Randomized, Double-Blind, Placebo-Controlled Study and Open-Label Extension of Liposomal Amikacin for Inhalation (LAI) in Patients with Recalcitrant Nontuberculous Mycobacterial Lung Disease (NTM-LD)

Poster # 293

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INTRODUCTION

- Nontuberculous mycobacteria (NTM) lung infections are increasing worldwide; NTM is associated with increased morbidity and mortality, and represents an emerging public health concern.[1-7]
- Liposomal amikacin for inhalation (LAI) is a novel formulation of amikacin that is currently being developed for the treatment of lung infections caused by NTM and *Pseudomonas aeruginosa*.[8-10]
  - 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.
  - The high lung concentration (C_{max}) and area under the curve (AUC) of amikacin are improved due to the half-life ($t_{½}$) of liposomes, which enables once-daily dosing of LAI.
- The efficacy and favorable tolerability of LAI have been demonstrated in phase 3 studies of patients with cystic fibrosis (CF) and chronic bronchopulmonary infections due to *P aeruginosa*.[10]
- The current study evaluates the efficacy, safety, and tolerability of LAI in patients with refractory NTM lung disease.

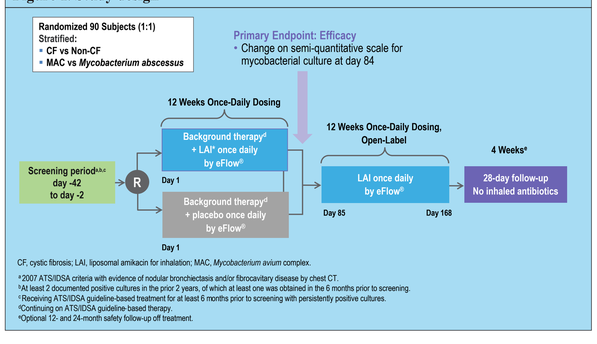
METHODS

Study Design

- The TR02-112 study design is summarized in **Figure 1**.
- Study TR02-112 is the first randomized, controlled, multicenter study in patients with NTM lung disease, conducted at 19 sites in the United States and Canada.
- For the 84-day double-blind phase, patients were eligible if they had been refractory to American Thoracic Society / Infectious Disease Society of America (ATS/IDSA) guideline-based therapy for ≥6 months prior to screening.
  - Patients were stratified by presence or absence of CF, and by *Mycobacterium avium* complex (MAC) versus *Mycobacterium abscessus* infection.
- Patients were randomized 1:1 to LAI 590 mg or placebo once daily via eFlow® nebulizer (PARI Pharma GmbH) added to their ongoing stable drug regimen.
- After completing the double-blind phase, all patients who consented to and continued in the open-label phase received LAI 590 mg once daily for 84 additional days.
- Efficacy endpoints during the double-blind and open-label phases included:
  - Change from baseline on the semi-quantitative scale for mycobacterial culture[a]
  - NTM culture conversion to negative
  - Change in distance walked in the 6-minute walk test (6MWT)
- Adverse events were monitored through the follow-up visit 28 days after the last dose of study drug, up to day 196.

[a]The semi-quantitative scale is a mycobacterial culture reporting method, expressed on a 7-step scale as culture-negative (confirmed with no growth in liquid medium); growth in liquid medium only (liquid-positive); 1-49 colonies (manual count on agar); 1+; 2+; 3+; and 4+.

Figure 1. Study design



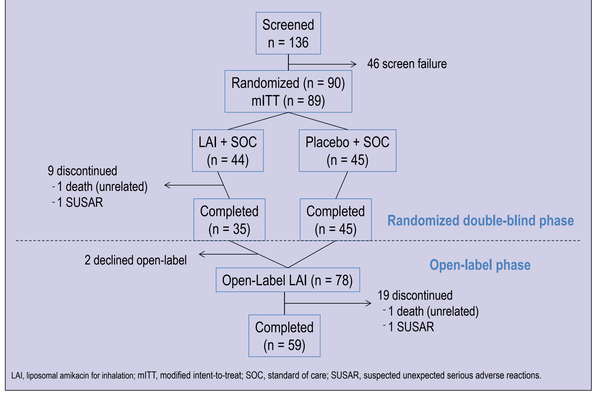
CF, cystic fibrosis; LAI, liposomal amikacin for inhalation; MAC, *Mycobacterium avium* complex.

[a]2007 ATS/IDSA criteria with evidence of nodular bronchiectasis and/or fibrocavitary disease by chest CT.
[b]At least 2 documented positive cultures in the prior 2 years, of which at least one was obtained in the 6 months prior to screening.
[c]Receiving ATS/IDSA guideline-based treatment for at least 6 months prior to screening with persistently positive cultures.
[d]Continuing on ATS/IDSA guideline-based therapy.
[e]Optional 12- and 24-month safety follow-up off treatment.

Patient Characteristics

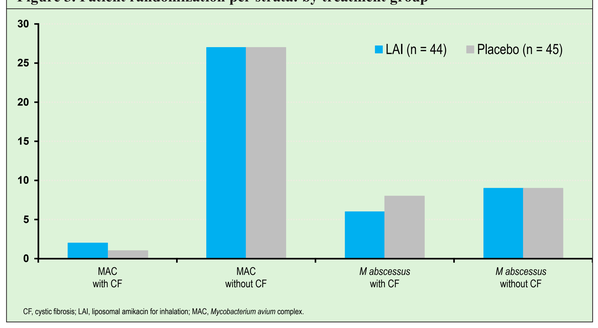
- Of 136 screened patients, 90 were randomized (19% CF; 81% non-CF; 64% with MAC infection and 36% with *M abscessus* infection), and 89 patients were included in the modified intent-to-treat (mITT) population (**Figures 2 and 3**).
- Majority of patients were female (78 [87.6%]), and the baseline mean (standard deviation [SD]) age was 58.5 (15.83) years (**Table 1**).
- At the end of the study, 80 and 59 patients had completed the double-blind and open-label phases, respectively (**Figure 2**).

Figure 2. Patient disposition



LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat; SOC, standard of care; SUSAR, suspected unexpected serious adverse reactions.

Figure 3. Patient randomization per strata: by treatment group



CF, cystic fibrosis; LAI, liposomal amikacin for inhalation; MAC, *Mycobacterium avium* complex.

Table 1. Demographics and Baseline Characteristics (mITT Population)

	LAI (n = 44)	Placebo (n = 45)	Overall (N = 89)
Gender, n (%)			
Male	6 (13.6)	5 (11.1)	11 (12.4)
Female	38 (86.4)	40 (88.9)	78 (87.6)
Race/Ethnicity			
Caucasian (not of Hispanic origin)	42 (95.5)	40 (88.9)	82 (92.1)
Hispanic	0	(4.4)	2 (2.2)
African	0	1 (2.2)	1 (1.1)
Asian	2 (4.5)	2 (4.4)	4 (4.5)
Other	0		0
Baseline age, years			
n	44	45	89
Mean (SD)	58.0 (16.61)	59.1 (15.20)	58.5 (15.83)
Median	61.5	63.0	63.0
Min, Max	18, 85	19, 80	18, 85
Baseline FEV_1 percent predicted			
n	44	45	89
Mean (SD)	63.56 (21.339)	62.56 (17.168)	63.06 (19.239)
Median	61.25	61.00	61.00
Min, Max	30.2, 114.9	34.4, 101.6	30.2, 114.9

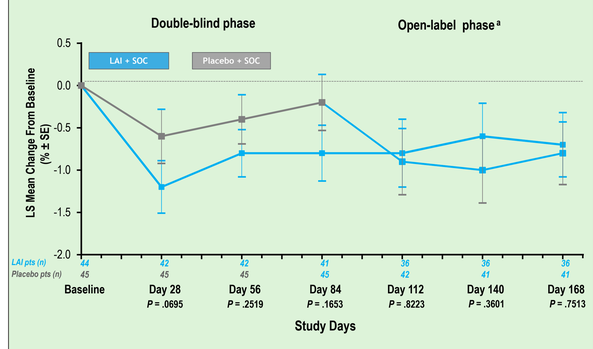
FEV_1, forced expiratory volume in 1 second; mITT, modified intent-to-treat; SD, standard deviation.

RESULTS

Efficacy Summary

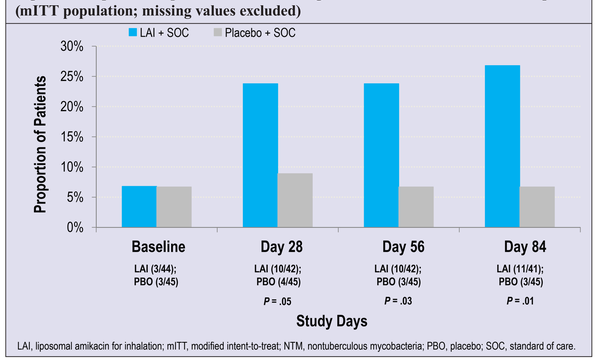
- Primary endpoint of change from baseline in the full semi-quantitative scale did not achieve statistical significance, although there was a positive trend in favor of the LAI arm (**Figure 4**).
- LAI achieved statistical significance in achieving a negative culture at day 84, with 11 of 44 patients on LAI versus 3 of 45 patients on placebo (P = .01) (**Figures 5** and **6**).
  - Six of the 11 patients who culture-converted on LAI had sustained negative sputum cultures throughout the open-label phase, including at the 28-day off-treatment follow-up visit.
  - Two patients on LAI achieved their first negative culture at day 112 and sustained negative sputum cultures throughout the open-label phase, including at the 28-day off-treatment follow-up visit.
  - Two patients on placebo achieved their first negative culture after entering the open-label phase and sustained negative sputum cultures through the 28-day off-treatment follow-up visit.
  - One patient on placebo had fluctuating culture results between negative and low positivity (broth-positive) during the double-blind phase. After entering the open-label phase, the patient achieved negative sputum cultures from day 112 to the 28-day off-treatment follow-up visit.
  - One patient entering the open-label phase from the placebo arm showed sustained negative sputum cultures from day 84 to the 28-day off-treatment follow-up visit.
- Patients with treatment-refractory NTM have a symptomatology that includes copious sputum, easy fatigability, and malaise. The 6MWT was used to assess the impact of LAI on overall physical function or capacity (**Figure 7**).
  - LAI demonstrated statistical significance in the 6MWT in the double-blind phase (LAI vs placebo: 23.895 vs -25.032 meters, P = .009).
  - In the open-label phase, patients in the LAI arm continued to improve on the 6MWT and patients in the placebo group who started LAI showed a decrease in the rate of deterioration.

Figure 4. Change from baseline on the full semi-quantitative scale for mycobacterial culture through end of the open-label phase (mITT population)



LAI, liposomal amikacin for inhalation; LS, least squares; mITT, modified intent-to-treat; SE, standard error; SOC, standard of care.
[a]All patients in the open-label phase received LAI.

Figure 5. Proportion of patients with NTM-negative cultures in the double-blind phase (mITT population; missing values excluded)



LAI, liposomal amikacin for inhalation; mITT, modified intent-to-treat; NTM, nontuberculous mycobacteria; PBO, placebo; SOC, standard of care.

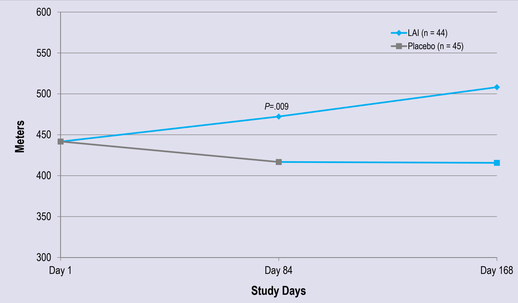
Figure 6. Culture conversion sustainability through 28-day follow-up (end of open-label phase)

Treatment Arm	CF Patient	NTM Organism	Length of NTM Prior to Baseline (Months)	Prior Amikacin Use	SQS at Screening	Baseline	Day 28	Day 56	Day 84	Day 112	Day 140	Day 168	28-Day Follow-up
LAI	Non-CF	MAC	>24		2								
			>24		5								
			>24		6								
			>24		2								Early Term
			>12-24		2								
			>12-24		2								
			>12-24	INH	3								
			>12-24		3								
			>12-24		3								
			6-12		3								
			6-12		4								
			6-12		3								
		M abscessus	>12-24	IV	5								
	CF	MAC	>12-24	INH	3								Early Term
		M abscessus	>24	INH	3								
			6-12	INH	6								
PBO	Non-CF Patient	MAC	>24		4								
			>24	INH	3								
			>24		3								
			>12-24		4								
			>12-24		2								
			>12-24		3								
			>12-24		3								
			6-12		2								Early Term
			6-12	INH	2								
		M abscessus	>24	INH	2								
			>24		3								
Number of patient with negative culture while being treated with LAI + SOC							10	10	11	19	19	21	
Number of patient with negative culture while being treated with PBO + SOC							4	3	3	NA	NA	NA	

Note. All negative cultures confirmed with no growth in liquid medium.
CF, cystic fibrosis; INH, inhalation; IV, intravenous; LAI, liposomal amikacin for inhalation; MAC, *Mycobacterium avium* complex; NA, not applicable; NTM, nontuberculous mycobacteria; PBO, placebo; SOC, standard of care; SQS, semi-quantitative scale.

= culture negative (LAI)
= culture negative (PBO)
= culture negative (off treatment)

Figure 7. Average meters walked in the 6MWT: end of open-label phase (day 168; all patients)



6MWT, 6-minute walk test; LAI, liposomal amikacin for inhalation.

Safety and Tolerability Summary

- Most treatment-emergent adverse events (TEAEs) were mild or moderate in severity, and the majority were respiratory in nature (**Table 2** and **Figure 8**).
  - Local respiratory events and infective exacerbation of the underlying lung disease were the most common TEAEs.
  - Few patients discontinued the study drug as a result of these events.

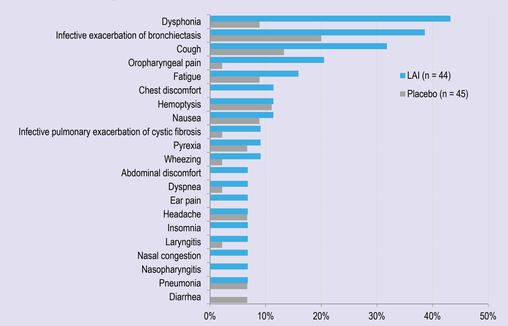
Table 2. Overview of Adverse Events by Treatment Phase (Safety Population)

	Double-Blind Phase[a]		Open-Label Phase[b]	
	LAI (n = 44)	Placebo (n = 45)	LAI[c] (n = 35)	Placebo[c] (n = 43)
Subjects with treatment-emergent adverse events (TEAEs), n (%)	41 (93.2)	40 (88.9)	31 (88.6)	42 (97.7)
TEAEs, n	240	140	107	160
Subjects with TEAEs by maximum severity, n (%)				
Grade 1 : Mild	12 (27.3)	25 (55.6)	16 (45.7)	10 (23.3)
Grade 2 : Moderate	24 (54.5)	10 (22.2)	10 (28.6)	24 (55.8)
Grade 3 : Severe	4 (9.1)	5 (11.1)	4 (11.4)	8 (18.6)
Grade 4: Life-threatening or disabling	0	0	0	0
Grade 5: Death[d]	1 (2.3)	0	1 (2.9)	0
Subjects with TEAEs by seriousness, n (%)				
Serious	8 (18.2)	4 (8.9)	5 (14.3)	5 (11.6)
Not serious	33 (75.0)	36 (80.0)	26 (74.3)	37 (86.0)
Treatment-emergent serious adverse events, n	12	5	10	5
Subjects with TEAEs by relationship to study drug, n (%)				
Related	32 (72.7)	17 (37.8)	17 (48.6)	26 (60.5)
Not related	9 (20.5)	23 (51.1)	14 (40.0)	16 (37.2)
Subjects with treatment-emergent audiovestibular adverse events, n (%)	5 (11.4)	5 (11.1)	2 (5.7)	2 (4.7)
Subjects with treatment-emergent renal adverse events, n (%)	1 (2.3)	0	1 (2.9)	0
Subjects with adverse events leading to study drug discontinuation, n (%)	7 (15.9)	0	6 (17.1)	12 (27.9)

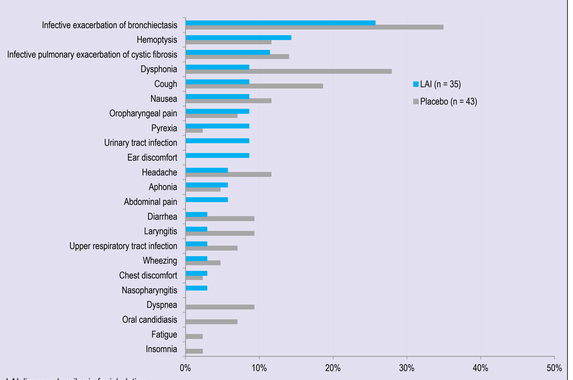
LAI, liposomal amikacin for inhalation.
[a]Adverse events during the double-blind phase are those with onset from the date of first dose of double-blind study drug.
[b]Adverse events during the open-label phase are those with onset from the date of first dose of open-label study drug.
[c]All patients in the open-label phase received LAI.
[d]Deaths were due to acute respiratory distress syndrome and urosepsis, and both were unrelated to study drug.

Figure 8. Treatment-emergent adverse events by preferred term (>5% occurrence)

A: Double-blind phase[a]



B: Open-label phase[b]



LAI, liposomal amikacin for inhalation.
[a]Adverse events during the double-blind phase are those with onset from the date of first dose of double-blind study drug.
[b]Adverse events during the open-label phase are those with onset from the date of first dose of open-label study drug.
All patients in the open-label phase received LAI.

CONCLUSIONS

- In patients with refractory NTM, LAI achieved statistical significance in culture conversion at day 84 in the double-blind phase.
- LAI demonstrated effectiveness in sustaining negative sputum cultures.
- LAI demonstrated improvement versus placebo in the 6MWT.
- The majority of TEAEs in the LAI arm were respiratory in nature; however, few patients discontinued study drug due to these events.
- These data increase our understanding of NTM disease management, including incorporating of new treatments in future NTM clinical trials, and creating potential new NTM management paradigms.

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