Subgroup Analyses of Baseline Demographics and Efficacy in Patients With Refractory Nontuberculous Mycobacteria (NTM) Lung Infection Treated With Liposomal Amikacin for Inhalation (LAI)

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INTRODUCTION

- Nontuberculous mycobacteria (NTM) lung infections are increasing worldwide. Over the past 2 decades, elderly and Caucasian women without apparent predisposing conditions have been reported with increased frequency to have pulmonary disease associated with NTM infections.[1-5]
- Pulmonary NTM disease is often chronic and may be refractory to current guideline-based antibiotic therapy.[5,6]
- Liposomal amikacin for inhalation (LAI) is a novel inhalational formulation of amikacin in development for the treatment of NTM lung infections.[7-10]
  - 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 LAI were evaluated in the recently completed phase 2, randomized, placebo-controlled study of patients with treatment-refractory NTM lung infection (Study TR02-112; ClinicalTrials.gov Identifier: NCT01315236).

OBJECTIVES

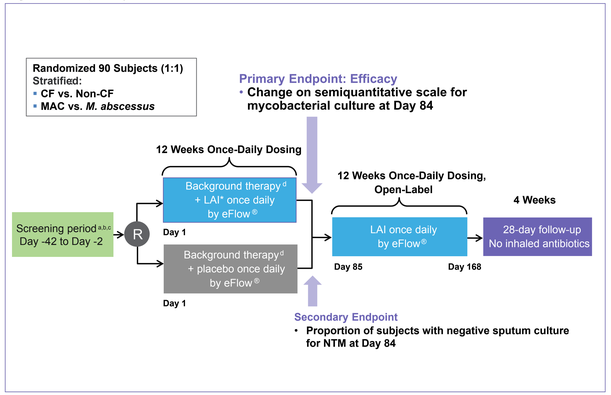
- To evaluate the differences in negative sputum cultures for NTM (defined as 1 culture-negative sputum sample) by treatment arm based on demographic and microbiological factors.
- To evaluate LAI treatment response in patients infected with *Mycobacterium avium* complex (MAC) or *Mycobacterium abscessus* using various subgroup analyses.

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 treatment-refractory NTM lung disease, conducted at 19 sites in the United States and Canada.
- 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 (CF), and by the presence of MAC versus *M. abscessus* infection.
- In the 84-day double-blind phase, 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 continue in the open-label phase received LAI 590 mg once daily for 84 additional days.
- Sputum was collected pre-dose at all visits (except Day 2), and was assessed for mycobacterial growth during the double-blind and open-label phases.

Figure 1. Study design



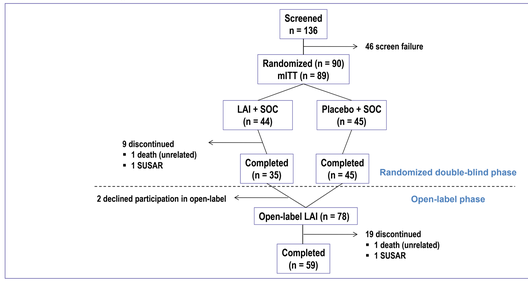
CF, cystic fibrosis; LAI, liposomal amikacin for inhalation; MAC, *Mycobacterium avium* complex; NTM, nontuberculous mycobacteria.

[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.

STUDY DISPOSITION

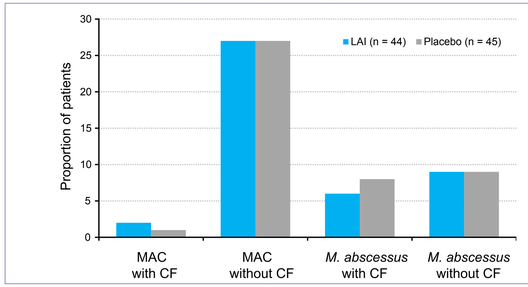
- Of 136 screened patients (**Figures 2** and **3**):
  - 90 were randomized (19% CF; 81% non-CF; 64% with MAC infection; and 36% with *M. abscessus* infection).
  - 89 patients were included in the modified intent-to-treat (mITT) population (ie, all patients who received ≥1 dose of study drug).
- Most patients were female (88%) and Caucasian (92%); baseline mean (standard deviation [SD]) age was 58.5 (15.8) years, and baseline median (range) age was 63.0 (18-85) years **(Table 1)**.
- 80 patients completed treatment in the double-blind phase and 59 patients 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.

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 of mITT Population

Characteristic	LAI (n = 44)	Placebo (n = 45)	Overall (N = 89)
Gender, n (%)			
Male	6 (14)	5 (11)	11 (12)
Female	38 (86)	40 (89)	78 (88)
Race/ethnicity, n (%)[a]			
Caucasian (not of Hispanic origin)	42 (96)	40 (89)	82 (92)
Hispanic	0	2 (4)	2 (2)
African	0	1 (2)	1 (1)
Asian	2 (5)	2 (4)	4 (5)
Other	0	0	0
Baseline age, years			
n	44	45	89
Mean (SD)	58.0 (16.6)	59.1 (15.2)	58.5 (15.8)
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)	63.6 (21.3)	62.6 (17.2)	63.1 (19.2)
Median	61.3	61.0	61.0
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.
[a] Percentages may not add up to 100 due to rounding.

UPDATED ANALYSIS

- Analyses of preliminary top-line data from this study have previously been presented. Closer inspection of the primary data revealed that specimens negative for AFB but positive for ordinary bacteria, indicating bacterial contamination, were categorized as 'positive for mycobacteria' in liquid media in the preliminary analysis; however, there was no growth of mycobacteria on subculture.
- Pursuant to standard practice, such specimens should be considered negative. In the updated analyses, the re-categorization was adopted. The appropriateness of this corrected categorization was further supported at each time point with at least one and in most cases two additional negative cultures.
- Appropriate categorization of these specimens does affect the efficacy outcomes such that the drug now appears to be more effective than was originally reported.

RESULTS

- The primary endpoint of change from baseline in the full semiquantitative scale did not achieve statistical significance, although there was a positive trend in favor of the LAI arm.
- The proportion of patients with negative sputum cultures for NTM in each subgroup by treatment arm at Day 84 and Day 168 (mITT population) are summarized in **Tables 2-4**.
- At Day 84, statistically significant between-group differences in patients achieving negative sputum cultures for NTM, in favor of LAI vs. placebo, were seen in patients without CF ($P = 0.004$), those with MAC infection ($P = 0.004$), females ($P = 0.0004$), Caucasians ($P = 0.015$), and patients aged <63 years (median age of population; $P = 0.016$) **(Table 2)**.
- At Day 168, there were no statistically significant differences in patients achieving negative sputum cultures for NTM between the group originally assigned to LAI and the group originally assigned to placebo **(Table 2)**.

Table 2. Proportion of Patients With Negative Sputum Cultures for NTM in Each Subgroup by Treatment Arm at Days 84 and 168 (mITT population)[a]

	Day 84 (double-blind phase)			Day 168 (open-label phase)		
Subgroup, n/n (%)	LAI (n = 44)	Placebo (n = 45)	*P* value[b]	Prior LAI[c] (n = 35)	Prior placebo[c] (n = 43)	*P* value[b]
MAC	12/27 (44)	3/28 (11)	**0.004**	13/24 (54)	9/27 (33)	0.131
MAB	2/14 (14)	1/17 (6)	0.377	2/10 (20)	3/14 (21)	0.955
CF	1/7 (14)	1/9 (11)	1.000	3/6 (50)	1/7 (14)	0.266
Non-CF	13/34 (38)	3/36 (8)	**0.004**	12/28 (43)	11/34 (32)	0.438
Gender						
Female	14/36 (39)	2/40 (5)	**0.0004**	14/30 (47)	10/36 (28)	0.131
Male	0/5	2/5 (40)	0.444	1/4 (25)	2/5 (40)	1.000
Ethnicity						
Caucasian	13/39 (33)	4/40 (10)	**0.015**	15/32 (47)	11/37 (30)	0.213
Non-Caucasian	1/2 (50)	0/5	0.286	0/2	1/4 (25)	1.000
Age[d]						
<63 years	9/21 (43)	2/22 (9)	**0.016**	9/19 (47)	6/20 (30)	0.333
≥63 years	5/20 (25)	2/23 (9)	0.222	6/15 (40)	6/21 (29)	0.499

CF, cystic fibrosis; LAI, liposomal amikacin for inhalation; MAB, *Mycobacterium abscessus*; MAC, *Mycobacterium avium* complex; mITT, modified intent-to-treat; NTM, nontuberculous mycobacteria; NA, not available.
[a] Missing values are excluded under the assumption of missing at random, for which missing baseline or post-baseline values are excluded but all non-missing data are included (ie, exclusion is not at subject-level but, rather, at time point−level).
[b] For pairwise comparisons of the LAI arm with the placebo arm, a stratified Cochran−Mantel−Haenszel test of treatment arm adjusting for the randomization strata was used.
[c] All patients received LAI in the open-label phase.
[d] Median age of population was 63 years.

Table 3. Subgroup Analysis of Patients With MAC Infection Who Achieved Negative Sputum Cultures for NTM by Treatment Arm at Days 84 and 168 (mITT population)[a]

	Day 84 (double-blind phase)			Day 168 (open-label phase)		
Subgroup, n/n (%)	LAI (n = 29)	Placebo (n = 28)	*P* value[b]	Prior LAI[c] (n = 24)	Prior placebo[c] (n = 28)	*P* value[b]
CF	0/2	0/1	NA	1/2 (50)	0/1	1.000
Non-CF	12/25 (48)	3/27 (11)	**0.005**	12/22 (55)	9/26 (35)	0.244
Cavitary disease	5/17 (29)	2/20 (10)	0.212	5/14 (36)	5/19 (26)	0.707
Non-cavitary disease	7/10 (70)	1/8 (13)	**0.025**	8/10 (80)	4/8 (50)	0.321
Gender						
Female	12/25 (48)	2/25 (8)	**0.004**	13/22 (59)	8/24 (33)	0.138
Male	0/2	1/3 (33)	1.000	0/2	1/3 (33)	1.000
Ethnicity						
Caucasian	12/27 (44)	3/25 (12)	**0.014**	13/24 (54)	8/24 (33)	0.244
Non-Caucasian	0/0	0/3	NA	0/0	1/3 (33)	NA
Age[d]						
<63 years	7/13 (54)	1/11 (9)	**0.034**	7/13 (54)	4/11 (36)	0.444
≥63 years	5/14 (36)	2/17 (12)	0.198	6/11 (55)	5/16 (31)	0.264

CF, cystic fibrosis; LAI, liposomal amikacin for inhalation; MAC, *Mycobacterium avium* complex; mITT, modified intent-to-treat; NA, not available.
[a] Missing values are excluded under the assumption of missing at random, for which missing baseline or post-baseline values are excluded but all non-missing data are included (ie, exclusion is not at subject-level but, rather, at time point−level).
[b] Pairwise comparisons of the LAI arm with the placebo arm were based on Fisher's Exact Test.
[c] All patients received LAI in the open-label phase.
[d] Median age of population was 63 years.

Table 4. Subgroup Analysis of Patients With MAB Infection Who Achieved Negative Sputum Cultures for NTM by Treatment Arm at Days 84 and 168 (mITT population)[a]

	Day 84 (double-blind phase)			Day 168 (open-label phase)		
Subgroup, n/n (%)	LAI (n = 15)	Placebo (n = 17)	*P* value[b]	Prior LAI[c] (n = 11)	Prior placebo[c] (n = 15)	*P* value[b]
CF	1/15 (20)	1/8 (13)	1.000	2/4 (50)	1/6 (17)	0.500
Non-CF	1/9 (11)	0/9	1.000	0/6	2/8 (25)	0.473
Cavitary disease	1/13 (8)	1/15 (7)	1.000	1/9 (11)	3/12 (25)	0.603
Non-cavitary disease	1/1 (100)	0/2	0.333	1/1 (100)	0/2	0.333
Gender						
Female	2/11 (18)	0/15	0.169	1/8 (13)	2/12 (17)	1.000
Male	0/3	1/2 (50)	0.400	1/2 (50)	1/2 (50)	1.000
Ethnicity						
Caucasian	1/12 (8)	1/15 (7)	1.000	2/8 (25)	3/13 (23)	1.000
Non-Caucasian	1/2 (50)	0/2	1.000	0/2	0/1	NA
Age[d]						
<63 years	2/8 (25)	1/11 (9)	0.546	2/6 (33)	2/9 (22)	1.000
≥63 years	0/6	0/6	NA	0/4	1/5 (20)	1.000

CF, cystic fibrosis; LAI, liposomal amikacin for inhalation; MAB, *Mycobacterium abscessus*; mITT, modified intent-to-treat; NA, not available.
[a] Missing values are excluded under the assumption of missing at random, for which missing baseline or post-baseline values are excluded but all non-missing data are included (ie, exclusion is not at subject-level but, rather, at time point−level).
[b] Pairwise comparisons of the LAI arm with the placebo arm were based on Fisher's Exact Test .
[c] All patients received LAI in the open-label phase.
[d] Median age of population was 63 years.

CONCLUSIONS

- The study failed to meet its primary endpoint, and these are post-hoc subgroup analyses of patients with NTM lung infection refractory to guideline-based therapy.
- LAI appeared superior to placebo with regard to negative sputum cultures for NTM in patients with non-CF underlying lung disease and MAC infection.
  - The subgroup of patients with non-CF MAC infection demonstrated a positive efficacy result within the timeframe of the study (ie, 12-week double-blind phase and 12-week open-label phase).
  - Evidence of the effect of LAI on other subgroups (eg, non-CF *M. abscessus* and CF in NTM disease) is insufficient to draw definitive conclusions and needs further study.

REFERENCES

1. Adjemian J, Olivier KN, Seitz AE, et al. *Am J Respir Crit Care Med.* 2012;185(8):881-886.
2. Mirsaeidi M, Machado RF, Garcia JGN, Schraufnagel DE. *PLoS One.* 2014;9(3):e91879.
3. Ringshausen FC, Apel RM, Bange FC, et al. *BMC Infect Dis.* 2013;13:231.
4. Marras TK, Chedore P, Ying AM, Jamieson F. *Thorax.* 2003;62(8):661-666.
5. Winthrop KL, McNelley E, Kendall B, et al. *Am J Resp Crit Care Med.* 2010;182(7):977-982.
6. Griffith DE, Aksamit TR. *Curr Opin Infect Dis.* 2012;25(2):218-227.
7. Meers P, Neville M, Malinin V, et al. *J Antimicrob Chemother.* 2008;61(4):859-868.
8. Clancy JP, Dupont L, Konstan MW, et al. *Thorax.* 2013;68(9):818-825.
9. Rose SJ, Neville ME, Gupta R, Bermudez LE. *PLOS One.* 2014;9(9):3108703.
10. Bilton D, Pressler T, Fajac I, et al. Poster presented at the 2014 North American Cystic FibrosisConference (NACFC); October 9-11, 2014; Atlanta, GA.

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DISCLOSURES

Kevin L. Winthrop is involved in clinical trials sponsored by, and is a consultant of Insmed Incorporated. Gina Eagle, John P. McGinnis II, and Liza Micioni are employees of Insmed Incorporated. Charles L. Daley is involved in clinical trials sponsored by Insmed Incorporated. Stephen Ruoss is involved in clinical trials sponsored by, and is a consultant of Insmed Incorporated. Doreen J. Addrizzo-Harris is involved in clinical trials sponsored by Insmed Incorporated and Aradigm Corporation. Patrick Flume has received grant support from, and is a consultant of Insmed Incorporated. Daniel Dorgan has no disclosures. Matthias Salathe has served on the advisory panel of Insmed Incorporated. Barbara A. Brown-Elliott is the Supervisor of the Mycobacteria/Nocardia Laboratory which performed mycobacterial identification and susceptibility testing for this study. Richard J. Wallace, Jr. is the Director of the Mycobacteria/Nocardia Laboratory at the University of Texas which performed molecular and microbiologic testing for this study. David E. Griffith is involved in clinical trials sponsored by Insmed Incorporated. Kenneth N. Olivier is supported by the Division of Intramural Research of the NHLBI/NIH, and had a Cooperative Research and Development Agreement between Insmed Incorporated and NIAID/NIH.

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