

Randomized Phase 3 Trial of Amikacin Liposome Inhalation Suspension (ALIS) for Treatment-Refractory Nontuberculous Mycobacterial (NTM) Lung Disease Caused by *Mycobacterium avium* Complex (MAC) in Adult Patients

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Conflict of Interest/Disclaimer

- I was a co-investigator on TR02-112, a study of amikacin liposome inhalation suspension for treatment of refractory *M. avium* complex and *M. abscessus* lung diseases.
- I am a co-investigator on INS-212 CONVERT and INS-312 CONVERT studies of amikacin liposome inhalation suspension for treatment of *M. avium* complex lung disease.
- I am a co-investigator on an Insmmed-sponsored IIR study of amikacin liposome inhalation suspension for treatment of *M. abscessus* lung disease.

Background

- *Mycobacterium avium* complex (MAC) accounts for 80% to 85% of NTM lung disease in the United States.¹
- MAC lung disease is chronic with high morbidity and mortality.
 - Therapeutic options are limited for treatment-refractory disease.²
- Amikacin is often reserved for fibrocavitary or severe nodular/bronchiectatic MAC lung disease due to inconvenience, renal and auditory toxicity.^{2,3}

NTM, nontuberculous mycobacteria.

1. Prevots DR, et al. *Clin Chest Med* 2015; 36:13-34; 2. Griffith DE, et al. *Curr Opin Infect Dis.* 2012; 25:219-227; 3. Griffith DE, et al. *Am J Respir Crit Care Med* 2007; 175:367–416.

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Amikacin Liposome Inhalation Suspension (ALIS)

- ALIS^a is amikacin sulfate (590 mg amikacin base)^b encapsulated in liposomes for inhalational delivery.
- ALIS was designed to increase amikacin uptake into alveolar macrophages, and limit systemic exposure.¹⁻⁴
- Phase 2: ALIS combined with guideline-based therapy (GBT) achieved early and sustained negative sputum cultures in refractory NTM lung disease.^{1,c}
- CONVERT: ongoing randomized, open-label, phase 3 study of ALIS + GBT in adults with treatment-refractory MAC lung disease (NCT02344004)

^a Previously referred to as Liposomal Amikacin for Inhalation or LAI.

^b 623 mg amikacin base per vial; to deliver 590 mg amikacin base to the nebulizer.

^c Primary endpoint not met in Phase 2 study.

1. Olivier KN, et al. *Am J Respir Crit Care Med* 2017; 195:814-23;
2. Rose SJ, et al. *PLoS One* 2014; 9:e108703;
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4. Zhang J, et al. *Front Microbiol* 2018, doi: 10.3389/fmicb.2018.00915.

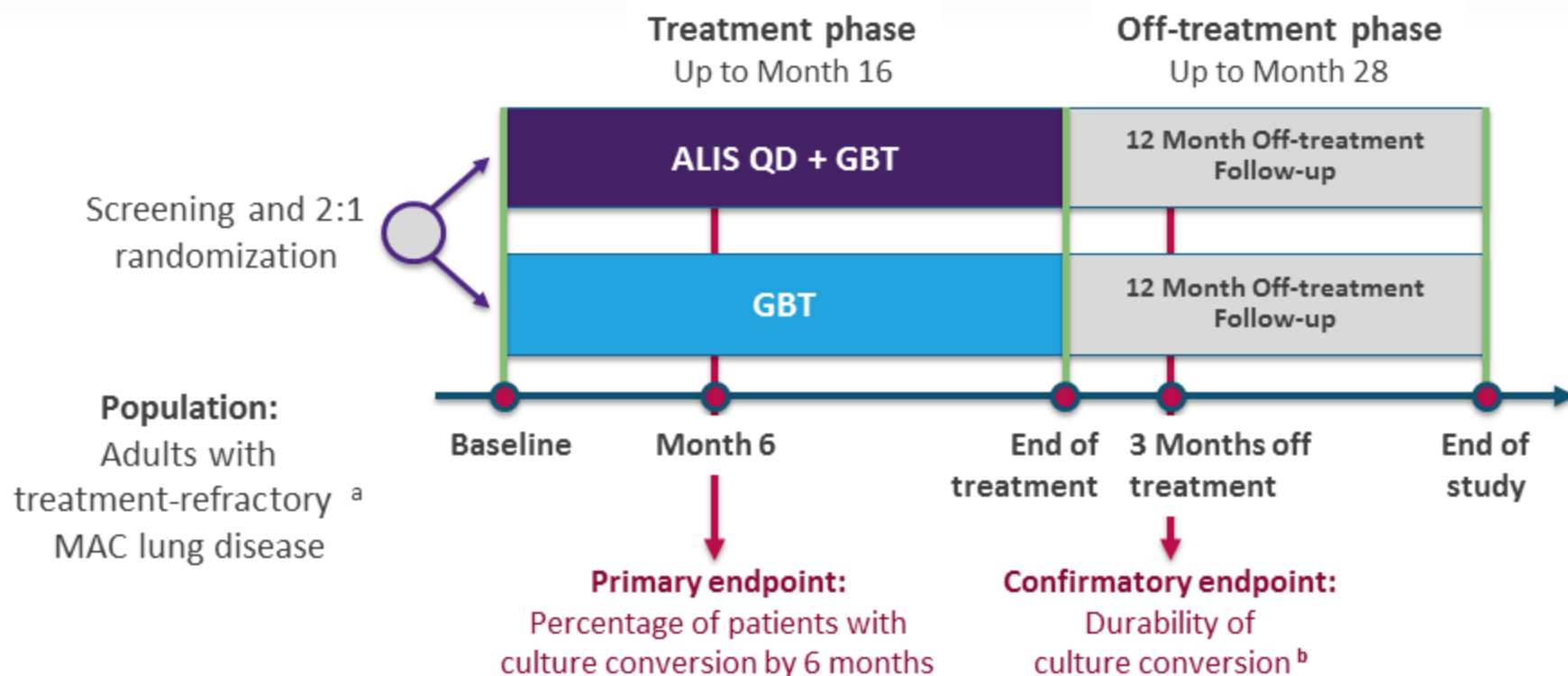
Key inclusion criteria

- ≥ 18 years of age with MAC lung infections documented by ≥ 1 positive sputum or bronchoscopy culture within 6 months and MAC-positive sputum at screening
- At least 6 months of GBT, either ongoing or stopped within 12 months before screening
- Evidence of characteristic lung findings (e.g. nodular infiltrate, cavity) on a chest radiograph or chest computed tomography

Key exclusionary conditions

- Cystic fibrosis
- Active pulmonary tuberculosis
- Immunodeficiency syndromes
- MAC isolates with amikacin MIC $> 64 \mu\text{g/mL}$
- Active malignancies within 1 year before screening

Randomized, Open-Label Phase 3 Study



^a At least 6 months treatment with persistently positive sputum cultures for MAC.

^b Final analysis at completion of study is durability of culture conversion 3 months off all MAC treatment for patients who complete 12 months of treatment from the first negative culture that defined conversion.

CONVERT Study

Patient Disposition

	ALIS + GBT	GBT Alone	Total
Screened			492
Screen failure			156
Intent to treat population (ITT) ^a	224	112	336
Safety population	223	112	335
Study withdrawal	44 (19.6%)	10 (8.9%)	54 (16.1%)

As of data cutoff on July 7, 2017.

7 ^a All randomized patients.

^b Randomized patients who received at least 1 dose of ALIS (ALIS+GBT arm) or GBT (GBT alone arm).

Patient Demographic and Disease Characteristics

Parameter	ALIS + GBT N = 224	GBT Alone N = 112	Overall N = 336
Age, mean yr (SD)	64.6 (9.6)	64.9 (10.2)	64.7 (9.8)
Female, n (%)	165 (73.7)	68 (60.7)	233 (69.3)
Body mass index, mean kg/m ² (SD)	21.4 (3.9)	21.0 (3.8)	NA
Race, n (%)			
White	158 (70.5)	77 (68.8)	235 (69.9)
Japanese	35 (15.6)	15 (13.4)	50 (14.9)
Other Asian	23 (10.3)	10 (8.9)	33 (9.8)
Other/not reported	5 (2.2)	7 (6.3)	12 (3.6)
Black/African American	3 (1.3)	3 (2.7)	6 (1.8)
Underlying lung disease, n (%)			
Bronchiectasis only	146 (65.2)	64 (57.1)	210 (62.5)
COPD only	29 (12.9)	19 (17.0)	48 (14.3)
COPD and bronchiectasis	22 (9.8)	18 (16.1)	40 (11.9)
Current smoker, n (%)	26 (11.6)	10 (8.9)	36 (10.7)

Primary Endpoint: Culture Conversion by Month 6^a

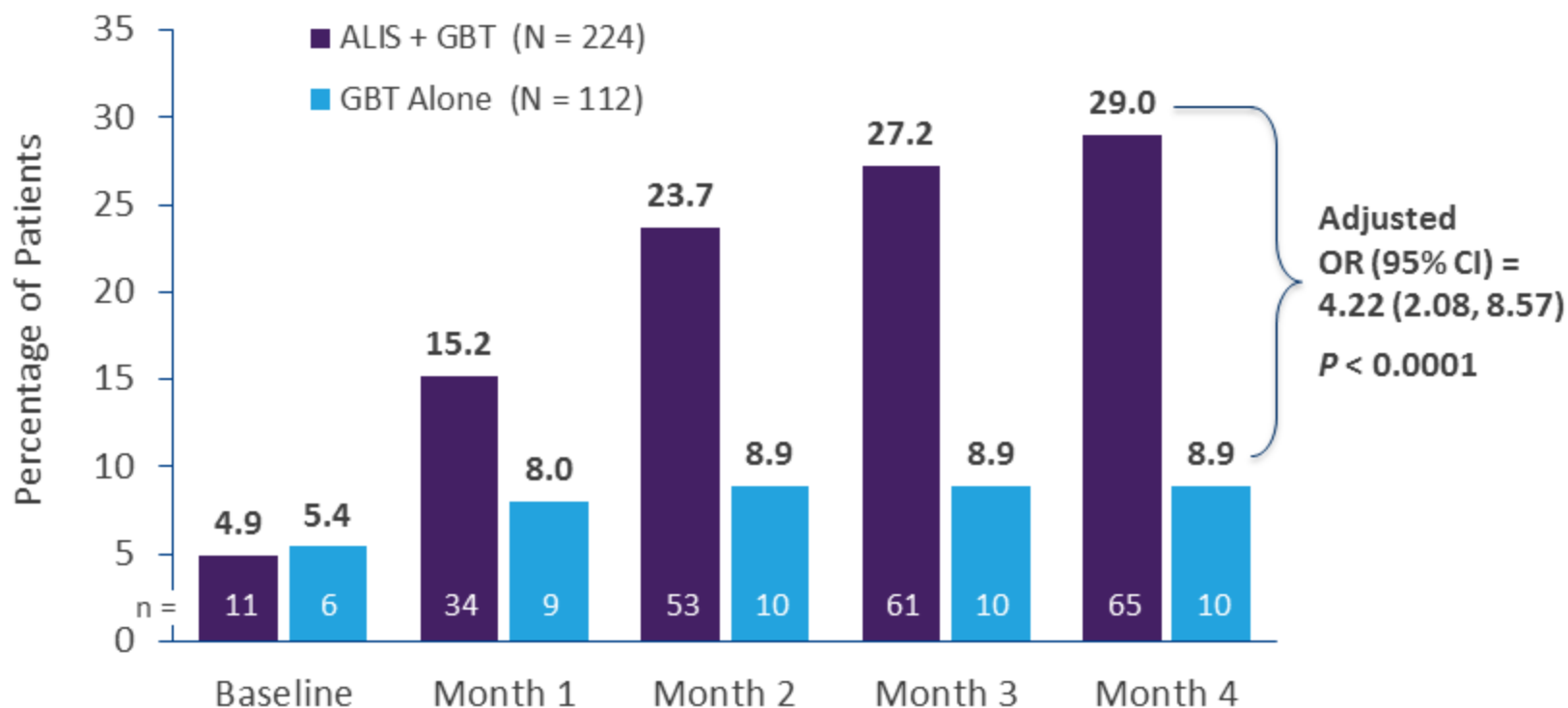
ITT Population	ALIS + GBT N = 224	GBT Alone N = 112
Converter	65 (29.0%)	10 (8.9%)
Non-converter	159 (71.0%)	102 (91.1%)
Adjusted odds ratio (95% CI) ^b	4.220 (2.078, 8.570)	
P value	< 0.0001	

^a Culture conversion defined as 3 consecutive monthly MAC-negative sputum cultures by Month 6

^b Adjusted Odds ratio and p-value are calculated using Cochran-Mantel-Haenszel test, with stratification factors of the combination of smoking status and prior GBT as fixed factors.

Cumulative Rate of Sputum Culture Conversion

Shown at the first month of conversion^a



^a The first of 3 consecutive negative sputum cultures must be achieved by Month 4 to meet the primary culture conversion endpoint by Month 6.

6 Minute Walk Test¹

Analysis Group (n) ^a	Baseline Mean meters (SD)	LS Mean Change at Month 6 vs Baseline (95% CI)	P Value
ALIS + GBT (220)	425.7 (127.6)	-1.9 (-24.0, 20.2)	0.72 ^b
GBT alone (111)	420.4 (126.7)	1.3 (-22.2, 24.9)	
All converters (70)	457.9 (120.6)	16.8 (-10.2 to 43.8)	0.011 ^c
All nonconverters (191)	427.7 (120.5)	-7.9 (-30.5 to 14.7)	

^a Baseline is defined as the last non-missing value prior to first dose of study drug; n is the number of patients with a baseline score and at least one post-baseline score.

^b MMRM model with pattern-mixture modeling of missing values due to dropout, which includes treatment, month, the treatment-by-month interaction, and the combination of smoking status and prior multi-drug regimen as fixed factors, the baseline 6MWT distance as a covariate and baseline 6MWT distance-by-month interaction.

^c ANCOVA model of change from baseline to each visit in 6MWT is based on 6-month completers and includes converter status, the combination of smoking status and prior multi-drug regimen as fixed factors, and the baseline 6MWT distance as a covariate.

LS, least squares.

¹Winthrop KL, et al. ATS 2018, Poster A1984.

Safety Population Summary

Parameter, n (%)	ALIS + GBT N = 223	GBT Alone N = 112
Any TEAE	219 (98.2)	102 (91.1)
Any serious TEAE	45 (20.2)	20 (17.9)
Any TEAE of Special Interest ^a	122 (54.7)	34 (30.4)
TEAE leading to death	6 (2.7)	5 (4.5)
Serious TEAE occurring in ≥ 3% of patients in either arm		
Pneumonia	8 (3.6)	2 (1.8)
COPD exacerbation	7 (3.1)	1 (0.9)
Hemoptysis	6 (2.7)	5 (4.5)
TEAE of Special Interest ^a occurring in ≥ 3% of patients in either arm		
Dyspnea	48 (21.5)	10 (8.9)
Hemoptysis	39 (17.5)	15 (13.4)
Wheezing ± bronchospasm	20 (8.9)	3 (2.7)
COPD exacerbation	18 (8.1)	3 (2.7)
Tinnitus	17 (7.6)	1 (0.9)
Dizziness	14 (6.3)	3 (2.7)
Hearing loss ^b	10 (4.5)	7 (6.3)

^a Defined as pre-specified events known to be attributed to parenteral amikacin and inhalation of antibiotics.

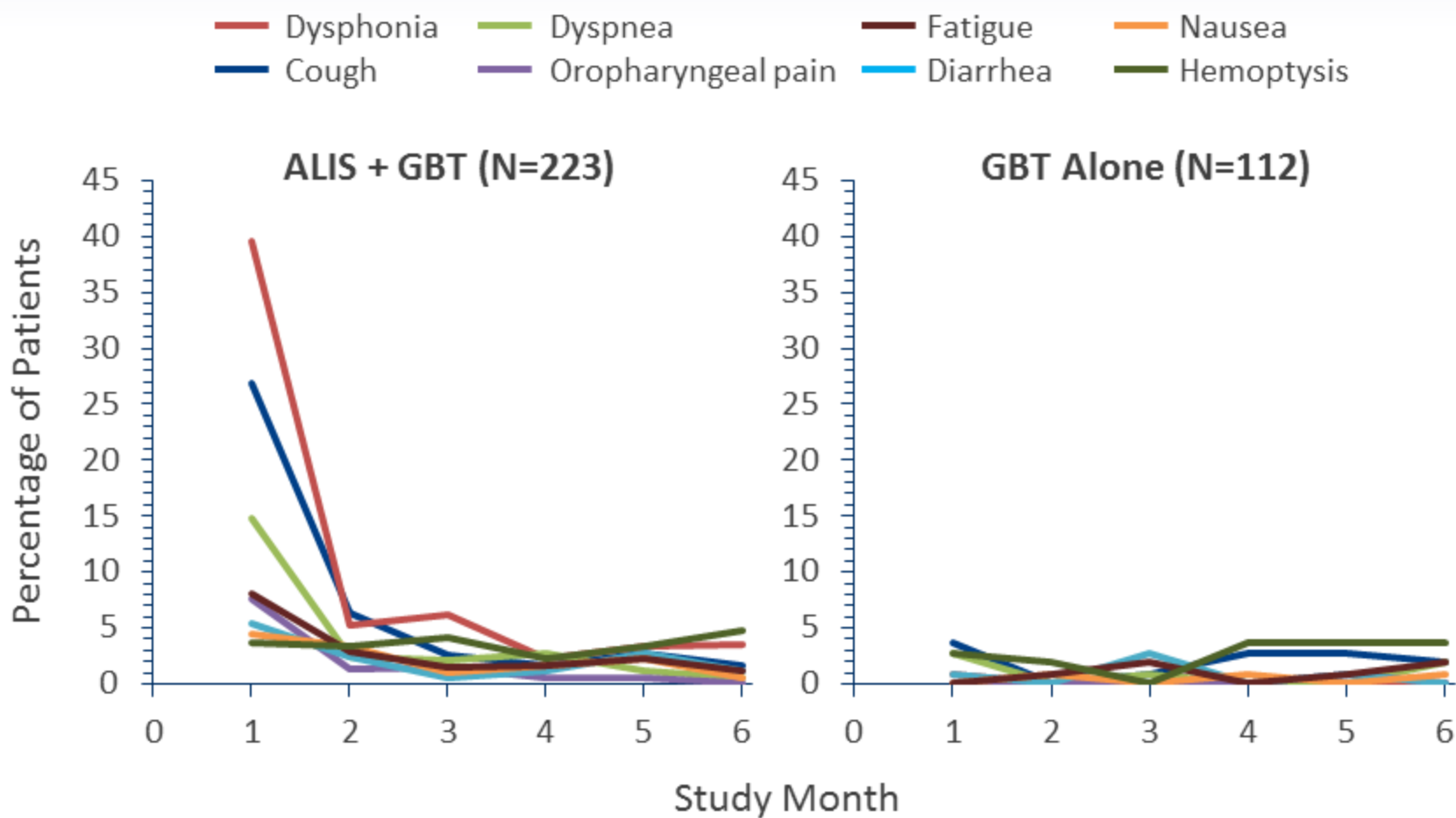
^b Includes preferred terms Hypoacusis, Deafness neurosensory, and Deafness.

TEAE, treatment-emergent adverse event.

Most Common TEAEs – Safety Population

Preferred Term	ALIS + GBT N = 223 Patients, n (%)	GBT Alone N = 112 Patients, n (%)
TEAEs occurring in ≥ 10% of patients in either arm		
Dysphonia	102 (45.7)	1 (0.9)
Cough	83 (37.2)	17 (15.2)
Dyspnea	48 (21.5)	10 (8.9)
Hemoptysis	39 (17.5)	15 (13.4)
Fatigue	36 (16.1)	8 (7.1)
Diarrhea	28 (12.6)	5 (4.5)
Nausea	25 (11.2)	4 (3.6)
Oropharyngeal pain	24 (10.8)	2 (1.8)

Common Adverse Event Onset Over Time ^a



^a TEAEs occurring in >10% of patients in either arm.

Summary

- ALIS is a novel amikacin formulation that, combined with GBT, improved sputum conversion rates in adults with amikacin-susceptible, treatment-refractory MAC lung disease compared with GBT alone.
- In an exploratory analysis, converters had a greater change from baseline to Month 6 than non-converters in the 6MWT distance regardless of treatment arm (LS mean difference, 24.71).
- Addition of ALIS to GBT was associated with higher rates of TEAEs, predominantly mild or moderate in severity and respiratory in nature. Incidences of most frequent TEAEs declined after the first month.
- Data from the CONVERT study demonstrate that ALIS may have a role in the treatment of refractory MAC lung disease and support further evaluation of ALIS in other MAC therapy roles, such as initial therapy, maintenance therapy, and treatment of other NTM pulmonary pathogens.

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