Poster #: PA371

Amikacin Minimum Inhibitory Concentrations and Mutational Resistance in Patients With Treatment-Refractory Nontuberculous Mycobacteria Lung Disease Treated With Liposomal Amikacin for Inhalation

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INTRODUCTION

- Nontuberculous mycobacterial (NTM) lung infections are increasing globally in both men and women.[1-4]
- NTM lung infections are often chronic and may be refractory to current guideline-based antibiotic therapy.[3-5]
- Liposomal amikacin for inhalation (LAI) is a novel inhalational formulation of amikacin in development for the treatment of NTM lung infections.[2,5-7]
  - LAI is composed of charge-neutral, highly biocompatible liposomes (~0.3 µm) that encapsulate charge-positive amikacin and penetrate the macrophages.
  - The high lung concentration and extended release of amikacin from liposomes enable once-daily dosing of LAI.
- The efficacy, safety, and tolerability of once-daily LAI were recently evaluated in a phase 2, randomized, double-blind, placebo-controlled study of patients with treatment-refractory NTM lung infections (Study TR02-112, ClinicalTrials.gov identifier: NCT01315236).
- Here we present a post hoc analysis from this study, focusing on the assessment of mutational resistance of the *A1408G* mutation at study entry and during treatment with LAI.

AIMS

- To evaluate mutational resistance in patients with *Mycobacterium avium* complex (MAC) or *Mycobacterium abscessus* (Mabs) lung infection who received LAI and the correlation between response to LAI administration and a mutation
- To evaluate the relationship between the minimum inhibitory concentrations (MICs) of an isolate and the presence of a mutation

METHODS

Study Design

- Study design is summarized in **Figure 1**.
- Study TR02-112 is the first randomized, placebo-controlled, multicenter clinical trial in patients with NTM lung disease, conducted at 19 sites in North America.
- The study assessed the efficacy, safety, and tolerability of LAI 590 mg once daily vs. placebo in patients with treatment-refractory NTM on a stable multidrug regimen.
- In the 84-day double-blind phase, patients were randomized 1:1 to LAI 590 mg or placebo once daily via a customized investigational eFlow® technology nebulizer (PARI Pharma GmbH) added to their ongoing, stable drug regimen.
- Those consenting to continue in the open-label (OL) phase received LAI 590 mg once daily as add-on therapy for 84 additional days.
- Sputum samples were collected predose at each monthly visit throughout the study. Mutational resistance was analyzed at Day 1, Day 84, and Day 168.

Eligibility Criteria

- Patients were eligible for enrollment if they had pulmonary NTM infection 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 the presence or absence of cystic fibrosis, and by the presence of MAC vs. Mabs infection.

Study Assessments/Treatments

- Amikacin MICs were assessed by broth microdilution assay.
- Mutation analysis was done by sequencing the 16S rRNA gene to detect the *A1408G* mutation associated with high-level amikacin resistance.

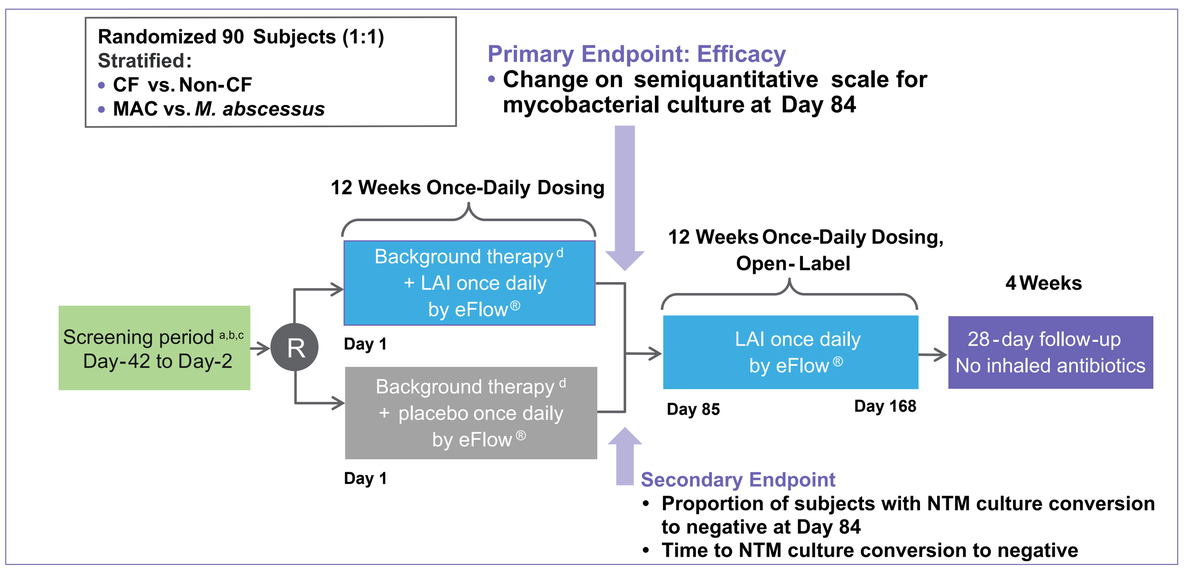
Primary and Key Secondary Endpoints

- The primary and key secondary endpoints assessed the microbiological response to LAI using the change from baseline on the semiquantitative scale (SQS) for mycobacterial culture for the LAI arm at Day 84 compared with the placebo arm at Day 84, and achievement of a negative sputum culture at Day 84, respectively.

Post Hoc Descriptive Analyses

- Presence or absence of *A1408G* mutation in the isolates cultured from all patients and the relationship between a mutation and response to LAI administration
- To assess the MIC of isolates cultured from all patients and the presence of a mutation

Figure 1. Study design

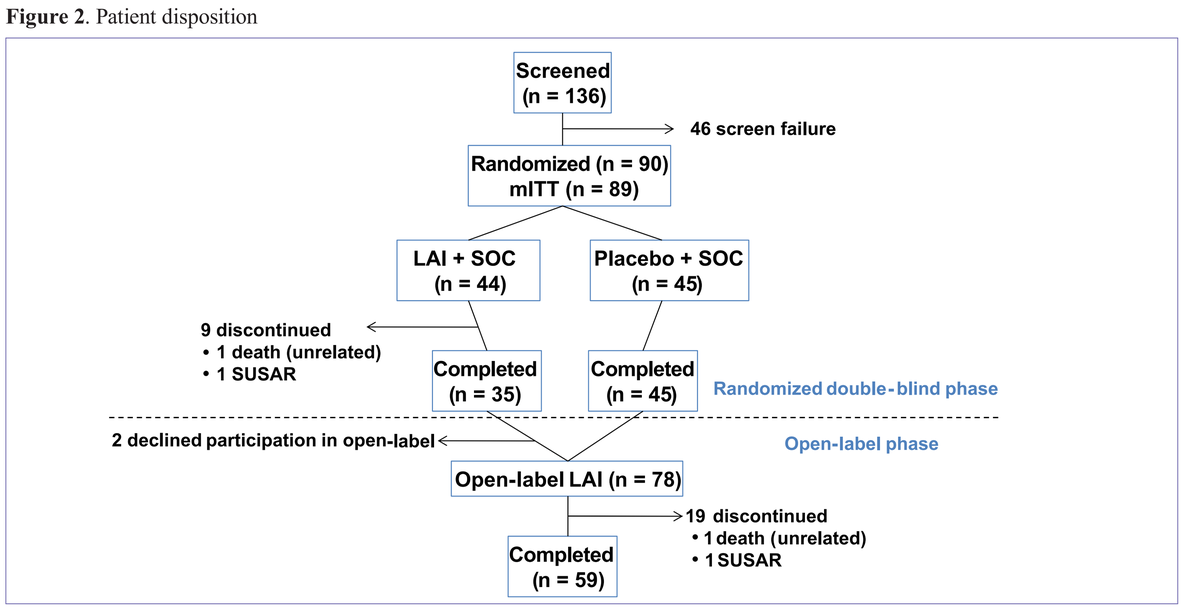


CF, cystic fibrosis; LAI, liposomal amikacin for inhalation; MAC, *Mycobacterium avium* complex.
[a] 2007 ATS/IDSA criteria with evidence of nodular bronchiectasis and/or fibrocavitary disease by chest CT.
[b] At least 2 documented positive cultures in the prior 2 years, of which at least one was obtained 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.

RESULTS

- Of the 136 patients screened, 90 were randomized, 89 were in the modified intent-to-treat (mITT) population (ie, all patients who received ≥1 dose of study drug) **(Figure 2)**.
- 80 patients completed treatment in the double-blind phase and 59 completed treatment in the open-label phase **(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 reaction.

Table 1. Demographics and Baseline Characteristics of the mITT Population

	LAI (n = 44)	Placebo (n = 45)
Gender, n (%)		
Male	6 (13.6)	5 (11.1)
Female	38 (86.4)	40 (88.9)
Race/ethnicity, n (%)		
Caucasian (not of Hispanic origin)	42 (95.5)	40 (88.9)
Hispanic	0	2 (4.4)
African	0	1 (2.2)
Asian	2 (4.5)	2 (4.4)
Other	0	0
Baseline age, years		
Mean (SD)	58.0 (16.61)	59.1 (15.20)
Median	61.5	63.0
Min, Max	18, 85	19, 80
Baseline MIC, n		
>64 µg/mL	3	4
64 µg/mL	2	5
32 µg/mL	7	7
16 µg/mL	19	15
8 µg/mL	7	8
No Baseline MIC*	6	6

MIC, minimum inhibitory concentration; mITT, modified intent-to-treat; SD, standard deviation.
*There were 6 patients in each arm with no Baseline MIC.

- Most patients were female (88%) and Caucasian (92%) **(Table 1)**.
- Baseline mean age (standard deviation [SD]) was 58.5 (15.8) years and median age (range) was 63.0 (18-85) years.
- No patient with an isolate, either MAC or Mabs, containing the *A1408G* mutation achieved a negative sputum culture for the duration of the study (84 days either on LAI or placebo added to multidrug regimen, followed by 84 days on open-label LAI added to multidrug regimen or during the 28-day off-LAI follow-up, with continued background multidrug regimen).
- 14 patients had isolates with mutations
  - 8 were MAC
  - 6 were Mabs
- Of these 14 patients:
  - 9 had isolates with mutations at either Screening or Baseline (Day 1) prior to any LAI administration (8 patients) or during placebo administration (1 patient)
  - 5 had isolates that showed a mutation after LAI administration
  - 12 of the 14 patients with isolates containing the *A1408G* mutation had prior exposure to amikacin
  - The 2 patients with no documented history of amikacin exposure had the mutation present at Baseline
- Of the isolates with MIC >64, all had a mutation detected at Baseline or during the course of the study.

SUMMARY AND CONCLUSIONS

- Mutations were detected in the isolates from 5/89 (5.6%) patients (mITT population) during LAI administration.
- The majority of patients with isolates containing the *A1408G* mutation had prior exposure to amikacin.
- There is a very high correlation between an MIC >64 and the presence of a mutation.
- The appearance of 16S rRNA gene mutations may represent the development of resistance mechanisms in the mycobacterium studied in TR02-112 during LAI administration. The background rate of mutation development in NTM organisms after exposure to amikacin is unknown, as mutational analysis is not routinely performed in microbiology laboratories. In the TR02-112 study, isolates with the presence of a mutation were seen in 9/89 (10.1%) patients prior to LAI administration.
- No patients with isolates with a 16S rRNA gene mutation to amikacin detected at any time before or during therapy had a microbiologic response to therapy with LAI, with the exception of 1 patient who had a mixed culture with mycobacteria that contained the mutation as well as susceptible mycobacteria at Baseline and who went on to achieve culture conversion at Day 140 with add-on LAI (negative at Day 140, Day 168, and 28-Day follow-up).

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DISCLOSURES

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