



# Amikacin Liposome Inhalation Suspension for *Mycobacterium avium* Complex Lung Disease

## A 12-Month Open-Label Extension Clinical Trial

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### Abstract

**Rationale:** Patients with refractory *Mycobacterium avium* complex (MAC) lung disease have limited treatment options. In the CONVERT study, amikacin liposome inhalation suspension (ALIS) added to guideline-based therapy (GBT) increased culture conversion rates versus GBT alone by Month 6. Limited data are available regarding >6-month treatment in a refractory population.

**Objectives:** Evaluate 12-month safety, tolerability, and efficacy of ALIS+GBT.

**Methods:** Adults with refractory MAC lung disease not achieving culture conversion by CONVERT Month 6 could enroll in this open-label extension (INS-312) to receive 590 mg once-daily ALIS+GBT for 12 months. Two cohorts enrolled: the “ALIS-naive” cohort included patients randomized to GBT alone in CONVERT, and the “prior-ALIS” cohort included those randomized to ALIS+GBT in CONVERT. Safety and tolerability of ALIS over 12 months (primary endpoint) and culture conversion by Months 6 and 12 were assessed.

**Results:** In the ALIS-naive cohort, 83.3% of patients ( $n=75/90$ ) experienced respiratory treatment-emergent adverse events (TEAEs), and 35.6% ( $n=32$ ) had serious TEAEs; 26.7% ( $n=24$ ) achieved culture conversion by Month 6 and 33.3% ( $n=30$ ) by Month 12. In the prior-ALIS cohort, 46.6% of patients ( $n=34/73$ ) experienced respiratory TEAEs, and 27.4% ( $n=20$ ) had serious TEAEs; 9.6% ( $n=7$ ) achieved culture conversion by Month 6 ( $\leq 14$  mo ALIS exposure) and 13.7% ( $n=10$ ) by Month 12 ( $\leq 20$  mo ALIS exposure). Nephrotoxicity-related TEAEs and measured hearing decline were infrequent in both cohorts.

**Conclusions:** In up to 20 months of ALIS use, respiratory TEAEs were common, nephrotoxicity and hearing decline were infrequent, and culture conversion continued beyond 6 months of therapy.

Clinical trial registered with [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT02628600).

**Keywords:** nontuberculous mycobacteria; culture conversion; *Mycobacterium avium*; amikacin liposome inhalation suspension; ALIS

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Nontuberculous mycobacteria (NTM) can cause debilitating lung disease, especially in individuals with chronic lung diseases such as bronchiectasis, cystic fibrosis, and chronic obstructive pulmonary disease (COPD) (1–3). The *Mycobacterium avium* complex (MAC) species are the most common causative agents of NTM lung disease (2–4). First-line therapy for nodular disease comprises a three-drug antibiotic regimen (a macrolide, ethambutol, and a rifamycin) and is generally continued until culture conversion (negative MAC sputum culture) is sustained for 12 months (5). Despite lengthy multidrug macrolide-based treatment, ≈30–40% of patients do not achieve sustained culture conversion (6, 7), and therapeutic options for patients refractory to first-line therapy are limited (6).

Systemic administration of amikacin, a potent antimycobacterial agent, is limited by exposure-dependent renal and auditory toxicities (3, 8–10), as well as the inherent risks and inconvenience of intravenous therapy (11, 12). Amikacin liposome inhalation suspension (ALIS) was developed to deliver high concentrations of amikacin to the site of infection while limiting systemic exposure. International guidelines for the treatment of MAC lung disease recommend the addition of ALIS to guideline-based therapy (GBT) in patients who fail to convert after 6 months of treatment (5). In previously reported phase 2 and 3 studies, ALIS added to GBT (ALIS+GBT) increased culture conversion rates in patients with refractory NTM lung disease compared with GBT alone (13, 14). In the phase 3 study (CONVERT), significantly more ALIS+GBT-treated patients met the definition of culture conversion (three consecutive monthly sputum cultures negative for MAC) by the Month 6 primary endpoint analysis versus patients treated with GBT alone (29.0% vs. 8.9%;  $P < 0.0001$ ) (14). Respiratory adverse events (AEs) were reported in 87.4% of ALIS+GBT-treated patients versus 50% of those treated with GBT alone, and most were mild or moderate.

The current study (INS-312; NCT02628600) was a 12-month open-label extension of CONVERT that evaluated the long-term safety, tolerability, and efficacy of once-daily ALIS+GBT. Preliminary results were presented previously as abstracts (15, 16).

## Methods

### Patients

Eligible patients were adults with treatment-refractory MAC lung disease who were enrolled in the CONVERT study and did not meet the primary endpoint of culture conversion by Month 6 or had recurrent MAC infection (positive MAC culture after conversion) by Month 6 (confirmed at Month 8 when sputum data were unblinded). See online supplement for complete INS-312 eligibility criteria.

### Study Design

INS-312, a 12-month open-label safety extension of CONVERT (14), assessed safety and tolerability of once-daily ALIS 590 mg plus continued GBT (Figure 1). Eligible patients who completed both Month 6 and Month 8 or end-of-treatment (EOT) visits in CONVERT could consent to enroll directly into INS-312, in which case the Month 8 or EOT visit served as INS-312 baseline. Visits were scheduled at INS-312 baseline and monthly throughout the 12-month treatment phase. A follow-up end-of-study safety visit occurred 28 days after the EOT visit.

All patients were treated with ALIS in INS-312; however, for the purpose of analyses, patients were grouped according to assigned treatment arm in CONVERT. The ALIS-naïve cohort comprised patients assigned to the GBT-alone arm in CONVERT, and the prior-ALIS cohort comprised patients assigned to the ALIS+GBT arm in CONVERT. Consequently, patients in the ALIS-naïve cohort received their first dose of ALIS in INS-312, and patients in the prior-ALIS

cohort were exposed to ALIS for up to 8 months at INS-312 study entry.

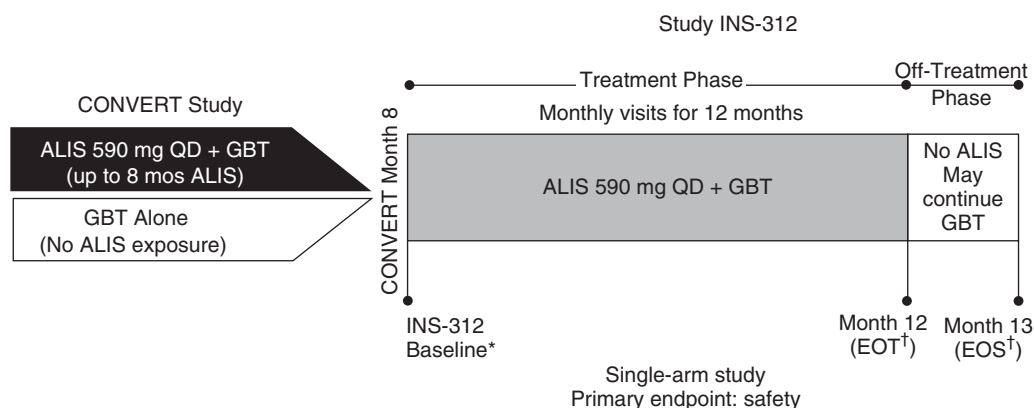
ALIS was administered by inhalation using a PARI eFlow Technology nebulizer (PARI Pharma GmbH). ALIS interruptions were allowed at the discretion of the investigator and after discussion with the medical monitor if patients experienced distressing respiratory events (e.g., dysphonia, oropharyngeal pain, hemoptysis, cough). If a temporary dose interruption was permitted, reintroduction of ALIS was recommended once symptoms had subsided. Changes to patients' concurrent antimycobacterial regimen were at the discretion of the investigator. Bronchodilator use was allowed, and patients who developed bronchospasm could be pretreated with a bronchodilator before ALIS administration. Treatment with other aminoglycosides with activity against MAC (e.g., streptomycin, kanamycin) was allowed as rescue medication but required discontinuation from the study.

### Endpoints and Assessments

The primary objective of INS-312 was to assess the long-term safety and tolerability of once-daily ALIS+GBT. AEs were coded using the Medical Dictionary of Regulatory Activities (MedDRA) v17.1 (17) and graded based on the Common Terminology Criteria for Adverse Events v4.0 (18). AEs that occurred on or after the first dose of ALIS in INS-312 and within 28 days after the last dose were considered treatment-emergent (TEAEs). Ongoing medical history conditions from CONVERT that were present at INS-312 baseline, including TEAEs or chronic conditions requiring medication, were included in medical histories (Table E1 in the online supplement). The frequency of TEAEs, TEAEs leading to study withdrawal, serious TEAEs, TEAEs of special interest, and clinically significant abnormalities in laboratory results and vital signs constituted the primary endpoint. Secondary endpoints included the percentage of patients

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Results are presented by treatment received in CONVERT

- ALIS-Naive Cohort: first ALIS dose received in INS-312
- Prior-ALIS Cohort: received ALIS up to 8 months at INS-312 BL

**Figure 1.** INS-312 study design. Adults with treatment-refractory MAC lung disease who were originally enrolled in the CONVERT study and did not achieve conversion or had recurrent MAC infection by Month 6 exited CONVERT at Month 8, and eligible patients were permitted to enroll in the INS-312 open-label safety extension. Patients originally randomized to receive ALIS+GBT in CONVERT (prior-ALIS cohort) continued their assigned treatment. Patients originally randomized to receive GBT alone in CONVERT (ALIS-naive cohort) had ALIS added to their ongoing GBT at INS-312 baseline. \*INS-312 baseline coincided with the EOT visit in CONVERT. †All patients, including those who terminated the study early, had their EOT visit and safety follow-up visit at EOS. ALIS = amikacin liposome inhalation suspension; BL = baseline; EOS = end of study; EOT = end of treatment; GBT = guideline-based therapy; MAC = *Mycobacterium avium* complex; QD = once daily.

achieving culture conversion by Month 6 (first negative sputum that defined conversion achieved by Month 4) and Month 12 (first negative sputum that defined conversion by Month 10), time-to-culture conversion, and change in 6-minute walk test (6MWT) distance from INS-312 baseline to Months 6 and 12.

At INS-312 baseline and all treatment visits, vital signs, pulse oximetry, and urine pregnancy tests were performed, and sputum for microbiological assessment was collected (at least two samples—spontaneous or induced—at each visit). Patients were instructed to interrupt ALIS 2 days before visits during which a sputum sample was scheduled to be collected. Sputum samples that defined conversion (up to nine samples over 3 mo) had to be MAC culture-negative in liquid and on solid media. Sputum collected at the CONVERT Month 8 or EOT visit served as the INS-312 baseline sample. Microbiological recurrence was defined as either one MAC-positive culture on solid media or three or more consecutive MAC-positive cultures on liquid media after meeting the criterion for culture conversion.

Recurrent MAC species were identified at the regional laboratory responsible for sputum culture by sequencing the 16S rRNA subunit or 65-kD heat shock protein gene or by line probe assay (19–21). If the recurrent

MAC isolate was the same MAC species at baseline, variable number of tandem repeat type was determined at a central laboratory (The University of Texas Health Science Center, Tyler, Texas) to verify whether the patient had acquired a different MAC strain (22–24). In accordance with the NTM-Network European Trials group outcome definitions, reinfection was defined as recurrent MAC infection caused by either a different MAC species or the same MAC species but different strain than was isolated at screening or baseline, and relapse was defined as recurrent MAC infection caused by the same MAC species and strain isolated at screening or baseline (25). Additional methodological details are in the online supplement.

Safety laboratory assessments (chemistry, hematology, and urinalysis) and physical examination were performed at INS-312 baseline and Months 1, 3, 6, 9, and 12 or EOT. Audiology testing using air conduction was performed at INS-312 baseline and Months 6 and 12 or EOT. Common Terminology Criteria for Adverse Events ototoxicity grade  $\geq 2$  was reported as an AE. 6MWT distance was assessed at INS-312 baseline and Months 6 and 12 or EOT. At the follow-up end-of-study visit, physical examination was performed. Additional details of study assessments are in the online supplement.

### Statistical Analyses

The safety population included all patients who received at least one dose of ALIS. Safety data, percentage of patients achieving culture conversion by Months 6 and 12, and changes in 6MWT distance from INS-312 baseline to Months 6 and 12 were reported using descriptive statistics. Kaplan-Meier estimates for the distribution of time-to-culture conversion were constructed for each cohort. All statistical analyses were performed using SAS v9.4 (SAS Institute Inc.) or later. No formal sample size or power calculations were conducted, and no subgroup analyses were planned.

### Study Conduct

The study protocol, informed consent form, and all other related materials were reviewed and approved by an independent ethics committee or institutional review board for each site. This study was conducted in accordance with the ethical principles of Good Clinical Practice and the Declaration of Helsinki (26). Written informed consent was obtained in accordance with the International Conference for Harmonisation (27) guidelines and regulatory and legal requirements of the respective countries.

## Results

Between February 5, 2016, and October 17, 2018, 163 patients from 77 sites in 16 countries were enrolled and treated with once-daily ALIS 590 mg plus patients' ongoing GBT. Because ALIS exposure at INS-312 baseline differed between the two cohorts, safety and efficacy results are presented according to the treatment assigned in the CONVERT study.

### ALIS-Naive Cohort

**Patients.** A total of 90 patients in the ALIS-naive cohort enrolled, including 2 who met the definition of culture conversion in CONVERT but had relapsed by CONVERT Month 6 (primary analysis). The mean (standard deviation [SD]) age of patients in the ALIS-naive cohort was 64.8 (10.3) years; most were female (60.0%) and white (66.7%), with a median NTM lung disease duration of 3.7 (range, 0.8–19.6) years (Table 1). At INS-312 baseline, 98.9% of ALIS-naive patients had respiratory disorders, including bronchiectasis

(72.2%) and COPD (30.0%) (Table 1). In this cohort, 27.8% had a history of prior bronchodilator use (before ALIS initiation), and 53.3% used bronchodilators during the study (on ALIS+GBT treatment). GBT regimens of most patients (83.3%) comprised at least three antibiotics; 51.1% received a combination consisting of a macrolide, a rifamycin, and ethambutol (Table E2); 18.9% had clarithromycin-resistant (minimum inhibitory concentration [MIC]  $\geq 32$   $\mu\text{g/ml}$ ) MAC isolates (Table 1) (28).

All patients received at least one dose of ALIS. The median duration of treatment was 11.6 (range, 0–13) months; 62.2% ( $n = 56$ ) completed the protocol-defined 12-month treatment phase and 64.4% ( $n = 58$ ) completed the end-of-study visit (Figure 2). Reasons for study discontinuation included AEs (22.2% [ $n = 20$ ]) and withdrawal by patient (8.9% [ $n = 8$ ]).

**Safety outcomes.** All patients in the ALIS-naive cohort experienced at least one TEAE; those reported in  $\geq 10\%$  of patients were respiratory TEAEs of special interest

(dysphonia, cough, dyspnea, hemoptysis), fatigue, infective exacerbation of bronchiectasis, nausea, and diarrhea (Table 2; see Table E3 for characteristics of cough and Table E4 for other respiratory preferred terms). TEAEs of special interest typically associated with parenteral amikacin (ototoxicity, nephrotoxicity, and neuromuscular disorders) were infrequent; the MedDRA preferred terms reported in  $\geq 5\%$  of patients were tinnitus (6.7% [ $n = 6$ ]), dizziness (5.6% [ $n = 5$ ]), hearing loss related (hypoacusis, deafness neurosensory, deafness unilateral, or deafness [7.8% ( $n = 7$ )]), and hematuria (5.6% [ $n = 5$ ]) (Table 2). Overall, auditory function did not worsen from baseline (Table E5) with continued ALIS use. Two patients with abnormal audiograms at INS-312 baseline had a moderate (grade 2) worsening at Month 12.

TEAEs leading to temporary ALIS interruption—reported in 46.7% of ALIS-naive patients ( $n = 42$ )—included dysphonia (22.2% [ $n = 20$ ]), cough (11.1% [ $n = 10$ ]), and COPD exacerbation

**Table 1.** Demographic and clinical characteristics at INS-312 baseline: safety population

Characteristic	Total (N = 163)	ALIS-Naive* Cohort (n = 90)	Prior-ALIS† Cohort (n = 73)
Age, mean (SD), years	64.8 (9.8)	64.8 (10.3)	64.9 (9.1)
Female, n (%)	105 (64.4)	54 (60.0)	51 (69.9)
Body mass index, mean (SD), kg/m <sup>2</sup>	20.8 (3.8)	21.0 (3.6)	20.5 (4.0)
Race, n (%)			
White	101 (62.0)	60 (66.7)	41 (56.2)
Asian: Japanese	31 (19.0)	14 (15.6)	17 (23.3)
Asian: other	19 (11.7)	8 (8.9)	11 (15.1)
Black/African American	5 (3.1)	3 (3.3)	2 (2.7)
Multiracial	1 (0.6)	0 (0)	1 (1.4)
Not reported	6 (3.7)	5 (5.6)	1 (1.4)
Respiratory, thoracic, and mediastinal disorders, n (%)‡			
Bronchiectasis	116 (71.2)	65 (72.2)	51 (69.9)
COPD	42 (25.8)	27 (30.0)	15 (20.5)
Cough	42 (25.8)	16 (17.8)	26 (35.6)
Pulmonary cavitation	33 (20.2)	16 (17.8)	17 (23.3)
Dyspnea	22 (13.5)	13 (14.4)	9 (12.3)
Asthma	15 (9.2)	10 (11.1)	5 (6.8)
Hemoptysis	15 (9.2)	6 (6.7)	9 (12.3)
Pulmonary mass	14 (8.6)	9 (10.0)	5 (6.8)
Dysphonia	13 (8.0)	0 (0)	13 (17.8)
Emphysema	13 (8.0)	9 (10.0)	4 (5.5)
Clarithromycin-resistant MAC, n (%)§	42 (25.8)	17 (18.9)	25 (34.2)
Current smoker, n (%)	17 (10.4)	8 (8.9)	9 (12.3)
Duration of NTM disease, median (range), years	4.6 (0.8–33.2)	3.7 (0.8–19.6)	5.4 (0.8–33.2)

*Definition of abbreviations:* ALIS = amikacin liposome inhalation suspension; COPD = chronic obstructive pulmonary disease; MAC = *Mycobacterium avium* complex; MIC = minimum inhibitory concentration; NTM = nontuberculous mycobacteria; SD = standard deviation.

\*Added ALIS at baseline.

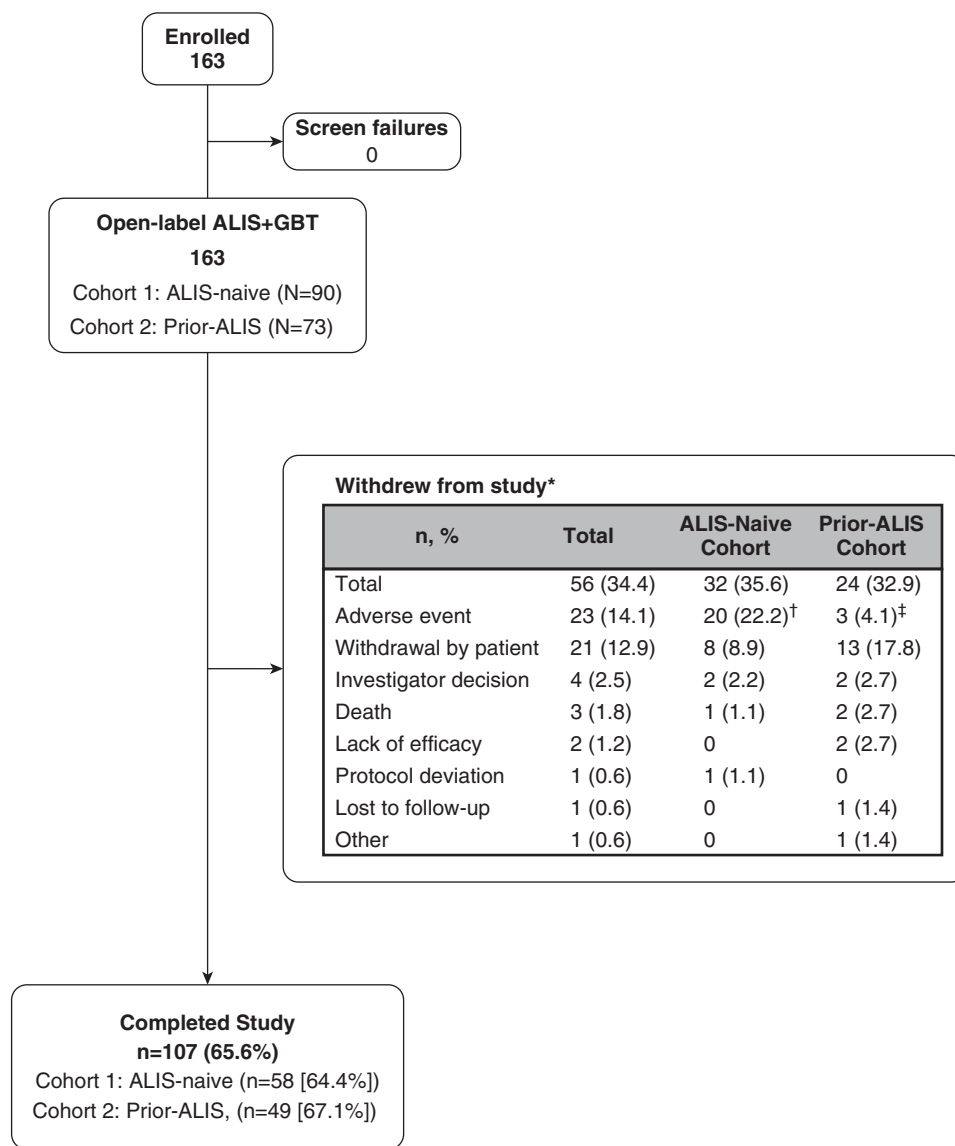
†Up to 8 months of ALIS exposure at baseline.

‡Derived from medical history.

§MIC  $\geq 32$   $\mu\text{g/ml}$ .

||Including E-cigarettes.

¶ $n = 88$ .



**Figure 2.** Patient disposition (EOS). Patient flow through the study is shown. Completion was defined as successfully completing 12 months of the same treatment regimen beginning with INS-312 baseline and completing the 28-day off-treatment EOS follow-up visit. Adverse events are reported and classified based on Medical Dictionary for Regulatory Activities preferred terms. \*Primary reason for study discontinuation as noted by the investigator on the case report form. <sup>†</sup>Bronchospasm ( $n=2$ ), dysphonia ( $n=2$ ), acute respiratory failure ( $n=1$ ), cough ( $n=1$ ), dyspnea at rest ( $n=1$ ), laryngeal granuloma ( $n=1$ ), pneumothorax ( $n=1$ ), pulmonary fibrosis ( $n=1$ ), respiratory failure ( $n=1$ ), balance disorder ( $n=1$ ), cerebral infarction ( $n=1$ ), hypoacusis ( $n=1$ ), vision blurred ( $n=1$ ), ascites ( $n=1$ ), chest pain ( $n=1$ ), electrocardiogram QT prolonged ( $n=1$ ), decreased appetite ( $n=1$ ), breast cancer ( $n=1$ ). <sup>‡</sup>Allergic alveolitis ( $n=1$ ), laryngitis ( $n=1$ ), *Mycobacterium avium* complex infection progression ( $n=1$ ). ALIS = amikacin liposome inhalation suspension; EOS = end of study; GBT = guideline-based therapy.

(3.3% [ $n=3$ ]) (Table E6). ALIS was permanently discontinued in 24.4% of ALIS-naive patients ( $n=22$ ), mostly due to respiratory events (13.3% [ $n=12$ ]): two patients each discontinued because of bronchospasm, dysphonia, and dyspnea and one patient each because of other events (Table E6).

Serious TEAEs were reported in 35.6% of patients ( $n=32$ ) (Table 2). Serious TEAEs

occurring in  $\geq 3\%$  of patients were MAC infection worsening or progression (5.6% [ $n=5$ ]), pneumonia (4.4% [ $n=4$ ]), COPD exacerbation (4.4% [ $n=4$ ]), and infective exacerbation of bronchiectasis (3.3% [ $n=3$ ]). One patient had a grade 4 (life-threatening) TEAE (interstitial pneumonia) resulting in hospitalization and interruption of ALIS. The patient was treated with intravenous corticosteroids and recovered;

ALIS was not restarted, and the patient discontinued the study. Four patients died: one each due to COPD exacerbation, acute respiratory failure, pneumothorax, and pulmonary fibrosis (Table 2).

Mean (SD) change from baseline to Month 12 in serum creatinine was 2.76 (9.37)  $\mu\text{mol/L}$  ( $n=57$ ), and mean (SD) change from baseline to Month 12 in glomerular filtration rate was  $-4.3$  (10.28)



**Table 2.** ALIS-naive cohort: safety profile among patients who added ALIS at baseline (safety population)

Parameter	ALIS-Naive Cohort (N = 90)
Any TEAE	90 (100)
Grade 1: mild	21 (23.3)
Grade 2: moderate	33 (36.7)
Grade 3: severe	29 (32.2)
Grade 4: life threatening	3 (3.3)
Grade 5: death	4 (4.4)
TEAE in ≥10% of patients	
Dysphonia	39 (43.3)
Cough	32 (35.6)
Dyspnea	16 (17.8)
Fatigue	13 (14.4)
Hemoptysis	11 (12.2)
Infective exacerbation of bronchiectasis	11 (12.2)
Nausea	9 (10.0)
Diarrhea	9 (10.0)
TEAE: pulmonary exacerbation*	29 (32.2)
TEAE leading to discontinuation of ALIS	22 (24.4)
TEAE leading to discontinuation of GBT	8 (8.9)
TEAE leading to discontinuation of ALIS and GBT	5 (5.6)
TEAE leading to death	4 (4.4)
COPD exacerbation	1 (1.1)
Acute respiratory failure†	1 (1.1)
Pneumothorax	1 (1.1)
Pulmonary fibrosis progression‡	1 (1.1)
Any serious TEAE§	32 (35.6)
Serious TEAE occurring in ≥3% of patients	
MAC infection worsening or progression	5 (5.6)
Pneumonia	4 (4.4)
COPD exacerbation	4 (4.4)
Infective exacerbation of bronchiectasis	3 (3.3)
Serious TEAE: pulmonary exacerbation	17 (18.9)
Serious TEAE leading to discontinuation of ALIS	9 (10.0)
Respiratory TEAEs of special interest	
Bronchospasm	
Dyspnea	16 (17.8)
Wheezing	5 (5.6)
Bronchospasm	2 (2.2)
Dyspnea exertional	2 (2.2)
Infective exacerbation of underlying disease	
Infective exacerbation of bronchiectasis	11 (12.2)
COPD exacerbation	6 (6.7)
Hemoptysis	
Hemoptysis	11 (12.2)
Allergic alveolitis	
Interstitial lung disease	1 (1.1)
TEAEs of special interest typically associated with parenteral amikacin	
Ototoxicity	
Hearing loss¶	7 (7.8)
Tinnitus	6 (6.7)
Dizziness	5 (5.6)
Vertigo	2 (2.2)
Balance disorder	1 (1.1)
Nephrotoxicity	
Hematuria	5 (5.6)
Renal impairment	3 (3.3)
Blood creatinine increased	2 (2.2)
Leukocyturia	1 (1.1)
Proteinuria	1 (1.1)
Neuromuscular disorders	
Peripheral neuropathy	1 (1.1)
Balance disorder	1 (1.1)

*Definition of abbreviations:* AE = adverse event; ALIS = amikacin liposome inhalation suspension; COPD = chronic obstructive pulmonary disease; GBT = guideline-based therapy; TEAE = treatment-emergent adverse event. Data are shown as *n* (%). The category of "other respiratory" is included in Table E4. Categories of special interest are not mutually exclusive. AEs are reported and classified based on Medical Dictionary of Regulatory Activities preferred terms. Adverse events that occurred on or after INS-312 baseline and within 28 days after the last dose were considered TEAEs.

\*Pulmonary exacerbation was defined based on the investigators' best clinical judgment.

†Acute mixed respiratory failure secondary to progressive lung infiltration, pulmonary mycobacterial infection, and cardiac arrest.

‡Onset before enrollment in CONVERT; death attributed to progressive deterioration of pleuroparenchymal fibroelastosis.

§A serious AE is any untoward medical occurrence that at any dose resulted in death, was life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, or was a congenital anomaly or birth defect.

¶Hearing loss includes preferred terms hypoacusis, deafness neurosensory, deafness unilateral, and deafness.

ml/min (*n* = 57). No clinically meaningful trends or changes in hematology and chemistry values, vital signs, physical examination findings, body mass index, and auditory function were observed beyond those reported as TEAEs per protocol.

**Efficacy outcomes.** Initiation of ALIS+GBT resulted in cumulative sputum culture conversion in 26.7% of patients (*n* = 24) by Month 6, increasing to 33.3% (*n* = 30) by Month 12 (Figure 3A; time-to-culture conversion is shown in Figure 3B). Both patients who met culture conversion criteria in CONVERT but met the definition of relapse by Month 6 achieved culture conversion in this study. Patients with clarithromycin-resistant isolates had a lower rate of culture conversion (17.3% [*n* = 3/17]) than those with clarithromycin-susceptible (MIC ≤ 8 µg/ml; 37.1% [*n* = 26/70]) or clarithromycin-intermediate (MIC = 16 µg/ml; 33.3% [*n* = 1/3]) isolates. Of 56 patients who completed 12 months of treatment, 32.1% (*n* = 18) and 39.3% (*n* = 22) achieved conversion by Months 6 and 12, respectively. Following culture conversion, five patients had MAC-positive sputum that met the definition of relapse and four had MAC-positive sputum that met the definition of reinfection. Four patients had a single liquid-positive culture after conversion and did not meet the definition of recurrent MAC. 6MWT distance did not improve from study baseline at Months 6 and 12 (Figure E1), nor was there a relationship suggesting benefit in converters compared with nonconverters.

### Prior-ALIS Cohort

**Patients.** A total of 73 patients in the prior-ALIS cohort enrolled, including one who met the definition of culture conversion in CONVERT and had a relapse before CONVERT Month 6. The mean (SD) age of patients in the prior-ALIS cohort was 64.9 (9.12) years; most were female (69.9%) and white (56.2%), with a median NTM lung disease duration of 5.4 (range, 0.8–33.2) years (Table 1). At baseline, 100.0% of patients in the prior-ALIS cohort had a respiratory disorder, including bronchiectasis (69.9%) and COPD (20.5%). In this cohort, 42.5% had a history of prior bronchodilator use (including the on ALIS+GBT treatment period in CONVERT), and 43.8% used bronchodilators during the study. GBT regimens of most patients (80.8%)

comprised at least three antibiotics, and 58.9% were receiving a drug combination consisting of a macrolide, a rifamycin, and ethambutol (Table E2); 34.2% had clarithromycin-resistant MAC isolates (Table 1).

All patients received at least one dose of ALIS. The median duration of treatment was 11.6 (range, 0–13) months; however, patients in this cohort had received up to 8 months of ALIS+GBT at study entry, providing a total exposure to ALIS of up to 20 months. Overall, 65.8% ( $n = 48$ ) completed the protocol-defined 12-month treatment phase and 67.1% ( $n = 49$ ) completed the study (Figure 2). The most common reason for treatment discontinuation ( $\geq 5\%$  of patients) was withdrawal by patient (17.8% [ $n = 13$ ]). Three patients (4.1%) withdrew because of an AE.

**Safety outcomes.** TEAEs were reported in 93.2% of patients in the prior-ALIS cohort; those reported in  $\geq 10\%$  of patients were respiratory TEAEs of special interest (hemoptysis, nasopharyngitis, cough, and dyspnea) (Table 3; see Table E3 for characteristics of cough and Table E4 for other respiratory preferred terms). TEAEs of special interest typically associated with parenteral amikacin were uncommon; the MedDRA preferred terms reported in  $\geq 5\%$  of patients were hearing loss related (hypoacusis, deafness neurosensory, deafness unilateral, or deafness; 9.6% [ $n = 7$ ]) and hematuria (5.5% [ $n = 4$ ]) (Table 3). There were no clinically meaningful mean changes in auditory function from baseline with continued ALIS use (Table E5). One patient in the prior-ALIS cohort with an abnormal audiogram at baseline had a severe (grade 3) worsening at Month 6 (up to 14 mo of total ALIS exposure) and continued ALIS without worsening auditory function.

TEAEs leading to temporary ALIS interruption were reported in 26.0% of patients ( $n = 19$ ); dyspnea was the only TEAE that led to temporary interruption in more than one patient (5.5% [ $n = 4$ ]) (Table E6). ALIS was permanently discontinued in 8.2% of patients ( $n = 6$ ) because of allergic alveolitis (2.7% [ $n = 2$ ]), laryngitis (1.4% [ $n = 1$ ]), MAC infection progression (1.4% [ $n = 1$ ]), nausea (1.4% [ $n = 1$ ]), and hip fracture (1.4% [ $n = 1$ ]) (Table E6). Serious TEAEs were reported in 27.4% of patients (Table 3); the most common ( $\geq 3\%$ ) was

pneumonia (4.1% [ $n = 3$ ]). Two patients died (COPD,  $n = 1$ ; lower respiratory tract infection,  $n = 1$ ). Two patients developed grade 2 (moderate) allergic alveolitis and permanently discontinued ALIS; one event was considered serious. Both patients were treated with oral prednisone, and the events resolved; one patient discontinued GBT treatment and withdrew from the study, and the other completed the study.

Mean (SD) change from baseline to Month 12 in serum creatinine was 0.31 (8.26)  $\mu\text{mol/L}$  ( $n = 49$ ), and mean (SD) change from baseline to Month 12 in glomerular filtration rate was  $-1.8$  (11.34) ml/min ( $n = 49$ ). No clinically meaningful trends or changes in hematology and chemistry values, vital signs, physical examination findings, body mass index, and auditory function were observed beyond those reported as TEAEs per protocol.

**Efficacy outcomes.** In the prior-ALIS cohort, continuation of ALIS+GBT therapy resulted in cumulative sputum culture conversion in 9.6% of patients ( $n = 7$ ) by Month 6 (up to 14 mo of total ALIS exposure), increasing to 13.7% ( $n = 10$ ) by Month 12 (up to 20 mo of total ALIS exposure) (Figure 4A; time-to-culture conversion is shown in Figure 4B). The patient who met culture conversion criteria in CONVERT but relapsed by Month 6 achieved culture conversion in this study. Mean (SD) ALIS exposure from the start of ALIS+GBT in CONVERT to the time of culture conversion in INS-312 was 11.5 (3.9) months (range, 7.8–18.0). The median time to achieving a sputum culture negative for MAC could not be estimated. Following culture conversion, three patients had MAC-positive sputum that met the definition of reinfection. One patient had a single liquid-positive culture after conversion and did not meet the definition of recurrent MAC. 6MWT distance did not improve from study baseline at Months 6 and 12 (Figure E1), nor was there a relationship suggesting benefit in converters compared with nonconverters.

## Discussion

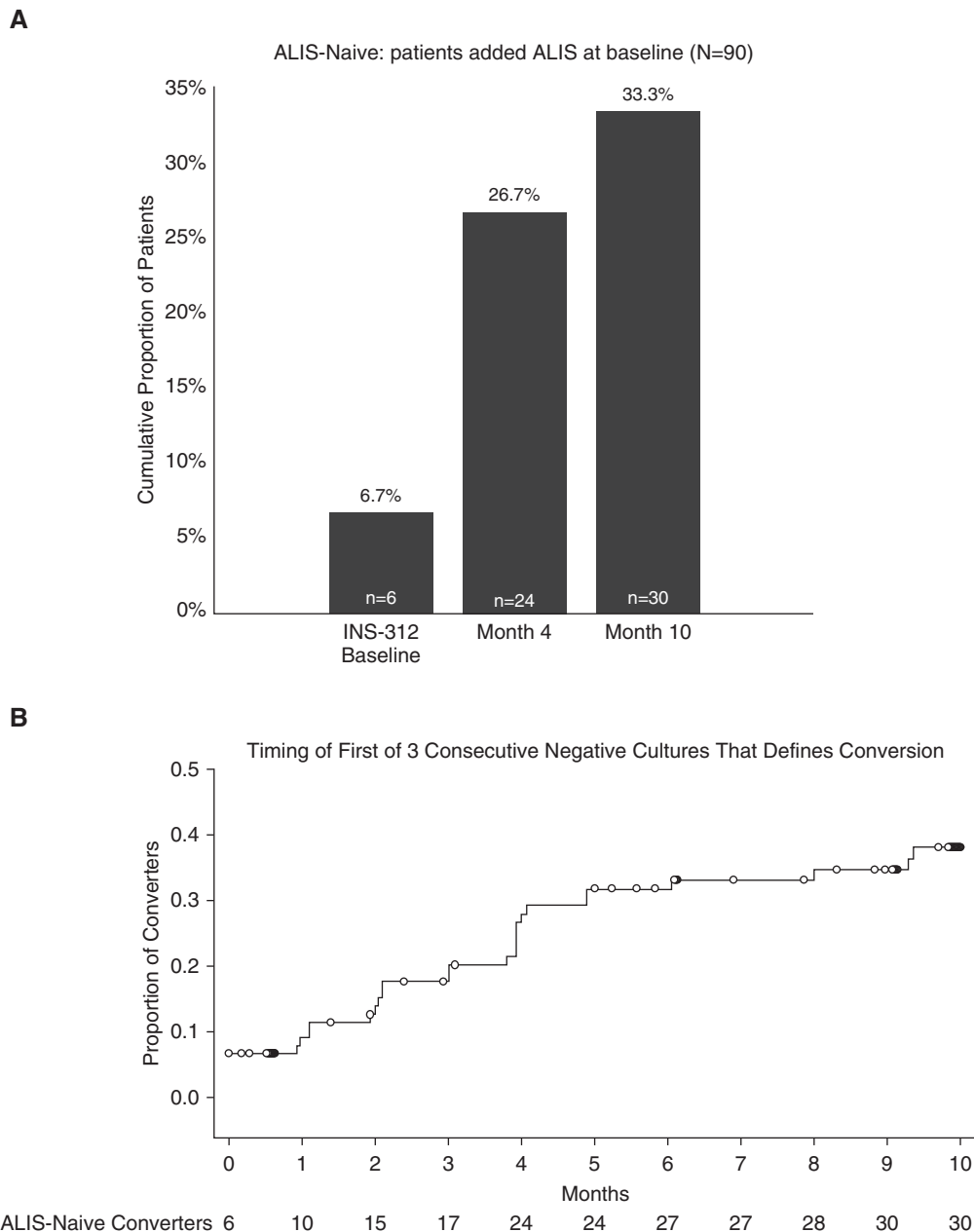
We evaluated the long-term safety of ALIS combined with GBT in patients with refractory MAC lung disease. Only infrequent events typically associated with aminoglycoside toxicity were observed with long-term ALIS exposures (up to 20 mo).

Furthermore, a subset of patients who initially failed to microbiologically respond by 6 months achieved culture conversion with longer-term ALIS+GBT therapy. Similar safety and efficacy trends were observed between the ALIS-naive cohort and the ALIS+GBT arm of the CONVERT study, and the results in the prior-ALIS cohort suggest the potential for ALIS use of greater than 1 year.

### ALIS-Naive Cohort

The ALIS-naive cohort comprised patients who received ALIS for the first time in INS-312, akin to those in the ALIS+GBT arm who initiated ALIS at baseline in CONVERT. Thus, the similarity between the safety profiles of the INS-312 ALIS-naive cohort and the CONVERT ALIS+GBT arm was expected (i.e., most TEAEs were respiratory in nature and consistent with MAC lung disease, underlying comorbidities, and the administration of an inhaled drug) (13, 14). TEAEs with the greatest incidence were dysphonia (43.3%) and cough (35.6%), which were associated with more than two-thirds of the temporary ALIS interruptions but uncommonly led to discontinuation of ALIS. As expected in this patient population with underlying respiratory comorbidities, bronchodilator use was common, especially selective  $\beta$ -2-adrenoreceptor agonists. The percentage of ALIS-naive patients with a prior history of bronchodilator use (27.8%) was similar to that seen in the original CONVERT treatment groups at baseline (ALIS+GBT, 34.4%; GBT alone, 30.4%). Bronchodilator use was permitted as a pretreatment strategy in patients with bronchospasm, and during the course of ALIS+GBT treatment, the percentage of patients using bronchodilators increased to approximately 50% during the study period (after ALIS initiation). Audiology results reflected those of the ALIS+GBT group in the CONVERT study in that changes from baseline did not reach the threshold mean of a grade 1 change at any frequency.

The culture conversion rate after 6 months of ALIS+GBT in the ALIS-naive cohort (26.7%) was similar to the culture conversion rate observed in the CONVERT ALIS+GBT arm by Month 6 (29.0%) (14). An additional six patients achieved culture conversion by Month 12, further supporting the potential benefit of long-term ALIS treatment. Additionally, some patients with macrolide-resistant isolates achieved culture conversion, albeit at a



**Figure 3.** (A) Cumulative proportion of patients in the ALIS-naive cohort with culture conversion, shown by the first month of conversion: safety population. The cumulative proportion of patients achieving culture conversion is displayed by the first month at which sputum cultures were negative for MAC. Month 10 was the latest time point at which a patient could achieve the first of three consecutive sputum cultures negative for MAC and be considered a converter by Month 12. Patients with cultures negative for MAC at INS-312 baseline, Months 1 and 2, were considered converters at baseline. A patient with missing monthly culture data was considered positive for MAC unless they were unable to produce sputum even after induction. (B) Proportion of patients with culture conversion over time (safety population). The study month at which patients first experienced a MAC-negative sputum culture is shown by Kaplan-Meier analysis. Open circles indicate patients who were censored. ALIS = amikacin liposome inhalation suspension; MAC = *Mycobacterium avium* complex.

lower rate than those with macrolide-susceptible isolates. This finding is encouraging considering the uniformly low conversion rates for macrolide-resistant MAC reported in other studies (29, 30), as well as the increased conversion rates that occurred with the addition of a single

inhalational drug to a standard oral regimen.

#### Prior-ALIS Cohort

The prior-ALIS cohort comprised patients who received up to 8 months of ALIS+GBT

in CONVERT and thus provided long-term safety and efficacy data for up to 20 months of total ALIS exposure. Consistent with the design of the study and potential for enrollment bias, patients who tolerated ALIS in CONVERT may have been more likely to enroll in INS-312. With up to 20 months of



**Table 3.** Prior-ALIS cohort: safety profile among patients with up to 8 months of ALIS exposure at baseline (safety population)

Parameter	Prior-ALIS Cohort (N = 73)
Any TEAE	68 (93.2)
Grade 1: mild	22 (30.1)
Grade 2: moderate	30 (41.1)
Grade 3: severe	13 (17.8)
Grade 4: life threatening	1 (1.4)
Grade 5: death	2 (2.7)
TEAE in ≥10% of patients	
Hemoptysis	11 (15.1)
Nasopharyngitis	10 (13.7)
Cough	9 (12.3)
Dyspnea	9 (12.3)
TEAE: pulmonary exacerbation*	22 (30.1)
TEAE leading to discontinuation of ALIS	6 (8.2)
TEAE leading to discontinuation of GBT	4 (5.5)
TEAE leading to discontinuation of ALIS and GBT	1 (1.4)
TEAE leading to death	2 (2.7)
COPD exacerbation	1 (1.4)
Lower respiratory tract infection	1 (1.4)
Any serious TEAE†	20 (27.4)
Serious TEAE occurring in ≥3% of patients	
Pneumonia	3 (4.1)
Serious TEAE: pulmonary exacerbation	7 (9.6)
Serious TEAE leading to discontinuation of ALIS	3 (4.1)
Respiratory TEAEs of special interest	
Bronchospasm	
Dyspnea	9 (12.3)
Wheezing	1 (1.4)
Infective exacerbation of underlying disease	
Infective exacerbation of bronchiectasis	7 (9.6)
COPD exacerbation	4 (5.5)
Hemoptysis	
Hemoptysis	11 (15.1)
Allergic alveolitis	
Alveolitis allergic	2 (2.7)
TEAEs of special interest typically associated with parenteral amikacin	
Ototoxicity	
Hearing loss‡	7 (9.6)
Dizziness	2 (2.7)
Tinnitus	1 (1.4)
Nephrotoxicity	
Hematuria	4 (5.5)
GFR decreased	2 (2.7)
Leukocyturia	1 (1.4)
Proteinuria	1 (1.4)
Azotemia	1 (1.4)
Renal failure	1 (1.4)
Neuromuscular disorders	
Peripheral neuropathy	1 (1.4)

*Definition of abbreviations:* ALIS = amikacin liposome inhalation suspension; COPD = chronic obstructive pulmonary disease; GBT = guideline-based therapy; GFR = glomerular filtration rate; TEAE = treatment-emergent adverse event.

Data are shown as *n* (%).

Adverse events are reported and classified based on Medical Dictionary of Regulatory Activities preferred terms.

\*Pulmonary exacerbation was defined based on the investigators' best clinical judgment.

†A serious adverse event is any untoward medical occurrence that at any dose resulted in death, was life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, or was a congenital anomaly or birth defect.

‡Hearing loss includes preferred terms hypoacusis, deafness neurosensory, deafness unilateral, and deafness.

total ALIS exposure, no new safety signals indicative of cumulative ototoxicity or nephrotoxicity were observed. Bronchodilator use was common (approximately 40%) and similar between prior and concomitant use (both on an ALIS+GBT treatment regimen). Similar to the CONVERT study (14), two patients in the prior-ALIS cohort developed allergic alveolitis considered to be ALIS related; however, no predictors were identified. Some patients achieved culture conversion after Month 6, indicating that culture conversion can occur with extended ALIS+GBT treatment in some patients who previously failed lengthy GBT.

### Study Limitations

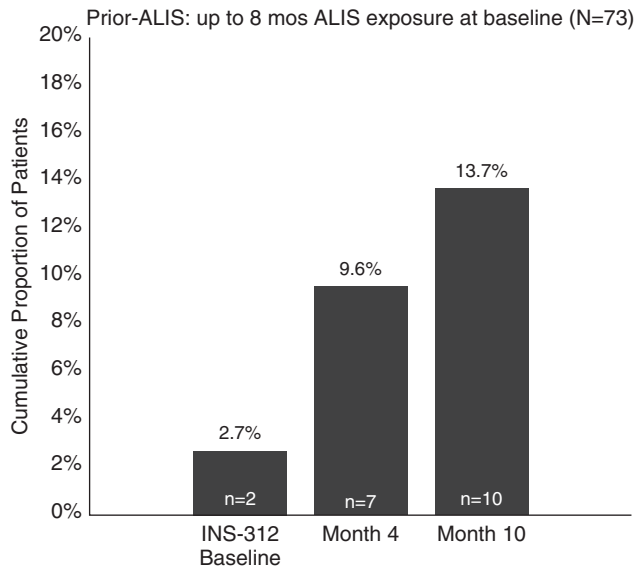
Limitations include the nonrandomized, open-label extension design with no comparator arm. Patients had different durations of postconversion treatment, limiting assessments of response sustainability. The relatively small size of the cohorts limited potential subanalyses and extrapolation to different subgroups of patients with refractory MAC lung disease. The inherent high variability in 6MWT distance among patients with refractory MAC lung disease found in CONVERT (31) and INS-312 makes it difficult to draw conclusions regarding potential functional improvement with treatment.

### Conclusions

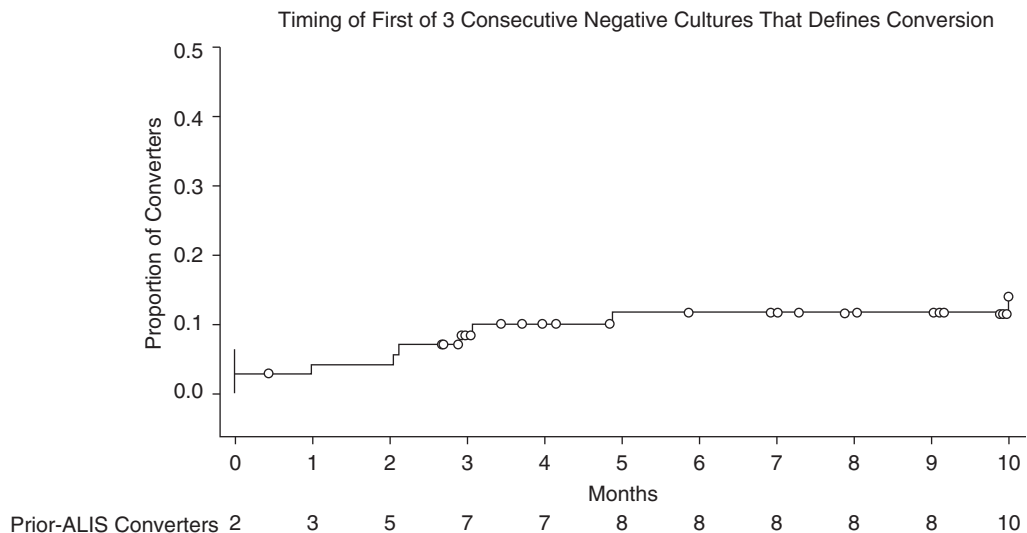
The safety and tolerability of ALIS+GBT in the INS-312 extension study was consistent with the CONVERT study (14); no new safety signals were detected with up to 20 months of total ALIS exposure. Respiratory AEs following ALIS initiation were common. Nephrotoxicity-related AEs and measured hearing decline were infrequent over the 12-month treatment phase in this extension study.

By indirect comparison, similar proportions of patients with treatment-refractory disease initiating ALIS achieved culture conversion by Month 6 in both INS-312 (27%) and CONVERT (29%). Culture conversion was observed at time points beyond 6 months of treatment, supporting the potential benefit of extended ALIS use in patients considered refractory to initial treatment. ■

A



B



**Figure 4.** (A) Cumulative proportion of patients in the prior-ALIS cohort with culture conversion, shown by the first month of conversion: safety population. The cumulative proportion of patients achieving culture conversion is displayed by the first month at which sputum cultures were MAC negative. Month 10 was the latest time point at which a patient could achieve the first of three consecutive negative sputum cultures and be considered a converter by Month 12. A patient with missing monthly culture data was considered MAC positive unless they were unable to produce sputum even after induction. (B) Proportion of patients with culture conversion over time (safety population). The study month at which patients first experienced a MAC-negative sputum culture is shown by Kaplan-Meier analysis. Open circles indicate patients who were censored. ALIS = amikacin liposome inhalation suspension; MAC = *Mycobacterium avium* complex.

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