FDA Briefing Document

Amikacin liposome inhalation suspension (ALIS) Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC)

August 7, 2018

The committee will discuss new drug application (NDA) 207356 for amikacin liposome inhalation suspension, sponsored by Insmed, Inc., for the proposed indication of treatment of nontuberculous mycobacterial (NTM) lung disease caused by Mycobacterium avium complex (MAC) in adults as part of a combination antibacterial drug regimen.

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought amikacin liposome inhalation suspension to this Advisory Committee to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Table of Contents

1 Introduction

This briefing document describes the safety and efficacy data for amikacin liposome inhalation suspension (ALIS), prepared by the FDA for panel members of the Antimicrobial Drugs Advisory Committee. We would like the committee to discuss whether the data are adequate to support the safety and efficacy of ALIS for the treatment of nontuberculous mycobacterial (NTM) lung disease caused by *Mycobacterium avium* complex (MAC) in adults as part of a combination antibacterial drug regimen.

2 Background

Lung disease caused by NTM is characterized by progressive, irreversible lung damage and increased mortality. The disease is more prevalent after age 60 where the prevalence is estimated at 26.7 per 100,000 persons [1]. About 80% of pulmonary NTM disease is caused by MAC.

NTM are thought to be acquired from the environment and not transmitted from person to person. The diagnosis requires the presence of respiratory or constitutional symptoms, nodules, bronchiectasis, or cavities on radiological studies, and positive cultures from two sputum samples or one bronchoalveolar lavage [2].

Treatment of MAC lung disease typically includes the combination of a macrolide, a rifamycin, and ethambutol and continues for 12 months after sputum cultures become negative [2].

The reported rates of treatment success of MAC lung disease have ranged from 20 to 90% [3]. Much of this variability depends on whether treatment success was calculated based on intention-to-treat analyses and whether relapses were included as failures. If patients who discontinued treatment, required surgery, died, or had a relapse are included, the cure rate is approximately 40%.

There is no standard definition for MAC lung disease treatment failure, but failure to convert sputum to culture negative after at least 6 months of treatment has been used to define refractory disease [4]. Treatment options for patients who do not respond to first line therapy are limited and may include switching from intermittent to daily therapy, parenteral administration of amikacin or streptomycin, use of clofazimine, or lung resection. The addition of inhaled amikacin to an optimized background regimen (OBR) may represent another treatment option.

3 Product Information

Amikacin liposome inhalation suspension (ALIS) contains amikacin sulfate as the active ingredient encapsulated in liposomes composed of dipalmitoylphosphatidylcholine and cholesterol in a 2:1 ratio; other inactive excipients include sodium chloride, sodium hydroxide for pH adjustment, and water for injection.

The product is to be administered via a specific nebulizer, the Lamira^{TM} Nebulizer System, at a dose equivalent to 590 mg of amikacin, once daily.

4 Regulatory History

ALIS was initially studied in cystic fibrosis (CF) patients with *Pseudomonas aeruginosa*. The development program then focused on the treatment of NTM lung infections. The key clinical trial (Study 212) in patients with pulmonary MAC infections submitted in the NDA to support the proposed indication, was conducted in patients with refractory MAC lung infections, defined as individuals who remained culture positive after 6 months of a multidrug OBR.

The NDA was submitted under the accelerated approval pathway (21 CFR part 314, subpart H). The accelerated approval provisions of FDASIA in section 506(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act provide that FDA may grant accelerated approval to: ". . . a product for a serious or life-threatening disease or condition . . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit." This application relies on a surrogate endpoint of sputum culture conversion defined as 3 consecutive negative monthly sputum cultures within 6 months of treatment. There are limited data that suggest a higher mortality in patients with NTM lung infections who remain culture positive despite treatment compared to those who are culture negative [5-6]. Although there are uncertainties with sputum culture conversion predicting clinical benefit in this patient population, the degree of uncertainty in the surrogate endpoint of sputum culture conversion was considered acceptable in Study 212, given the unmet need in patients with refractory MAC lung disease and the seriousness of the disease. In addition, there was an expectation of a finding supportive of efficacy in a clinical outcome such as the 6-minute walk test (6MWT). Data on the durability of sputum culture conversion 3 months after completion of MAC therapy and clinical outcomes are being collected in patients who are continuing in Study 212. Of note, considering the design of Study 212, which will be discussed further in this briefing document, a comparative assessment of later clinical outcomes may be limited.

ALIS was granted Orphan Drug Designation (March 2013), as well as, Fast Track and Qualified Infectious Disease Product (QIDP) designations (June 2013) for the treatment of NTM lung disease. In June 2014, ALIS was granted Breakthrough Therapy Designation based on preliminary data from a Phase 2 trial demonstrating sputum culture negativity with add-on ALIS in adult patients with NTM lung disease who were treatment refractory.

5 Clinical Pharmacology

Following a single oral inhalation of ALIS containing 590 mg of amikacin, the mean (min to max) peak concentration of amikacin in plasma (C_{max}) and total daily exposure (AUC_{0-24}) in adult NTM patients was 2.1 (0.50 to 6.6) $\mu g \cdot mL^{-1}$ and 19.0 (4.2 to 53.5) $\mu g \cdot hr \cdot mL^{-1}$ respectively. When compared to intravenous administration at approved clinical doses (e.g., 500 mg amikacin), C_{max} and AUC_{0-24} following oral inhalation were approximately 18- and 3.5-fold lower, respectively. Drug accumulation in plasma was minimal (approximately 6%) after repeat dosing of ALIS. Sputum concentrations were used for approximating drug exposure in the lung. One to four hours after once daily oral inhalation of ALIS containing 590 mg of amikacin, sputum concentrations were high and exhibited large inter-individual variability (CV%>100%). Sputum concentrations then decreased over time to < 5% of the dose at 24 to 72 hours. Accumulation in sputum is inconclusive due to the large variability in measured drug concentrations. Based on the low systemic exposure following oral inhalation of ALIS, no dose adjustment is recommended for patients with hepatic or renal impairment and patients taking concomitant medications.

6 Microbiology

Amikacin, targets the 30S ribosomal subunit of the 16S rRNA and disrupts protein synthesis in bacteria, including NTM. Resistance mechanisms may include mutations in the *rrs* gene of the 16S rRNA resulting in minimum inhibitory concentration (MICs) ≥ 64 mcg/mL.

Time kill studies indicate that exposing the mycobacteria to concentrations 4-32 times the MIC of amikacin result in bacterial killing within 5 to 10 days. Following exposure of MAC isolates to amikacin at 4-fold the MIC for 30, 60 and 120 minutes, the durations of post-antibiotic effect (PAE) were dose dependent at 18, 23 and 120 hours, respectively, and rose significantly when the concentration of amikacin was doubled and the exposure times were the same. Additionally, the killing kinetics of MAC isolates in macrophages with ALIS were significantly better than the killing of MAC in these cells with free amikacin.

7 Overview of the Clinical Development Program

The efficacy and safety of ALIS in the treatment of MAC lung disease was evaluated in two randomized clinical trials and an open-label extension study. The key study in support of the efficacy of ALIS is Study 212, a Phase 3, open-label, randomized trial comparing ALIS added to OBR versus OBR alone in subjects with refractory MAC lung infections. Supportive information is provided by Studies 312 and 112. Study 312 is an ongoing open-label, single-arm extension study of patients from either arm of Study 212 who did not achieve culture conversion or who had a relapse or recurrence by Month 6 and primarily provides supportive safety data. Study 112, is a Phase 2 study that enrolled

subjects with refractory MAC or *M. abscessus* lung infections, and included subjects with CF.

Study 212 is an ongoing Phase 3, open-label, randomized (2:1) study comparing ALIS added to OBR versus OBR alone (at least 2 antibacterial drugs with activity against MAC). An inhaled placebo was not administered to allow for a clearer assessment of the safety profile of ALIS. The study enrolled subjects with treatment-refractory NTM lung disease, defined as having positive MAC sputum cultures despite treatment with an OBR for a minimum duration of 6 consecutive months. A total of 336 subjects were randomized (ALIS plus OBR, n=224; OBR alone, n=112). For an assessment of the study based on a surrogate endpoint, the primary endpoint was sputum culture conversion defined as achieving 3 consecutive monthly negative sputum cultures within the first 6 months. It should be noted that the subject's culture results were not provided to the site until the subject's Month 8 visit. Study 212 is ongoing and will evaluate the durability of treatment success by assessing sustained culture negativity for 12 months after the first negative culture used to define culture conversion and through 3 months after completing MAC therapy. To provide a clinically relevant endpoint, the 6MWT is assessed at Month 6 and at the end of treatment (EOT) visit as a key secondary clinical endpoint. The EOT visit occurs after completion of 12 months of treatment following the first of 3 consecutive negative cultures in culture converters or at the time of study discontinuation in subjects who discontinued the study prematurely.

Safety and tolerability of ALIS was also evaluated in an ongoing open-label, single-arm extension study (Study 312). Study 312 enrolled subjects from either arm of Study 212 who did not achieve culture conversion or who had a relapse or recurrence after 6 months of treatment to receive ALIS plus OBR for up to 12 months. By the time of the data cutoff date for the NDA submission, the study had enrolled 133 subjects, 59 of whom had previously received ALIS plus OBR and 74 who had received OBR alone.

For Study 212, the open-label extension Study 312 limits comparative assessments of the safety of ALIS beyond 8 months, since subjects were selectively removed from Study 212 based on their outcome, and control subjects had the option to be treated with ALIS. In addition, the uncontrolled design of Study 312 along with its enrollment of previous Study 212 subjects makes the assessment of safety and efficacy from this study limited.

Additional data on the safety and efficacy of ALIS in the treatment of MAC are provided by Study 112. This Phase 2 study enrolled subjects with refractory MAC lung infections, those with *M. abscessus* lung infections, and included some subjects with CF. Subjects in the control arm received an inhaled placebo of liposomes that had a lower lipid concentration than ALIS. The primary endpoint was a change from baseline to Day 84 on a semi-quantitative mycobacterial growth scale. The Agency had questioned the clinical meaningfulness of this endpoint. The Applicant was of the opinion that the initial, 3-month, randomized, comparative portion of the study was too short to assess sputum culture conversion in the population under study.

In addition, various doses and durations of ALIS were evaluated in two Phase 1 pharmacokinetic studies (ALIS, n=18; placebo n=6), seven studies in CF patients with *P. aeruginosa* lung infection (ALIS, n=489, placebo n=204) and one study in patients with non-CF bronchiectasis with *P. aeruginosa* lung infection (ALIS, n=44, placebo n=22). The doses of ALIS in the non-NTM studies ranged from 90 mg to 590 mg daily, and the durations ranged from a single dose to up to 22 months of 28-day on/off cycles. These studies will not be discussed in this briefing document.

8 Clinical Trials

8.1 Study 212

8.1.1 Study Design

Study 212 is an ongoing randomized, open-label, multicenter study of ALIS in adult subjects with refractory MAC lung infections. Eligible subjects were males or females 18 years of age or older who were positive for MAC on sputum culture while being treated with an OBR (at least 2 antibacterial drugs) for a minimum of 6 months. OBR treatment must have been either ongoing or stopped for no more than 12 months prior to screening. All subjects were required to have a MAC-positive culture at screening and at least one other positive culture within 6 months of screening but no less than 1 month apart. Subjects could have had a negative culture at the baseline visit, but were still eligible to continue in the study.

Subjects were randomized 2:1 to ALIS administered once a day (QD) plus OBR or OBR alone, stratified by smoking status (current smoker or not) and prior OBR at screening (on treatment or off treatment for at least 3 months). Treatment continued for a minimum of 8 months and a maximum of approximately 16 months depending on the timing of culture conversion. Sputum culture results from baseline to Month 6 were made available to the site in time for the Month 8 visit. At that time, subjects were assessed as converters or non-converters. A converter was defined as a subject who had MAC-negative sputum cultures for 3 consecutive months at any time within the first 6 months of the study. A non-converter was defined as a subject who did not have 3 consecutive monthly MAC-negative sputum cultures at any time within the first 6 months of the study. Relapse or recurrence was defined as having MAC-positive sputum cultures in liquid broth media (agar negative) for 3 or more consecutive months or having at least 1 MAC-positive sputum culture on solid media (agar positive) after achieving culture conversion.

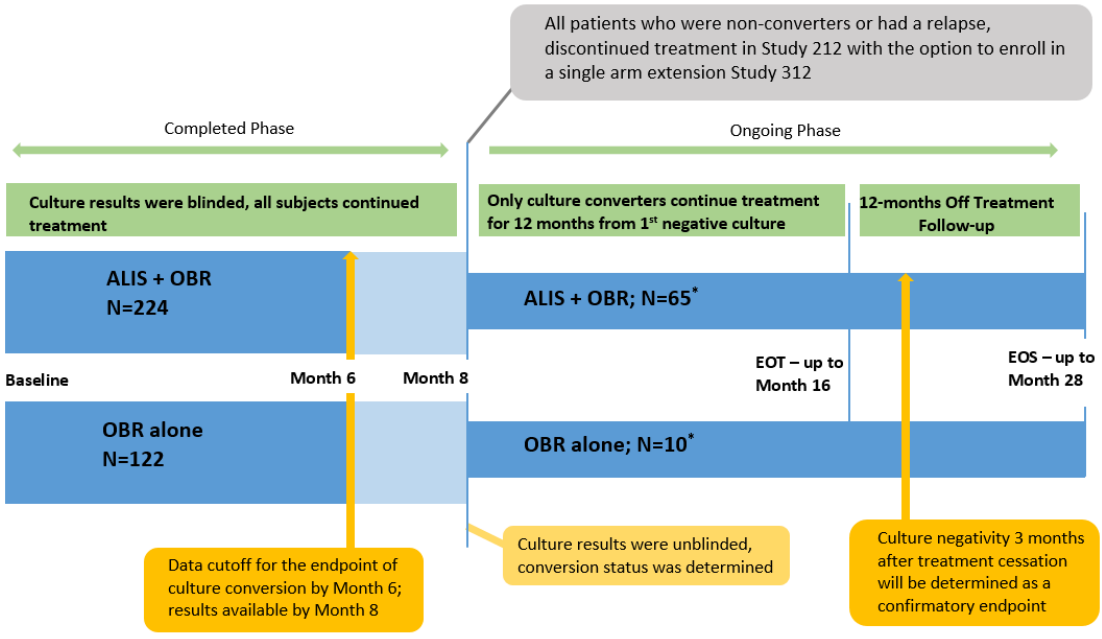
If a subject demonstrated culture conversion within the first 6 months, the total duration of treatment was to be 12 months from the first of 3 negative cultures that defined culture conversion. If culture conversion was not achieved with 6 months of treatment, the subject was discontinued from the study at the Month 8 visit. Additionally, subjects who

experienced a relapse or recurrence within 6 months of treatment were to be discontinued from the study at Month 8. This makes long-term follow up data difficult to interpret.

Study visits occurred monthly through Month 6, and at Months 8, 10, 12, 14, at EOT, and at 28 days, 3, 6, and 12 months off-treatment. At Month 8, when the culture conversion status was assessed, non-converters and those who experienced a relapse or recurrence within the first 6 months in either study arm were potentially eligible to enter Study 312 and initiate or continue ALIS. This further complicates interpretation of the long-term data.

If a subject prematurely discontinued the study prior to the Month 12 visit (excluding subjects enrolling in Study 312), the subject had an EOT visit and telephone contact at 28 days after the EOT visit, at Month 12 (counting from Day 1) for safety follow-up, and at 12 months after the EOT visit for safety follow-up and vital status. If a subject prematurely discontinued the study on or after the Month 12 visit, the subject had an EOT visit and telephone contact at 28 days after the EOT visit, and at 12 months after the EOT visit for safety follow-up and vital status. Please see Figure 1 for a schematic representation of the study design and patient disposition in Study 212.

Figure 1: Study 212 Study Design and Patient Disposition



EOT = End of Treatment; EOS = End of Study; OBR = Optimized Background Regimen

* 65 and 10 are the number of subjects who were considered converters at 6 months, not all these subjects will be available for the long-term efficacy assessment 12 months off-treatment, due to study discontinuation.

Source: FDA

The initial report of this trial was submitted in support of this NDA and is based on data through the cutoff date of July 7, 2017, the date when the last subject completed their Month 6 visit (all Month 6 culture results are available for analysis). These data are being used to support the efficacy of ALIS plus OBR for achieving culture conversion by Month 6 compared to OBR alone. Data to support efficacy after the Month 6 visit will be assessed once patients complete the long-term follow-up.

8.1.2 Statistical Methodology

The primary efficacy analysis population was the Intent-to-Treat (ITT) population which included all randomized subjects. The Safety population included all subjects who received at least 1 dose of randomized study treatment.

The primary efficacy endpoint was the proportion of subjects achieving culture conversion by Month 6. A Cochran-Mantel-Haenszel (CMH) test stratified by smoking status and prior OBR at a 2-sided significance level of 0.05 was conducted. Subjects with missing sputum culture results for which culture conversion could not be assessed were considered as non-converters.

A key secondary efficacy endpoint was change from Baseline (Day 1) to Month 6 in Six Minute Walk Test (6MWT) distance. Time to culture conversion was also summarized.

8.1.3 Subject Disposition

A total of 336 subjects were randomized and comprise the ITT population: 224 on ALIS plus OBR and 112 on OBR alone. The Safety population consists of all but 1 subject randomized to the ALIS plus OBR arm who did not receive ALIS treatment.

At the time of the initial analysis supporting this NDA, subjects were still on treatment, had completed treatment as defined in the protocol, or had discontinued treatment prematurely. A subject was considered as having completed treatment as defined in the protocol if they: 1) were a converter who successfully completed 12 months of their treatment regimen from the first of 3 negative cultures used to define conversion, or 2) were a non-converter who successfully completed all dosing and protocol requirements up to and including the Month 6 study visit. Of the 336 subjects in the ITT population, 84 discontinued treatment prematurely (75 on ALIS plus OBR and 9 on OBR alone), 185 completed treatment as defined in the protocol (106 on ALIS plus OBR and 79 on OBR alone), and in 77 treatment was ongoing (43 on ALIS plus OBR and 24 on OBR alone) at the time of data cutoff.

As noted in Table 1, four times as many subjects discontinued ALIS plus OBR as compared with OBR alone. The most common reasons for discontinuing treatment prematurely in the ALIS plus OBR arm were adverse events (17.4%) and withdrawal by subject (9.4%). In the OBR arm, the most common reason for discontinuing treatment

prematurely was withdrawal by subject (5.4%). The following table summarizes subject disposition.

Table 1: Subject Disposition- Study 212

	ALIS plus OBR	OBR alone
Randomized (ITT)	224	112
Safety	223	112
Completed treatment as defined in protocol	106 (47.3%)	79 (70.5%)
Ongoing treatment	43 (19.2%)	24 (21.4 %)
Discontinued treatment prematurely	75 (33.5%)	9 (8.0%)
Reason for treatment discontinuation		
Adverse Event	39 (17.4%)	1 (0.9%)
Withdrawal by subject	21 (9.4%)	6 (5.4%)
Death	5 (2.2%)	2 (1.8%)
Physician decision	3 (1.3%)	0
Rescue medication	3 (1.3%)	0
Other	2 (0.9%)	0
Protocol deviation	1 (0.4%)	0
Non-compliance with study medication	1 (0.4%)	0

Source: FDA Analysis

8.1.4 Baseline and Demographic Characteristics

Baseline and demographic characteristics were generally similar across treatment groups and are summarized in
Table 2. The mean age of the subjects was 64 years. Approximately 70% of the subjects were female with a slightly higher percentage of females randomized to the ALIS plus OBR arm (73.7%) than to the OBR alone arm (60.7%). The majority of the subjects were white (69.9%). Approximately 42% of the subjects were from the United States. Most of the subjects (approximately 90%, respectively) were on OBR treatment at screening and were not current smokers.

Table 2: Baseline and Demographic Characteristics (ITT population)- Study 212

	ALIS plus OBR (n=224)	OBR alone (n=112)
Age (years)		
mean (sd)	64.6 (9.6)	64.9 (10.2)
median	65	66
min, max	40, 87	32, 85
Sex, n (%)		
Male	59 (26.3)	44 (39.3

	ALIS plus OBR (n=224)	OBR alone (n=112)
Female	165 (73.7)	68 (60.7)
Race, n (%)		
White	158 (70.5)	77 (68.8)
Asian	58 (25.9)	25 (22.3)
Black	3 (1.3)	3 (2.7)
Other	2 (0.9)	1 (0.9)
Not recorded	3 (1.3)	6 (5.4)
Region, n (%)		
United States	93 (41.5)	48 (42.9)
Asia	48 (21.4)	20 (17.8)
Rest of the world	83 (37.1)	44 (39.3)
OBR at Screening, n (%)		
On treatment	201 (89.7)	101 (90.2)
Off treatment for at least 3 months	23 (10.3)	11 (9.8)
Smoking status, n (%)		
Current smoker	26 (11.6)	10 (8.9)
Not a current smoker	198 (88.4)	102 (91.9)

Source: FDA Analysis

8.1.5 Efficacy Results

The primary efficacy endpoint was the proportion of subjects with culture conversion based on three consecutive negative cultures by Month 6 in the ALIS plus OBR arm compared to the OBR alone arm. These results are summarized in Table 3. Significantly more subjects achieved culture conversion by Month 6 in the ALIS plus OBR arm (29.0%) compared to the OBR alone arm (8.9%).

The definition of culture conversion required 3 consecutive monthly negative sputum cultures at any point in time during the first 6 months of the study. However, it was possible that after meeting this definition, a subject could have recurrence of MAC by Month 6. Therefore, a sensitivity analysis was conducted that considered a subject who achieved culture conversion but met the protocol definition of recurrence by Month 6 as a failure (i.e., had at least one positive culture on solid media or greater than 2 consecutive monthly positive cultures on liquid media). Three subjects in each treatment arm met the protocol definition of recurrence by Month 6. Based on the sensitivity analysis, 27.7% of the subjects in the ALIS plus OBR arm compared to 6.3% of the subjects in OBR alone arm achieved culture conversion.

Table 3: Culture conversion by Month 6 (ITT population)- Study 212

	ALIS plus OBR (n=224)	OBR alone (n=112)
Primary analysis		
Converter	65 (29.0)	10 (8.9)

	ALIS plus OBR (n=224)	**OBR alone** (n=112)
Non-converter	159 (71.0)	102 (91.1)
CMH p-value*	p< 0.0001	
Adjusted odds ratio (95% CI)	4.22 (2.08, 8.57)	
Weighted difference (95% CI)**	20.5 (12.2, 28.7)	
Sensitivity Analysis* **		
Converter	62 (27.7)	7 (6.3)
Non-converter	162 (72.3)	105 (93.7)
CMH p-value*	p< 0.0001	
Adjusted odds ratio (95% CI)	5.71 (2.53, 12.89)	
Weighted difference (95% CI)**	21.7 (14.0, 29.4)	

*CMH p-value and adjusted odds ratio (ALIS plus OBR/OBR alone) are calculated using the Cochran-Mantel Haenszel test stratified by smoking status and OBR regimen at Screening. An adjusted odds ratio >1 indicates a response of conversion is more likely for subjects on ALIS plus OBR compared to those on OBR alone

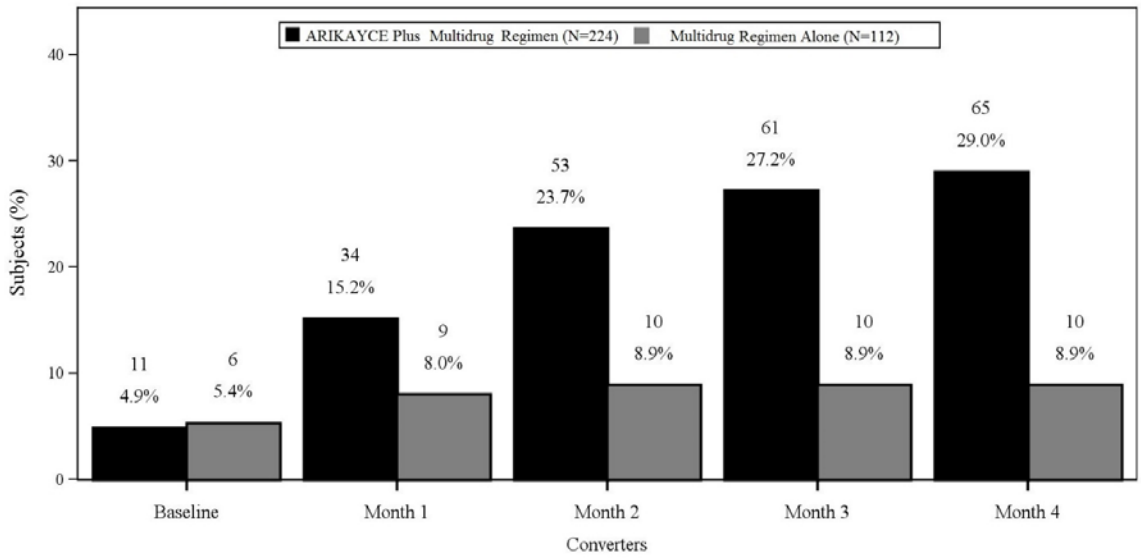
** Difference (ALIS plus OBR – OBR alone) in proportion of subjects with culture conversion weighted by stratification factors of smoking status and OBR regimen at Screening.

*** Analysis treats subjects who reached the protocol definition of recurrence by Month 6 as failures. 3 subjects on each treatment arm had a recurrence by Month 6 after achieving culture conversion

Source: FDA Analysis

Figure 2 (below) summarizes the cumulative proportion of subjects achieving culture conversion by the month of the first of the 3 consecutive negative cultures that was needed to define culture conversion. Data are shown through Month 4 since the first negative culture had to occur by Month 4 for a subject to be considered as having achieved culture conversion by Month 6. Note that approximately 5% of subjects in both arms had their first negative culture at the Baseline visit.

Figure 2: Cumulative Proportion of Subjects Achieving Culture Conversion by Month of First Negative Culture Used to Define Conversion (ITT Population)- Study 212



Source: Applicant's Figure 3 from Study INS-212 clinical study report

Note: Multi-Drug Regimen has been referred to OBR in the rest of this document.

Change from Baseline to Month 6 in the 6MWT distance was a key secondary endpoint. The analysis as reported by the Applicant used a mixed model repeated measures with pattern-mixture modeling and is summarized in Table 4. The LS mean change from baseline at Month 6 was a decrease of 1.9 meters for subjects in the ALIS plus OBR arm as compared to an increase of 1.3 meters for subjects in the OBR alone arm. The difference (ALIS plus OBR – OBR alone) in LS means was -3.2 meters (95% confidence interval: -21.1, 14.6) which was not statistically significant (p=0.7223).

Table 4: 6MWT distance (ITT population)- Study 212

	ALIS plus OBR (n=220)*	**OBR alone** (n=112)
Baseline (meters) mean (sd)	425.7 (127.6)	420.4 (126.7)
Month 6 (meters) mean (sd)	425.2 (141.2)	423.3 (132.7)
Change from Baseline to Month 6** (meters) LS mean (se) 95% CI of LS mean	-1.9 (11.23) (-24.0, 20.2)	1.3 (11.99) (-22.2, 24.9)
Difference (ALIS plus OBR- OBR alone**) in LS mean (95% CI)** **p-value of LS Mean Difference**	-3.2 (-21.1, 14.6) 0.7223	

Source: Adapted from Applicant's Table 14.2.2.1 of INS-212 clinical study report
*4 subjects in the ALIS plus OBR arm did not have a baseline value and were therefore not included in the analysis.
** Statistics are obtained from a mixed model repeated measures 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

In Study 212, *M. avium* was the predominant species isolated from both the ALIS plus OBR and OBR only groups. Against 335 baseline MAC isolates (obtained from 336 patients in both groups) the amikacin MIC90 ranged between 32 to 64 mcg/mL. The frequency of clarithromycin resistance was similar across treatment groups, 22.9% and 19.6% in the ALIS plus OBR and OBR only group, respectively.

Almost all subjects with MAC isolates with an amikacin MIC >64 mcg/mL did not achieve culture conversion. In the ALIS plus OBR group, 38 subjects with MAC reported a ≥4-fold increase in amikacin MIC over baseline and of these, 33/38 were non-converters.

8.2 Study 112

8.2.1 Study Design

Study 112 was a randomized placebo-controlled Phase 2 trial. It consisted of a double-blind, placebo-controlled phase through Day 84 followed by an open-label extension phase for an additional 84 days. In the double-blind phase, patients were randomized

(1:1) to receive either ALIS 590 mg QD in addition to OBR or placebo (empty liposomes) in addition to OBR. During the open-label phase, all patients received ALIS in addition to OBR. The open-label extension phase was followed by a 12-month post-treatment observational period.

Eligible subjects were male or female aged 18 to 85 years with a diagnosis of NTM lung disease in accordance with the 2007 ATS/IDSA criteria with evidence of nodular bronchiectasis and/or fibrocavitary disease by chest CT. Subjects must have been receiving an ATS/IDSA guideline-based treatment regimen for at least 6 months prior to screening with persistently positive mycobacterial cultures for MAC and/or *M. abscessus* and had to have a positive sputum culture at screening. At randomization, subjects were stratified based on the presence or absence of CF, and predominant NTM organism at baseline (MAC vs *M. abscessus*).

Study visits occurred every 28 days throughout the study. Multiple sputum samples were collected at the scheduled study visits. Sputum samples were also to be collected pre-dose at home during the week leading up to the study visit. The 6MWT was conducted at Baseline, Day 84 (end of double-blind phase), and Day 168 (end of open-label phase). All subjects were to have a 28 day post-EOT safety follow-up visit. This visit occurred at Day 112 for those subjects who did not continue in the open-label phase or at Day 196 for those subjects who continued in the open-label phase. Subjects completing the study had the option to enroll in a long-term safety follow-up and return for a visit 12 months after the last dose of study drug.

8.2.2 Statistical Methodology

The primary efficacy analysis population for the double-blind phase was the modified ITT (mITT) population defined as all randomized subjects who received at least 1 dose of study drug. The safety population was defined similarly. Subjects who went on to participate in the open-label phase comprise the open-label mITT (OLmITT) population.

The protocol defined primary endpoint was change from baseline on the semi-quantitative scale (SQS) for mycobacterial culture at Day 84. The SQS was a 7-step scale based on mycobacterial burden observed from culture results, see Table 5. The difference was calculated as the step number at Day 84 subtracted from the step number at baseline. The maximum improvement for a subject could be -6 steps and the maximum deterioration could be +6 steps. For subjects who died prior to Day 84, the change from baseline was imputed as +7 steps. A stratified Wilcoxon rank sum test adjusting for the randomization strata was used to compare the treatment arm at a 2-sided significance level of 0.05.

Table 5: Semi-quantitative Scale for Mycobacterial Culture

Step	Solid Media	Liquid Medium Result	Categorical Result
1	0 colonies	Negative	Culture negative (confirmed with no growth in liquid medium)
2	0 colonies	Positive	Growth in liquid medium only (liquid positive)
3	1-49 colonies	Positive	Agar positive
4	50-100 colonies	Positive	1+
5	>100-200 colonies	Positive	2+
6	>200-500 colonies	Positive	3+
7	>500 colonies	Positive	4+

Source: Table 9-6 of TR02-112 study report

The proportion of subjects with negative NTM culture at Day 84 was a secondary endpoint. This endpoint was analyzed using a stratified CMH test of treatment arm adjusting for the randomization strata.

Change from baseline in 6MWT distance at Day 84 was a tertiary endpoint. Treatment comparisons were made using an ANCOVA with factors for treatment and the randomization strata and the baseline value as a covariate. Missing data were imputed using the last observation obtained for a subject.

8.2.3 Subject Disposition

A total of 90 subjects were randomized into the double-blind portion of the study. One subject randomized to placebo did not receive study drug. Therefore, the mITT/Safety population consists of 89 subjects: 44 on ALIS and 45 on placebo, see Table 6.

Nine subjects, all in the ALIS group, discontinued treatment prematurely during the double-blind phase. Most discontinued treatment prematurely due to an adverse event (AE). Four subjects, all in the ALIS group, did not complete the double-blind phase. The reasons for discontinuing the study early were due to death, AE, withdrawal of consent, and lost to follow-up (one subject each).

Table 6: Subject Disposition in the Double-blind Phase- Study 112

	ALIS	Placebo
Randomized	44	46
mITT/Safety	44	45
Completed treatment	35 (79.5)	45 (100.0)
Discontinued treatment prematurely	9 (20.5)	0

	ALIS	Placebo
Reason for treatment discontinuation		
AE	7 (15.9)	0
Other	2 (4.5)	0
Completed double-blind phase	40 (90.9)	45 (100.0)
Discontinued double-blind phase prematurely	4 (9.1)	0

Source: FDA Analysis

Of the 80 subjects who completed dosing in the double-blind phase, 78 subjects enrolled in the open-label phase of the study and comprise the OLmITT population. Both subjects who declined participation in the open-label phase were randomized to placebo in the double-blind phase. Approximately 24% of the subjects did not complete treatment in the open label phase. More of these subjects were in the previously placebo-treated group than the previously ALIS-treated group. Most subjects discontinued study drug due to an AE. Table 7 summarizes subject disposition in the open-label phase of Study 112.

Table 7: Subject Disposition in the Open-label Phase- Study 112

	Previous ALIS	Previous Placebo	Total
Enrolled	35	43	78
Completed treatment	28 (80.0)	31 (72.1)	59 (75.6)
Discontinued treatment prematurely	7 (20.0)	12 (27.9)	19 (24.4)
Reason for treatment discontinuation			
AE	5 (14.3)	11 (25.6)	16 (20.5)
Persistent severe cough, study drug related	1 (2.9)	1 (2.3)	2 (2.36)
Other	1 (2.9)	0	1 (1.3)
Completed open-label phase	34 (97.1)	41 (95.3)	75 (96.2)
Discontinued open-label phase prematurely	1 (2.9)	2 (4.7)	3 (3.8)

Source: FDA Analysis

8.2.4 Baseline and Demographic Characteristics

Baseline and demographic characteristics were generally similar across treatment groups in the mITT population and are summarized in Table 8. The mean age of the subjects was 58.5 years. Approximately 88% of the subjects were female. The majority of the subjects were white (92%). Approximately 19% of the subjects had CF and two-thirds had predominantly MAC lung infection though some could have been co-infected with other NTM.

Table 8: Baseline and Demographic Characteristics (mITT population)- Study 112

	ALIS (n=44)	**Placebo** (n=45)
Age (years)		
mean (sd)	58.0 (16.6)	59.1 (15.2)
median	61.5	63.0
min, max	18, 85	19, 80
Sex, n (%)		
Male	6 (13.6)	5 (11.1)
Female	38 (86.4)	40 (88.9)
Race, n (%)		
White	42 (95.5)	40 (88.9)
Non-White	2 (4.5)	5 (11.1)
CF strata, n (%)		
Presence of CF	8 (18.2)	9 (20.0)
Absence of CF	36 (81.8)	36 (80.0)
Predominant NTM organism at baseline, n (%)		
MAC	26 (65.9)	28 (62.2)
M. abscessus	15 (34.1)	17 (37.8)

Source: FDA Analysis

8.2.5 Efficacy Results

Table 9 summarizes the baseline SQS category and the change from baseline at Day 84 on the SQS scale for the mITT population. Approximately 11% of subjects in both arms were culture negative at baseline. The change from baseline was not statistically significant between treatment groups (p=0.072).

Table 9: Baseline and Change from Baseline at Day 84 on the SQS Scale for Mycobacterial Culture (mITT population)- Study 112

	ALIS (n=44)	**Placebo** (n=45)
Baseline, n (%)		
Culture negative	5 (11.4)	5 (11.1)
Growth in liquid medium only	1 (2.3)	1 (2.2)
Agar positive (1-49 colonies)	17 (38.6)	10 (22.2)
1+ (50-100 colonies)	2 (4.5)	4 (8.9)
2+ (> 100-200 colonies)	2 (4.5)	2 (4.4)
3+ (>200-500 colonies)	3 (6.8)	4 (8.9)
4+ (>500 colonies)	14 (31.8)	19 (42.2)
Change from baseline at Day 84, n (%)		
-6	1 (2.3)	0
-5	0	0

	ALIS (n=44)	Placebo (n=45)
-4	1 (2.3)	0
-3	3 (6.8)	0
-2	6 (13.6)	6 (13.3)
-1	5 (11.4)	5 (11.1)
0	23 (52.3)	23 (51.1)
+1	2 (4.5)	5 (11.1)
+2	0	3 (6.7)
+3	1 (2.3)	0
+4	1 (2.3)	2 (4.4)
+5	0	1 (2.2)
+6	0	0
+ 7 (Death)	1 (2.3)	0
p-value for stratified Wilcoxon rank sum test of treatment arm adjusting for randomization strata	0.072	

Source: FDA Analysis

At Day 84, a greater proportion of subjects in the ALIS group (31.8%) achieved a negative culture than subjects in the placebo group (8.9%) (p=0.0057). It should be noted that these results are slightly different than those presented by the Applicant. In the Applicant's presentation, 3 subjects in the ALIS arm with missing data at Day 84 were excluded from the analysis. In the analyses presented here, subjects with missing data are treated as not having a negative culture. Please refer to Table 10.

Table 10: Negative Culture at Day 84 (mITT population)- Study 112

	ALIS	Placebo
Overall	14/44* (31.8)	4/45 (8.9)
CMH p-value**	p= 0.0057	
By Strata		
MAC / absence of CF	12/27 (44.4)	3/27 (11.1)
MAC/ presence of CF	0/2	0/1
M. abscessus/ absence of CF	1/9 (11.1)	0/9
M. abscessus/ presence of CF	1/6 (16.7)	1/8 (12.5)

*3 subjects with missing culture data
**CMH p-value stratified by presence/absence of CF and predominant NTM infection at baseline.
Source: FDA Analysis

Table 11 summarizes the baseline and the change from baseline to Day 84 in 6MWT distance. Overall, subjects in the ALIS group had a mean increase from baseline of 20.6 meters compared to a mean decrease of 25.0 meters in the placebo group. This difference was statistically significant (ANCOVA p=0.0102). When looking at the strata of MAC and non-CF subjects (the population studied in INS-212), subjects in the ALIS group had a mean increase from baseline of 16.3 meters compared to a mean decrease of 13.1 meters in the placebo group.

Table 11: 6MWT distance (mITT population)- Study 112

		ALIS	Placebo
Overall population		n=44	n=45
	Baseline (meters)		
	Mean (sd)	441.6 (133.6)	441.8 (111.6)
	Median	435	457
	Min, Max	53, 660	120, 751
	Change at Day 84 (meters)		
	Mean (sd)	20.6 (62.4)	-25.0 (100.2)
	Median	7	-6
	Min, Max	-99, 264	-387, 220
	p-value*	0.0102	
MAC/non-CF strata		n=27	n=27
	Baseline (meters)		
	Mean (sd)	441.6 (147.9)	429.3 (119.1)
	Median	435	456
	Min, Max	53, 660	120, 618
	Change at Day 84 (meters)		
	Mean (sd)	16.3 (62.0)	-13.1 (109.2)
	Median	7	-2
	Min, Max	-99, 264	-387, 220

*ANCOVA p-value for treatment from model including treatment, presence/absence of CF and predominant NTM infection at baseline strata as factors and baseline value as a covariate.
Source: FDA Analysis

8.3 Study 312

8.3.1 Study Design

Study 312 is an open label extension of Study 212. Enrolled subjects include those from Study 212 who did not achieve culture conversion or who had experienced a relapse or recurrence by Month 6. All enrolled subjects received open label treatment with ALIS in addition to OBR. Study 312 is currently ongoing. A cutoff date of July 7, 2017 (same as Study 212) was used for the data presented in the initial report of the study. From the Agency's perspective, Study 312 currently provides limited safety and no comparative efficacy data.

The primary objective of this study is to evaluate long-term safety and tolerability of ALIS for up to 12 months. Secondary efficacy assessments include culture conversion and change in 6MWT distance by Month 6 and Month 12/EOT.

Subjects had routine visits starting on Day 1 and monthly through Month 12/EOT. Subjects also returned for a safety follow-up visit one month after stopping ALIS treatment.

8.3.2 Subject Disposition

At the time of the initial analysis, 133 subjects had enrolled in the study: 59 had previously received ALIS plus OBR and 74 had previously received OBR alone in Study 212. Overall, 24 subjects completed treatment as defined in the protocol, 28 subjects discontinued treatment prior to completion, and 81 were still receiving ongoing treatment. The most common reasons for discontinuing the study were due to AEs and withdrawal by subject. More subjects who previously received OBR alone in Study 212 discontinued due to an AE than subjects who had previously received ALIS plus OBR in Study 212, see Table 12.

Table 12: Subject Disposition - Study 312

	Prior ALIS plus OBR in Study 212	**Prior OBR alone in Study 212**	**Total**
Enrolled	59	74	133
Completed study	9 (15.3)	15 (20.3)	24 (18.0)
Discontinued study prematurely	13 (22.0)	15 (20.3)	28 (21.1)
Ongoing on study	37 (62.7)	44 (59.4)	81 (60.9)
Reason for study discontinuation			
Death	2 (3.4)	0	2 (1.5)
Adverse event	2 (3.4)	11 (14.9)	13 (9.8)
Lack of efficacy	3 (5.1)	0	3 (2.3)
Withdrawal by subject	5 (8.5)	1 (1.4)	6 (4.5)
Other	1 (1.7)	3 (4.1)	4 (3.0)

Source: FDA Analysis

8.3.3 Baseline and Demographic Characteristics

Baseline and demographic characteristics for the Safety population are summarized in Table 13. The mean age of the subjects was 64 years. Approximately 64% of the subjects were female. The majority of the subjects were white (61.7%). Approximately 39% of the subjects were from the United States. Most of the subjects were not a current smoker.

Table 13: Baseline and Demographic Characteristics (Safety population)- Study 312

	Prior ALIS plus OBR in Study 212 (n=59)	**Prior OBR alone in Study 212** (n=74)	**Total** (n=133)
Age (years)			
mean (sd)	65.1(8.6)	64.4 (10.3)	64.7 (9.6)
median	65	65.5	65
min, max	46, 85	33, 83	33, 85
Sex, n(%)			
Male	18 (30.5)	30 (40.5)	48 (36.1)
Female	41 (69.5)	44 (59.5)	85 (63.9)
Race, n(%)			
White	33 (55.9)	49 (66.2)	82 (61.7)
Asian	23 (39.0)	17 (23.0)	40 (30.1)
Black	1 (1.7)	3 (4.1)	4 (3.0)
Other	1 (1.7)	0	1 (0.8)
Not recorded	1 (1.7)	5 (6.8)	6 (4.5)
Region, n (%)			
United States	19 (32.2)	33 (44.6)	52 (39.1)
Asia	20 (33.9)	14 (18.9)	34 (25.6)
Rest of the world	20 (33.9)	27 (36.5)	47 (35.3)
Smoking status, n (%)			
Current smoker	8 (13.6)	8 (10.8)	16 (12.0)
Not a current smoker	51 (86.4)	66 (89.2)	117 (88.0)

Source: FDA Analysis

8.3.4 Efficacy Results

Since Study 312 is currently ongoing and not all subjects had completed the Month 6 visit by the time of the data cutoff date of the report, efficacy data will not be presented.

9 Evaluation of Safety

9.1 Safety Summary

In the ALIS development program, 820 subjects were exposed to at least one dose of ALIS, 802 of whom received multiple doses of ALIS. Of the subjects that received multiple doses of ALIS, 355 (44.3%) were patients with refractory pulmonary MAC infection. The remaining were CF patients with chronic *P. aeruginosa* infection (n=387, 48.3%), bronchiectatic patients with chronic *P. aeruginosa* infection (n=43, 5.4%) and healthy volunteers (n=6, 0.7%). The primary safety population for our review is subjects in the three NTM studies (212, 312 and 112, n=388); the majority (90.5%) of these were

non-CF subjects infected with MAC. It should be noted that Study 112 included 17 subjects with CF and 32 with *M. abscessus* (14 of which had both CF and predominantly *M. abscessus* lung disease).

The doses of ALIS studied ranged from 70 mg to 590 mg, dosing frequency included a single dose, cyclic dosing, and daily dosing, and duration of treatment ranged from a single dose to up to 22 months of exposure. Of the 802 subjects who received multiple doses of ALIS, 646 (80.5%), including all subjects in the three NTM studies, were exposed to the proposed dose of 590 mg.

The subjects enrolled in the three NTM studies had varying exposure to ALIS ranging from 3-20 months. In Study 112, subjects received 84 days of daily ALIS in addition to their OBR in a randomized fashion followed by an additional 84 days of ALIS in subjects from either arm of the study who elected to continue in an open-label extension phase. In Study 212, subjects were initially randomized to receive 8 months of ALIS plus OBR vs. OBR alone, followed by an additional 12 months of randomized therapy (starting from the first negative culture that defined culture conversion) for subjects that achieved culture conversion. Subjects that did not achieve culture conversion in either arm of the trial were offered to participate in the extension Study 312 to receive 12 months of daily ALIS plus OBR.

Overall, there was no mortality imbalance between the ALIS plus OBR arm as compared to the control arm (OBR plus inhaled empty liposomes in Study 112, or OBR only in Study 212). However, there were more discontinuations from the studies in the ALIS-treated subjects due to treatment-emergent adverse events (TEAEs) and "withdrawal by subject". The majority of the TEAEs were in the "Respiratory, thoracic and mediastinal disorders" and "Infections and infestations" system organ classes. Notable TEAEs in the Phase 3 trial (Study 212) that were more common in the ALIS plus OBR arm as compared with the OBR alone arm included: dysphonia, cough, dyspnea, upper airway inflammation, fatigue and asthenia, diarrhea, nausea, tinnitus, wheezing, and rash. There were also slightly more Study 212 patients in the ALIS plus OBR arm who experienced serious adverse events (SAEs), including pneumonia and COPD exacerbations.

Evaluation of the data from the three NTM studies shows that the highest at-risk period for experiencing TEAEs was the first 6 weeks after initiation of ALIS.

9.2 Methods

The primary safety evaluation was based on the results of Studies 212, 312 and 112. Some safety analyses were also conducted using the integrated dataset of all 11 multiple-dose clinical studies, including studies in CF and non-CF bronchiectasis patients with *P. aeruginosa* infections.

Due to the differences in the study designs between Study 212 and Study 112 (different comparator arms, lengths of treatment, and study populations), the safety results from

these two studies will be presented separately. Study 312 will also be discussed separately.

Of note, for the safety analysis of Study 212, the Agency defined TEAEs as all AEs that occurred between Day 1 and the Month 8 visit. This definition allowed conducting a comparative safety analysis between patients randomized to the ALIS plus OBR and OBR alone arms since at the Month 8 visit all non-converters were discontinued from the study and some subjects from both arms enrolled in Study 312, where, depending on prior treatment assignments they either continued or started ALIS.

The Sponsor's definition of TEAE included all AEs that occurred between Day 1 and 28 days after the last dose of ALIS in the ALIS plus OBR arm, and all AEs between Day 1 and the End of Treatment visit (up to 16 months) for the OBR alone arm. This could result in potentially very different lengths of follow-up for AEs between subjects in the ALIS plus OBR arm and the OBR alone arm, as a higher proportion of subjects in the ALIS plus OBR arm as compared to the OBR alone arm discontinued study treatment prematurely, 33.5% and 8%, respectively.

9.3 Overall Exposure to ALIS

In the ALIS development program, 820 subjects were exposed to at least one dose of ALIS, 802 of whom received multiple doses of ALIS. Of the subjects that received multiple doses of ALIS, 352 (43.9%) were non-CF patients with refractory pulmonary MAC infection. The remaining subjects were CF patients with chronic *P. aeruginosa* infection (n=387, 48.3%), bronchiectatic patients with chronic *P. aeruginosa* infection (n=43, 5.4%) and healthy volunteers (n=6, 0.7%). Table 14 summarizes the overall exposure to ALIS.

Table 14: Overall Exposure to ALIS in Clinical Studies

Exposed to at least one dose of ALIS	820
Exposed to multiple doses of ALIS	802 (100%)
NTM population	388 (48.4%)
Non-CF NTM population	370 (46.1)
Non-CF, non-MAC NTM*	18 (2.2)
Non-CF MAC population**	352 (43.9)
Patients with *P. aeruginosa*[#]	430 (53.6%)
Healthy volunteers	6 (0.7%)
Exposed to 590 mg of ALIS	646 (80.5%)

*Subjects with predominantly *Mycobacterium abscessus* infection
**Includes one subject from the scintigraphy sub-study of Study 112
#Includes n=387 CF patients and n=43 non-CF bronchiectatic patients
Source: FDA Analysis

The doses of ALIS in the development program ranged from 70 mg to 590 mg, dosing frequency from a single dose to cyclic dosing to daily dosing, and duration of treatment from a single dose to up to 22 months. Of the 802 subjects that received multiple doses of ALIS, 646 (80.5%), including all subjects in the three NTM studies, were exposed to the proposed dose of 590 mg.

The subjects enrolled in the three NTM studies also had varying exposure to ALIS ranging from 3-20 months. In Study 112, subjects received 84 days of daily ALIS in addition to their OBR in a randomized fashion followed by an additional 84 days of ALIS for subjects that elected to continue from either arm of the study in an open-label extension phase. In Study 212, subjects were initially randomized to receive 6 months of ALIS plus OBR vs. OBR alone, followed by an additional 12 months of randomized therapy (starting from the first negative culture that defined culture conversion) for subjects that achieved culture conversion. However, subjects remained on their respective treatment regimens at least until Month 8 since the Month 6 visit culture results were not known until the Month 8 visit. Therefore, for the safety analysis of Study 212, the Agency defined TEAEs as all AEs that occurred between Day 1 and the Day 247 (Month 8 visit). Subjects that did not achieve culture conversion from either arm of Study 212 were offered to participate in the extension Study 312 where they were offered 12 months of daily ALIS plus OBR.

9.4 Safety Analyses for Study 212

Please refer to
Table 2 for the baseline characteristics of subjects in Study 212. Table 15 below shows pertinent baseline medical history for subjects in Study 212.

Table 15: Pertinent Baseline Medical History of Study 212 Subjects

	ALIS plus OBR N=223 n (%)	**OBR N=112 n (%)**
Prior nebulized inhaled amikacin use	24 (10.8)	15 (13.4)
Current smoker	25 (11.2)	10 (8.9)
Bronchiectasis	168 (75.3)	82 (73.2)
COPD	50 (22.4)	37 (33)
Deafness[a]	47 (21.1)	34 (30.4)
Hemoptysis	28 (12.6)	15 (13.4)
Cough	28 (12.6)	22 (19.6)

Pulmonary cavitation	26 (11.7)	19 (17)
Pneumonia[b]	28 (12.6)	17 (15.2)
Tinnitus	24 (10.8)	13 (11.6)
Pulmonary resection[c]	24 (10.8)	6 (5.4)
Asthma	22 (9.9)	14 (12.5)
Dyspnea	18 (8.1)	15 (13.4)
Hypoacusis	19 (8.5)	11 (9.8)
Emphysema	16 (7.2)	10 (8.9)
Tuberculosis[d]	12 (5.4)	7 (6.3)
Pneumothorax[e]	11 (4.9)	8 (7.1)
Pulmonary fibrosis	7 (3.1)	2 (1.8)
Vertigo and balance disorder	6 (2.7)	3 (2.8)

[a]Includes deafness, deafness neurosensory, deafness bilateral, deafness unilateral
[b]Includes pneumonia and pneumonia bacterial[c]Includes pulmonary resection and lung lobectomy
[d]Includes tuberculosis (TB) and pulmonary TB
[e]Includes pneumothorax and spontaneous pneumothorax
Source: FDA Analysis

Subject disposition in Study 212 is presented in Table 1. There were significantly higher discontinuation rates in the ALIS plus OBR arm as compared to OBR alone due to AEs (17.4% vs. 0.9%) and voluntary withdrawal from the study by subjects (9.4% vs. 5.4%), respectively.

Deaths in Study 212

There were 17 deaths in Study 212; 3 of these occurred prior to randomization. Of the remaining 14 deaths, 9 (4%) and 5 (4.5%) occurred in the ALIS plus OBR and OBR alone arms, respectively.

Table 16 provides a summary of the deaths by treatment arm.

Table 16: Summary of Deaths in Study 212

Age in yrs	**Sex***	**Study day of death**	**Treatment Duration with study drug**	**Reported Immediate Cause of Death**
ALIS plus OBR				
71	F	372	189	Acute respiratory failure
70	M	187	143	COPD exacerbation & acute respiratory failure

60	M	81	70	COPD exacerbation & respiratory failure
67	F	61	61	Pulmonary embolism, *Pseudomonas* pneumonia, ongoing MAC infection
79	M	54	54	COPD exacerbation and respiratory failure
61	M	23	23	Respiratory failure and cachexia
60	M	175	43	COPD
69	F	191	170	Lung infection
76	M	202	83	Empyema
OBR Only				
69	M	429	388	Interstitial lung disease
75	F	42	29	MAC infection
70	M	14	14	Cardiogenic shock
63	F	229	217	Pneumonia
74	M	173	143	Respiratory failure

*F=Female; M=Male
Source: FDA Analysis

Serious Adverse Events in Study 212

As stated in section 9.2, all AEs that occurred between Day 1and Day 247 were considered as TEAEs. During this period, 45 (20.2%) of ALIS plus OBR subjects and 18 (16.1%) of OBR alone subjects experienced at least one SAE. Table 17 shows SAEs experienced by >1 subject in the ALIS plus OBR arm.

Table 17: SAEs Experienced by >1 Subject in the ALIS plus OBR arm in Study 212

MedDRA Preferred Term	**ALIS plus OBR N=223 n (%)**	**OBR N=112 n (%)**
Patient with at least one SAE	45 (20.2)	18 (16.1)
Pneumonia[a]	12 (5.4)	4 (3.6)
COPD exacerbation[b]	8 (3.6)	2 (1.8)
Hemoptysis	5 (2.2)	4 (3.6)

Allergic alveolitis[c]	4 (1.8)	0 (0)
Pneumothorax	4 (1.8)	1 (0.9)
Respiratory failure[d]	4 (1.8)	1 (0.9)
Infective exacerbation of bronchiectasis	4 (1.8)	3 (2.7)
Dyspnea	3 (1.3)	0 (0)
Pneumonitis	2 (0.9)	0 (0)
Anxiety	2 (0.9)	0 (0)

[a]Included pneumonia, lung infection, empyema, infectious pleural effusion, lung infection *Pseudomonas*, pneumonia aspiration, and pneumonia pseudomonas
[b]Included COPD and infective exacerbation of COPD
[c]Included allergic alveolitis, pneumonitis and interstitial lung disease
[d]Included respiratory failure and acute respiratory failure
Source: FDA Analysis

In addition to the SAEs presented**Error! Reference source not found.** there was one report of hypersensitivity to ALIS. Additional analyses of these AEs are presented in section 11.7 under "AEs of Interest".

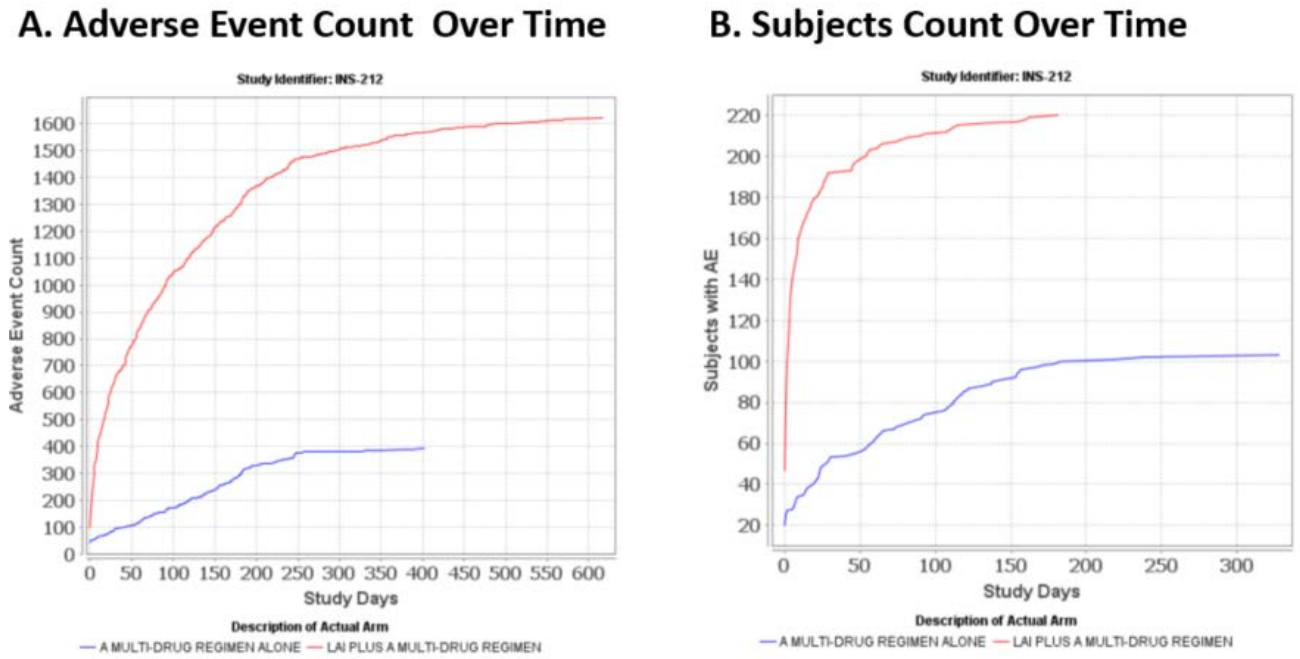
Hospitalizations Up to Month 8 Visit During Study 212

There were 92 hospitalizations in 47 (21.1%) subjects in the ALIS plus OBR arm compared to 24 hospitalizations in 15 (13.4%) subjects in the OBR alone arm. The most common reasons for hospitalization in the ALIS plus OBR arm included pneumonia, exacerbation of underlying lung disease (COPD, bronchiectasis), hemoptysis, respiratory failure, and dyspnea. The most common reasons for hospitalization for the OBR alone arm included hemoptysis, exacerbation of underlying lung disease, MAC infection and acute myocardial infarction. This component of the review is ongoing.

Treatment Emergent Adverse Events in Study 212

The majority of the study subjects (98.2% in ALIS plus OBR arm and 90.2% in OBR alone arm) experienced at least one TEAE by the Month 8 visit. Most of these TEAEs occurred in the first 6 weeks after initiation of ALIS. Figure 3 A and B below depicts the timing of these TEAEs by event count and subject count, respectively. Please note that "LAI plus Multi-Drug Regimen" refers to the ALIS plus OBR arm, and "Multi-Drug Regimen Alone" refers to the OBR alone arm.

Figure 3: Timing of TEAEs in Study 212



Source: FDA Analysis

Table 18 summarizes the TEAEs that occurred in >10 subjects in the ALIS plus OBR arm.

Table 18: Study 212 Treatment Emergent Adverse Events by MedDRA Preferred Term

MedDRA Preferred Term	ALIS plus OBR N=223 n (%)	OBR N=112 n (%)
Subjects with at least 1 TEAE	219 (98.2)	102 (91.1%)
Dysphonia[a]	105 (47.1)	1 (0.9)
Cough[b]	87 (39)	20 (17.9)
Dyspnea[c]	48 (21.5)	10 (8.9)
Upper airway inflammation[d]	40 (17.9)	2 (1.8)
Hemoptysis	40 (17.9)	14 (12.5)
Musculoskeletal pain[e]	39 (17.5)	12 (10.7)
Fatigue and asthenia	36 (16.1)	11 (9.8)
Diarrhea	29 (13)	5 (4.5)
Upper respiratory infection[f]	26 (11.7)	20 (17.9)
Nausea	26 (11.7)	4 (3.6)

Pneumonia[g]	22 (9.9)	9 (8)
Headache	22 (9.9)	5 (4.5)
COPD exacerbation[h]	19 (8.5)	4 (3.6)
Tinnitus	17 (7.6)	1 (0.9)
Wheezing	16 (7.2)	2 (1.8)
Pyrexia	16 (7.2)	5 (4.5)
Infective exacerbation of bronchiectasis	15 (6.7)	8 (7.1)
Rash[j]	15 (6.7)	1 (0.9)
Vomiting[i]	15 (6.7)	4 (3.6)
Weight decreased	14 (6.3)	1 (0.9)
Decreased appetite	14 (6.3)	8 (7.1)
Dizziness	14 (6.3)	3 (2.7)
Change in sputum[k]	13 (5.8)	1 (0.9)
Chest discomfort	12 (5.4)	3 (2.7)

[a]Includes “aphonia” and “dysphonia”
[b]Includes “cough”, “productive cough” and “upper airway cough syndrome”
[c]Includes “dyspnea” and “dyspnea on exertion”
[d]Includes “oropharyngeal pain”, “oropharyngeal discomfort”, “throat irritation”, “pharyngeal erythema”, “upper airway inflammation”, “pharyngeal edema”**,** “vocal cord inflammation”, “laryngeal pain”, “laryngeal erythema”, “laryngitis”, “laryngitis fungal”
[e]Includes “back pain”, “arthralgia”, “myalgia”, “pain/body aches”, “muscle spasm” and “musculoskeletal pain”
[f]Includes “nasopharyngitis/cold”, “pharyngitis”, “sinusitis”, and “upper respiratory infection”
[g]Includes “atypical pneumonia”, “empyema”, “infection pleural effusion”, “lower respiratory tract infection”, “lung infection”, “lung infection pseudomonas”, “pneumonia”, “pneumonia aspiration”, “pneumonia pseudomonas”, “pseudomonas infection” and “respiratory tract infection”
[h]Includes “COPD” and “infective exacerbation of COPD”
[i]Includes “vomiting” and “post-tussive vomiting”
[l]jncludes “rash”, “rash maculo-papular”, “drug eruption” and “urticaria”
[k]Includes “increased sputum”, “sputum purulent”, and “sputum discolored”
Source: FDA Analysis

9.5 Safety Analyses for Study 312

The safety analysis for Study 312 compares AEs that occurred in previously ALIS naïve subjects (non-converters in the OBR alone arm of Study 212) to subjects who continued on ALIS (non-converters in the ALIS plus OBR arm in Study 212). It is important to note that the non-converters in the ALIS plus OBR arm does not include patients who dropped out of Study 212 due to TEAEs, so one might incorrectly conclude that TEAEs improve with time.

Subject Disposition in Study 312

Subject disposition in Study 312 is presented in **Error! Reference source not found.**. Similar to the observation noted in Study 212, subjects initiated on ALIS treatment for

the first time (previously in the OBR alone arm in Study 212) had higher discontinuation rates due to AEs.

Deaths in Study 312

There were three deaths in Study 312; all three occurred in subjects who had received ALIS plus OBR in Study 212 and were nonconverters. These deaths are summarized in Table 19. All three subjects had underlying disease that may have resulted in death, but the contribution of ALIS cannot be ruled out.

Table 19: Summary of Deaths in Study 312

Age in yrs	Sex*	Study day of death	Treatment Duration in Study-312 (days)	Treatment Duration in Study -212 (days)	Reported Immediate Cause of Death
63	F	124	124	237	COPD
71	F	112	90	248	Chest infection
79	F	59	31	238	Respiratory failure

*F=female, M=male
Source: FDA Analysis

Serious Adverse Events in Study 312

There were no imbalances in SAEs between the two groups, with SAEs reported in 20.3% of subjects in the prior OBR alone arm vs. 18.6% in previously treated with ALIS. Summaries of SAEs are presented in Table 20.

Table 20: SAEs that Occurred in ≥1 Subject in Study 312

Preferred Terms	**Previously ALIS Naïve (Prior OBR only) N=74 n (%)**	**Continuing ALIS (Prior ALIS plus OBR) N=59 n (%)**
	15 (20.3)	11 (18.6)
Pneumonia	3 (4.1)	1 (1.7)
Infective exacerbation of bronchiectasis	2 (2.7)	1 (1.7)
Atrial fibrillation	2 (2.7)	0 (0)
COPD	2 (2.7)	1 (1.7)
Hemoptysis	2 (2.7)	1 (1.7)

Source: FDA Analysis

Treatment Emergent Adverse Events in Study 312

Table 21 below summarizes the treatment emergent adverse events in Study 312. Similar to the observation in Study 212, subjects who had previously received only OBR (and were now receiving ALIS for the first time) experienced a higher incidence of TEAEs, and in particular, significantly higher incidences of dysphonia, cough, dyspnea, and upper airway inflammation.

Table 21: Treatment Emergent Adverse Events in Study 312

PT Terms	Prior OBR only N=74 n, (%)	Prior ALIS plus OBR N=59 n, (%)
Subjects with at least 1 TEAE	69 (93.2)	43 (72.9)
Dysphonia[a]	33 (44.6)	3 (5.1)
Cough[b]	30 (40.5)	4 (6.8)
Dyspnea[c]	12 (16.2)	3 (5.1)
Upper airway inflammation[d]	10 (13.5)	2 (3.4)
Fatigue and asthenia	10 (13.5)	1 (1.7)
Hemoptysis	9 (12.2)	5 (8.5)
Diarrhea	9 (12.2)	3 (5.1)
Upper respiratory infection[e]	7 (9.5)	7 (11.9)
Exacerbation of bronchiectasis	6 (8.1)	3 (5.1)
Nausea	6 (8.1)	1 (1.7)
COPD exacerbation	6 (8.1)	3 (5.1)
Changes in sputum[f]	6 (8.1)	1 (1.7)
Abdominal pain[g]	6 (8.1)	2 (3.4)
Tinnitus	5 (6.8)	1 (1.7)
Dizziness	5 (6.8)	1 (1.7)
Pneumonia[i]	4 (5.4)	4 (6.8)
Chest discomfort	4 (5.4)	0 (0)
Hematuria	4 (5.4)	4 (6.8)
Headache	4 (5.4)	1 (1.7)
Weight decreased	4 (5.4)	1 (1.7)

[a]Includes dysphonia and aphonia
[b]Includes cough and productive cough
[c]Includes dyspnea, dyspnea at rest and dyspnea on exertion
[d]Includes laryngitis, larynx irritation, oropharyngeal pain, pharyngeal erythema, throat irritation and vocal cord inflammation
[e] Includes upper respiratory tract infection, viral upper respiratory infection, nasopharyngitis
[f]Includes increased sputum, sputum discolored

[g]Includes abdominal pain, abdominal pain, abdominal discomfort, abdominal pain upper and abdominal pain lower
[h]Includes pneumonia, Pseudomonas infection, Klebsiella infection, and lower respiratory infection
Source: FDA Analysis

9.6 Safety Analyses for Study 112

As previously mentioned, Study 112 had a heterogenous study population, with inclusion of non-CF subjects infected with *M. abscessus* (n=9 in ALIS plus OBR, n=9 in OBR plus inhaled empty liposomes) and subjects with CF (n=8 in ALIS plus OBR, n=9 in OBR plus inhaled empty liposomes). The safety analyses included all subjects. Of note, this was the only study that included an inhaled placebo (empty liposomes) plus OBR arm. This provided an opportunity to compare the AEs associated with ALIS plus OBR verses an inhaled liposome vehicle control plus OBR.

Deaths in Study 112

There were 4 deaths in the ALIS plus OBR arm (n=1 in double-blind phase, n=1 in open-label phase, n=2 in the 12-month long-term follow up period), and 5 deaths in the OBR plus inhaled empty liposomes arm (n=5 in the 12-month long term follow up period).

Serious Adverse Events in Study 112

Serious adverse event that occurred in the double-blind phase of Study 112 (the first 84 days) are summarized in Table 22.

Table 22: SAEs during the Double-blind Phase of Study 112

System Organ Class (SOC) and Preferred Term (PT)	ALIS plus OBR N=44 n (%)	OBR plus Placebo* N=45 n (%)
Patient with at least one SAE	8 (18.2)	4 (8.9)
Infections and infestations	5 (11.4)	3 (6.7)
Infective exacerbation of bronchiectasis	2 (4.6)	1 (2.2)
Infective exacerbation of cystic fibrosis	1 (2.3)	0 (0)
Viral gastroenteritis	1 (2.3)	0 (0)
Pneumonia	1 (2.3)	2 (4.4)
Respiratory, thoracic & mediastinal disorders	2(4.6)	1 (2.2)
Acute respiratory distress syndrome	1 (2.3)	0 (0)
Eosinophilic pneumonia	0 (0)	1 (2.2)
Hemoptysis	1 (2.3)	0 (0)
Respiratory disorder (Hypersensitivity lung reaction)	1(2.3)	0 (0)

Cardiac disorders	1 (2.3)	0 (0)
Supraventricular tachycardia	1 (2.3)	0 (0)
Injury, poisoning & procedural complications	1 (2.3)	0 (0)
Fractured left femur and humerus	1 (2.3)	0 (0)
Gastrointestinal disorders	0	1 (2.2)
Small intestine obstruction	0	1 (2.2)

*Placebo was inhaled empty liposomes
Source: FDA Analysis

TEAE during the Randomized Double-blind Phase of Study 112

TEAEs that occurred in the double-blind phase are summarized in

Table 23.

Table 23: Treatment Emergent Adverse Events During the Randomized Double-blind Phase of Study 112

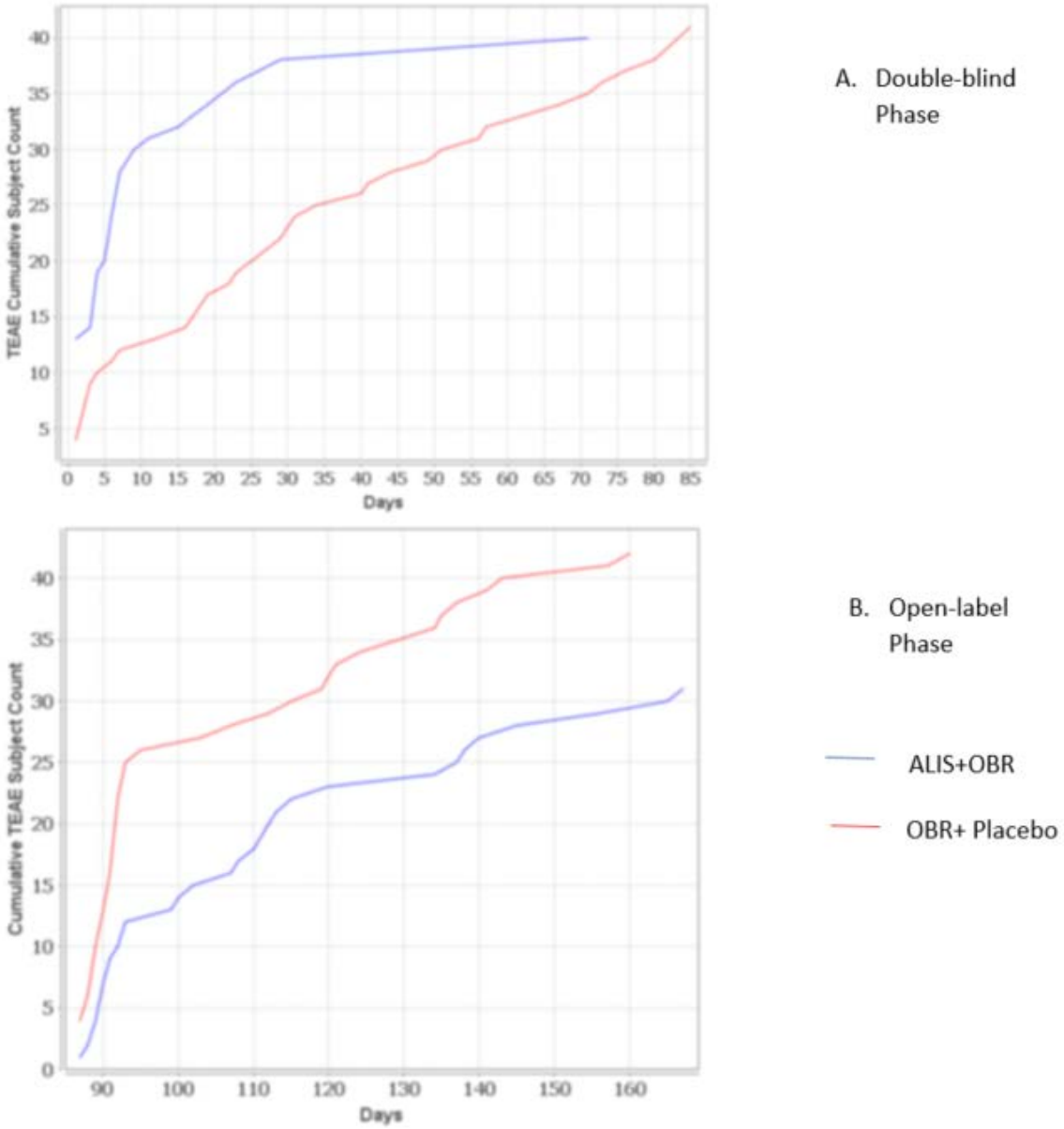
MedDRA Preferred Term	**ALIS N=44 n (%)**	**Placebo* N=45 n (%)**
Exacerbation of underlying lung disease[a]	22 (50)	10 (22.2)
Infective exacerbation of bronchiectasis	17 (38.6)	9 (20)
Infective exacerbation of cystic fibrosis	4 (9.1)	1 (2.2)
COPD exacerbation	1 (2.3)	0 (0)
Dysphonia[b]	20 (45.5)	4 (8.9)
Cough[c]	16 (36.4)	6 (13.3)
Upper airway inflammation[d]	11 (25)	2 (4.4)
Fatigue	7 (15.9)	4 (8.9)
Chest discomfort	5 (11.4)	0 (0)
Hemoptysis	5 (11.4)	5 (11.1)
Musculoskeletal pain[e]	5 (11.4)	4 (8.9)
Nausea	5 (11.4)	4 (8.9)
Abdominal pain/discomfort	4 (9.1)	1 (2.2)
Pneumonia[f]	4 (9.1)	4 (8.9)
Pyrexia	4 (9.1)	3 (6.7)

Upper respiratory infection[g]	4 (9.1)	2 (4.4)
Wheeze	4 (9.1)	1 (2.2)
Dyspnea	3 (6.8)	1 (2.2)
Headache	3 (6.8)	3 (6.7)
Rash[h]	3 (6.8)	0 (0)

*Placebo means inhaled empty liposomes
[a]Includes “infective exacerbation of bronchiectasis”, “infective exacerbation of CF” and “COPD exacerbation”
[b]Includes “aphonia” and “dysphonia”
[c]Includes “cough”, “productive cough” and “upper airway cough syndrome”
[d]Includes “oropharyngeal pain”, “throat irritation”, “laryngitis”
[e]Includes “back pain”, “arthralgia”, “myalgia”, “pain/body aches”, “muscle spasm”, “musculoskeletal discomfort” and “musculoskeletal pain”
[f]Includes “pneumonia”, “eosinophilic pneumonia”, and “respiratory tract infection bacterial”
[g]Includes “nasopharyngitis/cold” and “upper respiratory infection”
[h]Includes “rash” and “urticaria”
Source: FDA Analysis

Figure 4 shows the timing of TEAEs experienced by patients in the two treatment arms during: (A) the double-blind phase, and (B); the open-label phase of Study 112.

Figure 4: Timing of TEAEs in Double-blind and Open-label Phase of Study 112



Source: FDA Analysis

9.7 Adverse Events of Interest

Adverse Events of Interest (AEI) were identified based on AEs known to be caused by aminoglycosides, as well as route of administration. Table 24 outlines the pooled terms that constitute each AEI. AEIs identified by the Applicant are identified by asterisk.

Table 24: Preferred Terms Included in the Adverse Events of Interests

TEAE of Interest	Included preferred terms
Allergic alveolitis*	Alveolitis allergic, interstitial lung disease, pneumonitis
Bronchospasm*	Asthma, bronchial hyperreactivity, bronchospasm, dyspnea, dyspnea exertional, prolonged expiration, throat tightness, wheezing
Cough	Cough, productive cough, upper airway cough syndrome
Dysphonia	Aphonia, dysphonia
Exacerbation of underlying lung disease	COPD, infective exacerbation of COPD, infective exacerbation of bronchiectasis
Hemoptysis	Hemoptysis
Nephrotoxicity*	Blood creatinine increased, glomerular filtration rate decreased, hematuria, leukocyturia, proteinuria, renal failure, urinary casts, urinary casts present
Neuromuscular disorder*	Muscular weakness, neuropathy peripheral, balance disorder
Ototoxicity*	Deafness, deafness neurosensory, deafness unilateral, dizziness, hypoacusis, presyncope, tinnitus, vertigo
Pneumonia	Atypical pneumonia, empyema, infectious pleural effusion, lower respiratory tract infection, lung infection, lung infection pseudomonal, pneumonia, pneumonia aspiration, pneumonia pneumococcal, pneumonia pseudomonal, pseudomonal infection, respiratory tract infection
Pneumothorax	Pneumo-mediastinum, pneumothorax, pneumothorax spontaneous
Upper airway inflammation	Laryngeal erythema, laryngeal pain, laryngitis, oropharyngeal discomfort, oropharyngeal pain, pharyngeal erythema, pharyngeal edema, pharyngitis, upper respiratory tract inflammation, vocal cord inflammation

Source: Modified from Sponsor's Table 24 in Study 212 Clinical Study Report

Table 25, Table 26 , and Table 27 summarize the incidence of AEIs in Studies 212, 312 and 112, respectively.

Table 25: Incidence of Adverse Events of Interest in Study 212 up to Month 8 Visit

Adverse Events of Interest	**ALIS plus OBR N=223 n (%)**	**OBR only N=112 n (%)**
Dysphonia	105 (45.7)	1 (0.9)
Cough	87 (39)	19 (17)
Bronchospasm	64 (28.7)	12 (10.7)
SAE	3 (1.3)	0 (0)
Hemoptysis	40 (17.9)	14 (12.5)
Ototoxicity	38 (17)	11 (9.8)
Upper Airway Inflammation	37 (16.6)	2 (1.8)
Exacerbation of underlying lung disease	33 (14.8)	11 (9.8)
SAE	11 (4.9)	4 (3.6)
Pneumonia	22 (9.9)	9 (8)
SAE	12 (5.4)	2(1.8)
Allergic Alveolitis	7 (3.1)	0 (0)
SAE	4 (1.8)	0 (0)
Pneumothorax	5 (2.2)	1 (0.9)
SAE	4(1.8)	1 (0.9)
Nephrotoxicity	5 (2.2)	3 (2.7)
Neuromuscular Disorder	2 (0.9)	0 (0)

Source: FDA Analysis

Table 26: Incidence of Adverse Events of Interest in Study 312

Study 312 Pooled Terms for AEs of Interest	Prior OBR only N=74 n (%)	Prior ALIS plus OBR N=59 n (%)
Dysphonia	33 (44.6)	3 (5.1)
Cough	30 (40.5)	4 (6.8)
Bronchospasm	15 (20.3)	3 (5.1)
Exacerbation of underlying lung disease	10 (13.5)	4 (6.8)
SAE	4 (5.4)	1 (1.7)
Hemoptysis	9 (12.2)	5 (8.5)
	2 (2.7)	1 (1.7)
Upper airway inflammation	8 (10.8)	2 (3.4)
SAE	1 (1.4)	0 (0)
Ototoxicity	10 (13.5)	3 (5.1)

Source: FDA Analysis

Table 27: Incidence of Adverse Events of Interest in the Double-Blind Phase of Study 112

AE of Interest Term	ALIS N=44 n (%)	Placebo* N=45 n (%)
Dysphonia	21 (47.7%)	6 (13.3%)
Exacerbation of underlying lung disease	18 (40.9%)	10 (22.2%)
SAE	2 (4.5)	1 (2.2)
Cough	16 (36.4%)	9 (20.0%)
Upper Airway Inflammation	10 (22.7%)	2 (4.4%)
Bronchospasm	7 (15.9%)	4 (8.9%)
Ototoxicity	5 (11.4%)	4 (8.9%)
Pneumonia	3 (6.8%)	3 (6.7%)
SAE	1 (2.3)	2 (4.4)
Changes in Sputum	2 (4.5%)	2 (4.4%)
Allergic Alveolitis	1 (2.3%)	1 (2.2%)
SAE	1 (2.3)	1 (2.3)
Nephrotoxicity	1 (2.3%)	0 (0.0%)
Neuromuscular Disorder	1 (2.3%)	1 (2.2%)

Source: FDA Analysis

10 Summary

Efficacy

The data provided to support the safety and efficacy of ALIS in the treatment of MAC lung disease are primarily based on the results of Study 212, a Phase 3, open-label, randomized trial comparing ALIS added to an OBR versus OBR alone in patients with refractory MAC lung disease. No data are available for the treatment of a broader patient population with MAC lung disease.

In Study 212, significantly more subjects in the ALIS plus OBR arm achieved the primary endpoint of culture conversion (three consecutive negative cultures with 6 months of treatment), 65/224 (29%) compared to the OBR alone arm, 10/112 (8.9%). However, given the design of the trial with the option to switch to ALIS in the OBR alone arm after Month 8, assessment of the long-term outcomes in the initially randomized treatment groups will be very limited.

Supportive efficacy information is provided by Study 112, in patients with refractory MAC/*M. abscessus* lung infections. In this trial, at Day 84, a greater proportion of subjects in the ALIS group (31.8%) achieved a negative culture than subjects in the placebo group (8.9%). This was a secondary endpoint in a trial that did not meet its primary endpoint of a change in semi-quantitative scale (SQS) for mycobacterial culture at Day 84.

The only clinical outcome that has been assessed in the clinical trials conducted thus far is the 6MWT, the results for which were not significant in Study 212 at the 6-month visit. A trend in favor of ALIS was seen in Study 112 at Day 84.

Efficacy data from Study 312 are difficult to interpret at this time as the study is ongoing and not all subjects have completed the Month 6 visit by the time of the data cutoff date. Additionally, it will be very difficult to compare outcomes between the two non-randomized groups.

Safety
While ALIS appears to have a treatment effect on sputum culture conversion, in Study 212, there appears to be a higher frequency of treatment discontinuations and AEs in patients treated with ALIS as noted below:

- More ALIS plus OBR-treated patients discontinued treatment prematurely, 33.5% compared to 8% OBR alone-treated patients.
- More ALIS plus OBR-treated subjects discontinued treatment due to AEs, 17.4% compared to 0.9% in the OBR alone arm.
- The frequency of SAEs was slightly higher in the ALIS plus OBR arm (20.2%) compared to the OBR alone arm (16.1%).
- A considerably higher proportion of ALIS plus OBR versus OBR alone treated subjects experienced AEs, including dysphonia (47.1% vs. 0.9%), cough (39% vs. 17.9%), dyspnea (21.5% vs. 8.9%), upper airway inflammation (17.9% vs. 1.8%), hemoptysis (17.9% vs. 12.5%), tinnitus (7.6% vs. 0.9%). Except for upper respiratory infection, (11.7 vs. 17.9%), infective exacerbation of bronchiectasis, (6.7% vs.7.1%), and decreased appetite (6.3% vs. 7.1%), all AEs reported by more than 10 patients were more common in the ALIS plus OBR arm compared to the OBR alone arm.
- All AEs of interest, such as dysphonia, cough, bronchospasm, hemoptysis, allergic alveolitis, and upper airway inflammation were more common in the ALIS plus OBR arm compared to the OBR alone arm.
- More ALIS plus OBR-treated subjects were hospitalized compared to those receiving OBR alone. During the initial 8 months of the trial, there were 92 hospitalizations in 47 (21.1%) patients in the ALIS plus OBR arm as compared to 24 hospitalizations in 15 (13.4%) patients in the OBR alone arm. All hospitalizations in ALIS-treated patients were related to respiratory conditions. This component of the review is ongoing.

Safety data from studies 112 and 312 also suggest that AEs related to the respiratory tract were more common in ALIS-treated patients. Of interest in Study 112, these were more common compared to patients who received inhaled placebo (diluted liposomes).

In summary, the following should be considered in the risk-benefit assessment of ALIS in the treatment of refractory MAC lung disease:

- There are uncertainties with the clinical significance of the surrogate endpoint of sputum culture conversion by Month 6. Although there are uncertainties with sputum culture conversion predicting clinical benefit in this patient population, the degree of uncertainty in the surrogate endpoint of sputum culture conversion was considered acceptable in Study 212, given the unmet need in patients with refractory MAC lung disease and the seriousness of the disease. In addition, there was an expectation of a finding supportive of efficacy in a clinical outcome such as the 6-minute walk test. Data on the durability of sputum culture conversion 3 months after completion of MAC therapy and clinical outcomes are being collected in patients who are continuing in Study 212. Of note, considering the design of Study 212, a comparative assessment of later clinical outcomes may be limited.

- Given the design of Study 212 with the option to switch to ALIS in the OBR alone arm, assessment of the long-term clinical and microbiologic outcomes in the initially randomized treatment groups is very limited. Only a small proportion of the subjects (~29%) achieved sputum conversion and non-converters were either discontinued from the study after Month 8 or enrolled in an open-label extension study, Study 312. This limits assessments of the safety and efficacy of ALIS beyond 8 months.

- The rates of AEs, treatment discontinuations, and AEs of interest were higher in ALIS plus OBR-treated patients compared to the OBR alone-treated patients.

- In the supportive studies, 112 and 312, assessment of safety and efficacy is limited. In Study 112, there was no treatment benefit demonstrated on the primary endpoint of change in SQS of mycobacterial culture. However, a trend at Day 84 in the number of subjects achieving a negative culture and the 6MWT was seen. There was a higher incidence of treatment discontinuations and AEs in ALIS-treated patients compared to those treated with placebo.

- An assessment of the safety and efficacy of ALIS in Study 312 is limited because the study is uncontrolled and solely includes subjects who had already been enrolled in Study 212.

11 Draft Points for Advisory Committee Discussion

1. Is the surrogate endpoint of sputum culture conversion based on three consecutive negative sputum cultures reasonably likely to predict clinical benefit?

2. Has the applicant provided substantial evidence of the safety and effectiveness of ALIS for the treatment of nontuberculous mycobacterial lung disease caused by *Mycobacterium avium* complex as part of a combination antibacterial drug regimen for adult patients?

    a. If yes, please provide any recommendations regarding labeling and please comment on the design of the trial that will need to be conducted to demonstrate clinical benefit.
    b. If no, please provide recommendations regarding additional studies/analyses that are needed.

3. Has the applicant provided substantial evidence of the safety and effectiveness of ALIS for the treatment of nontuberculous mycobacterial lung disease caused by *Mycobacterium avium* complex as part of a combination antibacterial drug regimen for adult patients with limited or no treatment options?

    a. If yes, please provide any recommendations regarding labeling and please comment on the design of the trial that will need to be conducted to demonstrate clinical benefit.

    b. If no, please provide recommendations regarding additional studies/analyses that are needed.

12 References

1. Prevots, D.R., et al., *Nontuberculous mycobacterial lung disease prevalence at four integrated health care delivery systems.* Am J Respir Crit Care Med, 2010. **182**(7): p. 970-6.
2. Griffith, D.E., et al., *An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases.* Am J Respir Crit Care Med, 2007. **175**(4): p. 367-416.
3. Field, S.K., D. Fisher, and R.L. Cowie, *Mycobacterium avium complex pulmonary disease in patients without HIV infection.* Chest, 2004. **126**(2): p. 566-81.
4. Griffith, D.E. and T.R. Aksamit, *Therapy of refractory nontuberculous mycobacterial lung disease.* Curr Opin Infect Dis, 2012. **25**(2): p. 218-27.
5. Griffith DE, et al. *Clinical and molecular analysis of macrolide resistance in Mycobacterium avium complex lung disease.* Am J Respir Crit Care Med, 2006. **174**(8): p. 928-34.
6. Jenkins PA, et al. *Clarithromycin vs ciprofloxacin as adjuncts to rifampicin and ethambutol in treating opportunist mycobacterial lung diseases and an assessment of Mycobacterium vaccae immunotherapy.* Thorax, 2008. **63**(7): p. 627-34.