (CF) that meets US Food and Drug Administration psychometric requirements for PROs, containing both generic and CF-specific scales[2,3]
- All CFQ-R scales are standardized on a 0 to 100 point scale with higher scores representing better HRQoL. Thus, improvements in Respiratory Symptoms and Treatment Burden, for example, are reflected in *higher* scores
- A change of 4 points of the CFQ-R Respiratory Symptoms score has been identified as the minimal important difference (MID), the smallest difference that can be reliably detected by patients[4]

CLEAR-108: Primary Objective

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

Methods

Figure 2. CLEAR-108 Study Design

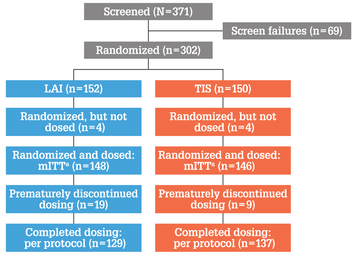


CF, cystic fibrosis; CFQ-R, Cystic Fibrosis Questionnaire-Revised; CFU, colony-forming units; FEV_1, forced expiratory volume in 1 second; LAI, liposomal amikacin for inhalation; *Pa, Pseudomonas aeruginosa*; PFT, pulmonary function testing; TIS, tobramycin inhalation solution.

- A multicenter study in which patients were randomized in 70 sites in Europe and Canada (**Figure 2**)
- Upon completion of CLEAR-108, eligible patients were rolled over to a multicycle (up to 2 years) study of LAI (CLEAR-110)

Results

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; TIS, tobramycin inhalation solution.

Table 1. Demographic and Baseline Characteristics (mITT Population)

Variable		LAI 590 mg Once Daily (n=148)	TIS 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 (years)	Mean (SD)	22.8 (10.24)	22.0 (10.00)	22.4 (10.11)
	6–12, n (%)	27 (18.2)	26 (17.8)	53 (18.0)
	13–18, n (%)	34 (23.0)	33 (22.6)	67 (22.8)
	>18, n (%)	87 (58.8)	87 (59.6)	174 (59.2)
Height (cm), mean (SD)		162.3 (14.98)	162.2 (15.55)	162.3 (15.24)
Weight (kg), mean (SD)		54.5 (17.19)	53.1 (15.89)	53.8 (16.54)
BMI (kg/m^2), mean (SD)		20.1 (4.03)	19.7 (3.72)	19.9 (3.88)
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 (21.45)	61.9 (22.03)	63.2 (21.74)
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)	2.1 (0.86)	2.0 (0.85)	2.1 (0.85)

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

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 (TIS; 78.8%) treatment groups experienced ≥1 treatment-emergent adverse event (TEAE); most were mild or moderate. There were no unexpected adverse events (AEs), and the TEAEs were consistent with underlying CF disease (**Table 3**)
- Serious adverse events (SAEs) were experienced by 17.6% and 19.9% of LAI and TIS patients, respectively. These consisted primarily of hospitalizations for the treatment of pulmonary exacerbations. SAEs were considered related to study drug in 1 patient given LAI (forced expiratory volume in 1 second [FEV_1] decreased) and 1 patient given TIS (infective pulmonary exacerbation of CF) (**Table 3**)

Table 2. Baseline Values for CFQ-R Scales (mITT Population)

Scale	LAI 590 mg Once Daily (n=148)	TIS 300 mg Twice Daily (n=146)	Total (n=294)
Respiratory Symptoms, mean (SD)	69.0 (18.37)	70.5 (17.15)	69.7 (17.77)
Treatment Burden, mean (SD)	62.9 (19.22)	61.5 (18.81)	62.2 (19.00)
Physical Functioning, mean (SD)	75.5 (21.87)	74.5 (22.02)	75.0 (21.91)
Vitality,[a,b] mean (SD)	64.3 (17.84)	64.7 (18.79)	64.5 (18.28)
Health Perceptions,[a] mean (SD)	65.4 (21.66)	64.5 (20.98)	65.0 (21.28)
Social Functioning, mean (SD)	71.8 (16.66)	68.6 (17.43)	70.3 (17.09)
Role Functioning, mean (SD)	83.8 (16.81)	84.4 (18.27)	84.1 (17.51)

[a]Completed by participants aged ≥14 years. [b]Recorded as Energy/Well-Being during the study.
CFQ-R, Cystic Fibrosis Questionnaire-Revised; LAI, liposomal amikacin for inhalation; SD, standard deviation; TIS, tobramycin inhalation solution.

Table 3. Summary of AEs (Safety Population[a])

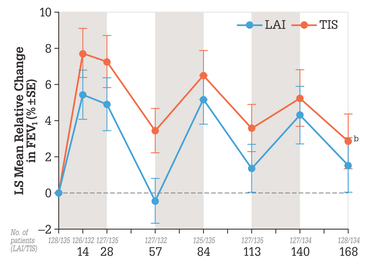
Variable	LAI 590 mg Once Daily (n=148)	TIS 300 mg Twice Daily (n=146)	Total (n=294)
Patients with TEAEs, n (%)	125 (84.5)	115 (78.8)	240 (81.6)
Patients with TEAEs by strongest relationship to study drug, n (%)			
Related	57 (38.5)	21 (14.4)	78 (26.5)
Not related	68 (45.9)	94 (64.4)	162 (55.1)
Patients 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)
Grade 5: death	0	0	0
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 (%)[b]	15 (10.1)	7 (4.8)	22 (7.5)

[a]All patients who received at least 1 dose of study drug. [b]Three patients in each arm (LAI: 0303-801, 1102-809, and 1910-810; TIS: 0708-801, 1910-809, and 2106-803) were marked in error as having an AE that led to study drug discontinuation.
AEs, adverse events; LAI, liposomal amikacin for inhalation; SAEs, serious AEs; TEAEs, treatment-emergent AEs; TIS, tobramycin inhalation solution.

CLEAR-108: Efficacy Summary

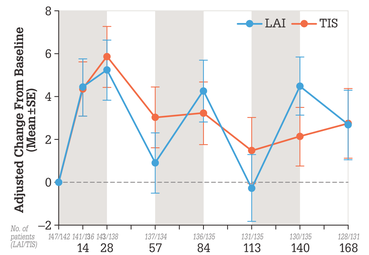
- The study achieved its primary endpoint by demonstrating that LAI administered once daily was noninferior to TIS administered twice daily with respect to the relative change in FEV_1 from baseline to end of study (Day 168)
- Relative change in FEV_1 observed at the end of the treatment period in Cycle 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 4**)

Figure 4. Primary Endpoint: Relative Change in FEV_1 (Per-Protocol Population[a])



NOTE: Shaded regions represent 28 days on-treatment; dashed line represents baseline.
[a]Patients who completed dosing during treatment as per protocol.
[b]LS mean difference (LAI – TIS) 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 TIS.
FEV_1, forced expiratory volume in 1 second; LAI, liposomal amikacin for inhalation; LS, least squares; SE, standard error; TIS, tobramycin inhalation solution.

Figure 5. Change From Baseline in CFQ-R Respiratory Symptoms Score (mITT Population)



NOTE: Shaded regions represent 28 days on-treatment; dashed line represents baseline.
CFQ-R, Cystic Fibrosis Questionnaire-Revised; LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat; SE, standard error; TIS, tobramycin inhalation solution.

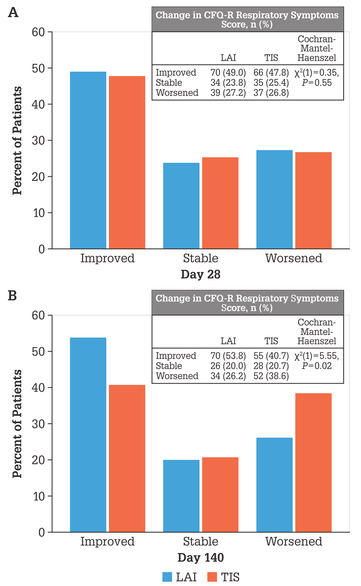
- Mean increases of the CFQ-R Respiratory Symptoms score adjusted for baseline assessment suggested clinically meaningful improvement (score ≥4 points) at the end of the on-treatment phase of each cycle for LAI (Cycle 1 [Day 28]: 5.23; Cycle 2 [Day 84]: 4.25; Cycle 3 [Day 140]: 4.94), but only at the end of Cycle 1 for TIS (5.85) (**Figure 5**)
- Using the MID, by Day 140 there were significant differences favoring LAI vs TIS (P=0.02), with more patients reporting improved and fewer reporting worsened respiratory symptoms from baseline (**Figure 6**)
- Based on the random effects model analysis of the CFQ-R (**Table 4**):
  - —Respiratory Symptoms, Physical Functioning, Vitality, and Health Perceptions scores were improved on- vs off-treatment with LAI; Physical Functioning and Vitality improved with TIS
  - —Changes from baseline of the Respiratory Symptoms, Physical Functioning, Vitality, and Health Perceptions scores on- vs off-treatment were greater with LAI vs TIS; however, the difference in the Respiratory Symptoms score was within the MID of 4 points
  - —Treatment Burden worsened on- vs off-treatment for TIS, but not LAI

Table 4. Random Effects Model Estimates[a] of the CFQ-R Scales: On- vs Off-treatment

Scale	On- vs Off-treatment				On- vs Off-treatment Δ LAI–TIS	
	LAI		TIS			
	Fixed Effect (SE)	*P* Value	Fixed Effect (SE)	*P* Value	Fixed Effect (SE)	*P* Value
Respiratory Symptoms	3.64 (0.89)	<0.01	0.84 (0.89)	0.34	2.80 (1.25)	0.03
Treatment Burden	−0.07 (0.68)	0.92	−2.60 (0.68)	<0.01	2.53 (0.97)	<0.01
Physical Functioning	1.96 (0.78)	0.01	1.86 (0.78)	0.02	0.10 (1.10)	0.96
Vitality[b]	2.09 (0.95)	0.03	2.16 (0.94)	0.02	−0.07 (1.33)	0.96
Health Perceptions[b]	2.67 (0.88)	<0.01	0.19 (0.87)	0.82	2.47 (1.23)	0.05
Social Functioning	0.55 (0.56)	0.33	−0.24 (0.57)	0.67	0.80 (0.80)	0.32
Role Functioning	1.10 (0.77)	0.15	0.72 (0.76)	0.35	0.38 (1.09)	0.73
School Functioning (parent-reported)	1.78 (2.27)	0.43	1.55 (2.42)	0.52	0.24 (3.35)	0.94

[a]Mixed models were fit using an unstructured within-subject covariance matrix, with subject nested within treatment arm, and Kenward and Roger corrections. Fixed effects: Day 14 intercept, randomization strata, linear change (months), on- vs off-drug, Day 1 values, the interactions of Day 1 values with linear change and on- vs off-drug, treatment, and the interactions of treatment with linear change and on- vs off-drug. Random effects: intercept, linear change, and on- vs off-drug. [b]Completed by participants aged ≥14 years.
CFQ-R, Cystic Fibrosis Questionnaire-Revised; LAI, liposomal amikacin for inhalation; SE, standard error; TIS, tobramycin inhalation solution.

Figure 6. CFQ-R Respiratory Symptoms Score, Based on the MID[a]: Day 28 (Panel A) and Day 140 (Panel B; mITT Population)



[a]Based on the MID, patients were categorized as: improved (increase ≥4 points), worsened (decrease ≥4 points), or stable (change <4 points in either direction).
CFQ-R, Cystic Fibrosis Questionnaire-Revised; LAI, liposomal amikacin for inhalation; MID, minimal important difference; mITT, modified intent-to-treat; TIS, tobramycin inhalation solution.

Conclusions

- LAI was well tolerated, and no unexpected AEs were observed
- LAI administered once daily is comparable with TIS administered twice daily, the standard of care in patients with CF chronically infected with *Pa*, in improving lung function
- Random effects model analysis of the CFQ-R provides additional evidence of the benefit of LAI
- Lower CFQ-R Treatment Burden was associated with use of LAI. Lower perceptions of Treatment Burden may promote adherence and may have positive effects on health outcomes in the long-term

References **1.** Goss CH, Quittner AL. Patient-reported outcomes in cystic fibrosis. *Proc Am Thorac Soc.* 2007;4(4):378–386. **2.** Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of The Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. *Chest.* 2005;128(4):2347–2354. **3.** Quittner A, Sawicki G, McMullen A, et al. Psychometric evaluation of the Cystic Fibrosis Questionnaire-Revised in a national sample. *Qual Life Res.* 2012;21(7):1267–1278. **4.** Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic Pseudomonas aeruginosa airway infection. *Chest.* 2009;135(6):1610–1618.

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