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New Drug Evaluation: Arikayce™ (amikacin liposome) suspension for oral inhalation

Date of Review: November 2019
Generic Name: amikacin liposome inhalation suspension

End Date of Literature Search: September 2019
Brand Name (Manufacturer): Arikayce® (Insmed Incorporated)
Dossier Received: yes

Research Questions:

1. What is the efficacy of amikacin liposome inhalation suspension compared to placebo or currently available therapy for treatment-refractory mycobacterium avian complex (MAC) lung disease?
2. Is amikacin liposome inhalation suspension safer than alternative therapeutic agents used in treatment-refractory MAC lung disease?
3. Are there any subgroups (based on age, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with amikacin liposome inhalation suspension?

Conclusions:

- There is low quality evidence based on one phase 2 randomized controlled trial (RCT) that amikacin liposome inhalation suspension 590 mg resulted in a greater proportion of patients with one negative sputum culture by month 6 compared to placebo in patients with treatment-refractory Mycobacterium Avian Complex (MAC) lung disease (31.8% vs. 8.9%, respectively, p=0.0057; Number Needed to Treat [NNT]=5).[1,2]
- There is low quality of evidence based on one phase 3 open label trial that amikacin liposome inhalation suspension 590 mg plus an optimized background antibacterial regimen (OBR) demonstrated a greater proportion of patients with sputum culture conversions at month 6 compared to OBR alone in patients with treatment-refractory MAC lung disease (29.0% vs. 8.9%, respectively, adjusted odds ratio 4.22; 95% CI, 2.08 to 8.57; p<0.0001; NNT=5).[2,3] Culture conversion was defined as 3 consecutive monthly MAC-negative sputum cultures by month 6 of the study. [2,3]
- There is insufficient evidence that use of amikacin liposome inhalation suspension in patients with treatment-refractory MAC lung disease is associated with any clinically significant change in functional status. Functional improvement was evaluated with the 6-minute walk test (6MWT). [1-3] The phase 2 study reported a statistically significant difference in 6MWT distance from baseline to day 84 that favored the amikacin group compared to placebo (20.6 m increase vs. 25 m decrease, respectively, p=0.0102), but no statistically significant difference was observed for the same endpoint in the phase 3 study. [1-3]
- There is low quality evidence of increased discontinuations due to adverse events and serious adverse events in patients treated with amikacin liposome inhalation suspension compared to patients on a background regimen alone for treatment-refractory MAC lung disease.[1-4] The FDA issued a Black Boxed Warning regarding amikacin liposome inhalation suspension for increased risk of respiratory adverse reactions including hypersensitivity pneumonitis, hemoptysis, bronchospasm, and exacerbation of underlying pulmonary disease that have led to hospitalizations.[4] The safety of amikacin liposome inhalation suspension has not been evaluated in pregnancy, breastfeeding women, pediatric patients, or patients with hepatic or renal impairment.[2,4]

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Recommendations:

- Designate amikacin liposome inhalation suspension as non-preferred on the preferred drug list (PDL).
- Implement clinical prior authorization criteria for amikacin liposome inhalation suspension to ensure appropriate utilization (**Appendix 2**).

Background:

Nontuberculosis mycobacteria (NTM) encompass a broad spectrum of mycobacterial pathogens some of which are a frequent cause of skin and soft tissue infection, lung disease, and disseminated disease.[5] NTM lung disease is a progressive and debilitating condition that is a major public health concern with annual United States (U.S.) health care cost of roughly $1.7 billion.[6] Risks for development of NTM pulmonary disease include host factors such as the presence of structural lung defects (e.g. COPD or bronchiectasis), certain genetic disorders (e.g. cystic fibrosis [CF]), or host-susceptibility (e.g. hypersensitivity pneumonitis or weakened immune responses due to HIV). [5,7] Patients treated with particular pharmacological agents may also be at increased risk of NTM lung disease such as those on chronic gastric acid suppression and individuals treated with immunosuppressive agents such as TNF-alpha inhibitors and corticosteroids. [5,7,8] NTM lung disease may also occur in individuals without any known predisposing condition.[5,9] The most frequent group of NTM organisms responsible for pulmonary infection in the U.S. is free-living Mycobacterium Avian Complex (MAC). [7,8] Lung infections caused by MAC (*M. avium*, *Mycobacterium intracellulare,* and *M. chimaera*) can result in irreversible bronchial damage and increased mortality. [9]

MAC is commonly found throughout the environment in soil, groundwater, and surface water but is usually not of great pathologic concern.[10] These mycobacteria are aerobic, non-motile microorganisms with a dense lipid cell wall.[5] The waxy protective cell envelope enables MAC to be resistant to most disinfectants, high temperatures, and antibiotics.[5] With its ability to withstand environmental insult, MAC can easily colonize treated indoor water systems such as swimming pools and hot tubs.[11,12] The glycopeptidolipids produced by NTM form a biofilm to enhance survival even in showerheads and household plumbing.[5] Due to its hydrophobic nature, MAC can aerosolize from water and spread via inhalation from contaminated sources, but there is little evidence to demonstrate person-to-person transmission of MAC.[12] Although MAC is generally not a concern for disease in healthy individuals, pathogenic capability may vary based on host susceptibility, pathogen virulence, and environmental risk factors.[5,9] MAC can cause progressive lung disease and subsequent respiratory failure even in individuals with no history of smoking or underlying lung disease as seen in a type of nodular bronchiectasis known as Lady Windermere Syndrome.[13] MAC disease prevalence has significantly increased in recent years and is most common in parts of Northern Europe, Japan, and the United States, particularly in the West and Southwest regions.[14] In a large study at 56 sites worldwide, MAC was isolated in 47% of the NTM-related pulmonary disease cases.[14] Early Centers for Disease Control and Prevention (CDC) data collected in the U.S. found higher rates of NTM lung disease in women, African Americans, and Hispanics.[9] In 2018, there were 32 unique cases of pulmonary mycobacterial infection identified from claims data in the Oregon Medicaid Fee-for-Service (FFS) population.

The American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) guidelines define NTM lung disease as the presence of pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or multifocal bronchiectasis with nodules on chest X-ray/CT scan, plus positive cultures from either two sputum samples, one bronchoalveolar wash or lavage, or one lung biopsy.[11] MAC symptoms are non-specific and may present differently if the patient has pre-existing lung disease such as COPD or bronchiectasis.[13] Asymptomatic cases may be discovered by a fortunate chest radiograph screening, however, even symptomatic cases may remain undetected for months to years before diagnosis.[9,11] Non-specific warning signs such as chronic cough, dyspnea, and malaise are common, but fever, hemoptysis and weight loss may also occur, especially in fibrocavitary disease.[9,11] Treatment for MAC lung disease are generally dependent upon radiologic criteria and cultures to determine the appropriate regimen.[9,11] Patients with nodular bronchiectatic disease tend to progress much more slowly than fibrocavitary disease and may require long follow-up periods to observe clinical or radiographic changes.[9,11] Therefore, frequent clinical monitoring, routine sputum cultures, and radiographic imaging may be preferred until risks of multi-drug therapy are weighed against benefits of treatment.[9,11] However, patients

with fibrocavitary disease (cavities, fibrosis, and pleural involvement) generally require more aggressive treatments at the time of initial diagnosis due to the rapid progression and destructive nature of this type of disease.[9,11]

ATS-IDSA guidelines suggest that the medical treatment regimen chosen for MAC lung disease be driven by the clinical presentation and individual goals of therapy for each patient (see **Table 1**).[11] Treatment typically consists of a combination of a rifamycin, ethambutol, and a macrolide until sputum cultures become negative and then ongoing treatment for 12 months.[11] Previous studies had reported 20-90% treatment success rates for MAC lung disease with the 3-drug regimen, but estimates were closer to 40% when discontinuations, relapses, surgical requirements and deaths were included in the calculation.[9] For nodular/bronchiectatic disease, a three times per week regimen is preferred for due to better tolerability.[11] For cavitary disease, however, a daily 3-drug regimen is preferred. In the cases of advanced MAC disease or those previously treated, the addition of an intravenous aminoglycoside active against MAC is preferred.[11]

Table 1. Therapy for Mycobacterium Avium Complex Lung Disease: Recommendations According to Disease Status and/or Severity (modified) [11]

Condition	Drug Class	Agent/Dose	Evidence Quality [b]
Initial Therapy for Nodular/Bronchiectatic Disease [a]	Macrolide	Clarithromycin 1000 mg TIW or azithromycin 500-600 mg TIW	B, II
	Ethambutol	25 mg/kg TIW	
	Rifamycin	Rifampin 600 mg TIW	
	IV aminoglycoside	None	
Initial Therapy for Cavitary Disease	Macrolide	Clarithromycin [c] 500-1000 mg daily or azithromycin 250-300 mg daily	A, II
	Ethambutol	15 mg/kg daily	
	Rifamycin	Rifampin [c] 450-600 mg daily	
	IV aminoglycoside	Streptomycin or amikacin [d] or none	
Advanced (Severe) or Previously Treated Disease	Macrolide	Clarithromycin [c] 500-1000 mg daily or azithromycin 250-300 mg daily	B, II
	Ethambutol	15 mg/kg daily	
	Rifamycin	Rifabutin [c] 150-300 mg daily or rifampin 450-600 mg daily	
	IV aminoglycoside	Streptomycin or amikacin [d]	
Category A = Good evidence to support a recommendation for use Category B = Moderate evidence to support recommendation for use Grade II = Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center, from multiple time-series studies or from dramatic results in uncontrolled experiments			

Abbreviations: IV = intravenous; TIW = three times weekly

Note: *a* = Not recommended for severe or previously treated disease; *b* = Rating for entire multidrug regimen; *c* = Lower dose for weight < 50kg; *d* = variable dosing; see original document for details

Clinical outcome definitions for NTM treatment have been developed by the Nontuberculosis Mycobacteria Network European Trials group (NMT-MET) to improve consistency in the interpretation of therapy efficacy (see **Table 2**).[15] Culture conversion may require 3 to 6 months, but inability to convert sputum to

culture negative by 6 months is generally recognized as treatment failure or refractory disease.[12,15] Patients who do not respond to first-line therapy have limited treatment options which may require expert consultation and the possibility of surgical resection.[12]

Table 2. Treatment Outcome Definitions for Nontuberculous Mycobacterial Pulmonary Disease [15]

Outcome	Definition
Culture conversion	≥ 3 consecutive negative mycobacterial cultures from respiratory samples collected ≥ 4 weeks apart during treatment
Microbiologic cure	Multiple consecutive negative and no positive cultures with the causative species from respiratory samples after culture conversion through the end of treatment
Clinical cure	In the absence of evidence of culture conversion or microbiologic cure, patient-reported and/or objective improvement in symptoms on treatment that is sustained through end of treatment
Cure	Treatment completion with both microbiologic and clinical cure
Treatment failure	Re-emergence of ≥ 2 positive cultures or persistence of positive cultures with causative species from respiratory samples after ≥ 12 months of treatment while still on treatment
Recurrence	Re-emergence of ≥ 2 positive cultures with causative species from respiratory samples after ending treatment; may be relapse or reinfection
Relapse	Emergence of ≥ 2 positive cultures with same causative strain after treatment
Reinfection	Emergence of ≥ 2 positive cultures with a different causative strain after treatment

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

In September 2018, the U.S. Food and Drug Administration (FDA) approved amikacin liposome inhalation suspension (Arikayce®) for the treatment of patients with refractory MAC lung disease.[2] Amikacin liposome inhalation suspension (ALIS) is an antibacterial aminoglycoside that disrupts and inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit.[2,4] The positively charged molecules enter the bacterial cell and interact with negatively charged particles on the cell surface to disrupt cell wall integrity which ultimately leads to bacterial cell death.[2,4] ALIS is indicated for adults who have limited or no alternative treatment options for MAC lung disease as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy.[2,4] ALIS was approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) as an antibacterial agent intended to treat a serious infection in a very limited population with unmet needs.[2,4] The evidence did not support a favorable benefit-risk profile for use in a broader population of patients with non-refractory MAC lung disease.[2,4] The efficacy and safety of ALIS for this indication was evaluated with data from one phase 2 trial and one phase 3 trial which are described below and summarized in **Table 5.**

Study 112 was a 12-week, phase 2 double blind RCT (N=89) to evaluate the safety and tolerability of ALIS 590 mg (n=44) compared to placebo (n=45) plus guideline-based background therapy (GBT) (Table 1) in patients with treatment-refractory NTM lung infection.[1,2] All patients were on a stable, guideline-based multidrug regimen which was continued throughout the trial.[1,2] The randomized phase was followed by a 12-week open-label extension study.[1,2] Patients characteristics were generally similar between groups for mean age, gender, race, BMI, percent predicted mean forced expiratory volume in one second (FEV_1),

presence of disease and type of microorganism (see **Table 5**).[1,2] Only adults with pulmonary nontuberculous mycobacteria with evidence of nodular bronchiectasis and/or cavitary disease by chest computed tomography (CT) and a chronic MAC or *M. abscessus* infection were included.[1,2] Patients with clinically significant cardiac, pulmonary, hepatic, or renal disease were excluded, however, no definition for clinical significance was given.[1,2] Full inclusion and exclusion criteria may be found in **Table 5.**

The primary endpoint was change from baseline on a semi-quantitative scale (SQS) for mycobacterial culture growth in the ALIS plus GBT group at day 84 compared to placebo plus GBT within the same timeframe.[1,2] SQS is a 7-step reporting method that has been used to evaluate mycobacterial burden observed from culture samples.[1,16] However, the FDA reviewer noted that the primary endpoint of mycobacterial density assessed by the SQS had unclear clinical relevance as this tool had not been used in previous NTM studies.[2] The data are limited whether SQS is predictive of clinical response to therapy or if it correlates with subjective measures of response such as symptom improvement or changes radiographic appearance.[16] Media were examined for the presence and number of mycobacterial culture colonies then given a categorical result that ranged from step 1 (culture negative; 0 colonies; no liquid medium growth) to step 7 ("4+"; >500 colonies; positive liquid medium growth observed).[1,2] At baseline, there were a higher percentage of patients evaluated at step 3 in the ALIS group compared to placebo (39% vs. 22%, respectively), but fewer ALIS subjects at step 7 compared to the placebo group (32% vs. 42%).[1,2] Roughly 11% of subjects in both groups were culture negative at baseline.[1,2] The clinically relevant secondary and tertiary endpoints were proportion of subjects with NTM negative culture at Day 84 and change in the six-minute walk test (6MWT) distance, respectively.[1,2] The 6MWT is a self-paced test of walking capability where patients are asked to walk on a flat surface for as long as possible in a 6-minute timeframe and distance in meters is documented.[17]

Study 112 outcomes were analyzed with modified intention-to-treat (mITT) population defined as all randomized patients given one dose or more amikacin LIS.[1,2] At day 84, there was not a statistically significant difference in SQS change from baseline in ALIS-treated patients compared to placebo (52.3% vs. 51.1%, respectively; p=0.072).[1,2] A greater proportion of subjects in the ALIS group achieved one negative culture reading compared to placebo at 84 days (32% vs. 9%, respectively; p=0.0057), and there was a statistically significant difference in change from baseline in 6MWT distance at day 84 that favored the ALIS group compared to placebo (20.6 m increase vs. 25 m decrease, respectively; p=0.0102).[1,2]

Study 212 was a 6-month, phase 3, randomized, open-label, multicenter trial of ALIS in adult patients (N=336) with refractory MAC lung disease.[2,3] Subjects were considered to have refractory MAC lung disease if they had a positive sputum culture after at least 6 months of treatment with guideline-based, optimized background regimen (OBR) of 3 antibiotics.[2,3] Patients were excluded for comorbidities including cystic fibrosis, active pulmonary tuberculosis, immunodeficiency syndromes, amikacin resistance, or active malignancy.[2,3] Full inclusion and exclusion criteria may be found in the evidence table (**Table 5**). Patients were stratified by smoking status at screening; most were not current smokers (89%) and many had bronchiectasis (62.5%).[2,3] Patients who met criteria were randomized 2:1 to either ALIS plus OBR (n=224) or OBR alone (n=112).[2,3] Baseline characteristics were generally similar except for a larger percentage of females in the ALIS plus OBR group compared to OBR alone (73.7% vs. 60.7%, respectively).[2,3] Most of the patients were from the United States (42%), white (70%), and were on OBR at screening (>90%).[2,3] The OBR regimens typically included a macrolide, a rifamycin, and ethambutol.[2,3] Specific doses were not reported. Concomitant use of other medication combinations and antibacterial agents were allowed during the trial as well as rescue medications which are highlighted in **Table 5.**

The surrogate primary endpoint was proportion of patients with negative sputum culture conversion based on monthly assessments from baseline to month 6.[2,3] Secondary endpoints included change from baseline in the 6-minute walk test (6MWT) at 6 months and change from baseline in the St George's Respiratory Questionnaire (SGRQ).[2,3] The SRGQ is a 76-item questionnaire that assesses health-related quality of life (HRQOL) in respiratory disease with a minimum score

of 0 (no effect on HRQOL) maximum score of 100 (maximum perceived distress).[18] Some studies have suggested a minimal clinically important difference (MCID) on the SGRQ to be 4 units.[18]

There was a statistically significant greater proportion of patients with a negative sputum culture conversion by month 6 in the ALIS plus OBR group compared to the OBR group alone (29.0% vs. 8.9%, respectively, P<0.0001). [2,3] After a sensitivity analysis was performed there were 3 subjects in each group who did not demonstrate sustained sputum culture conversion. [2,3] The long-term clinical significance of a sputum culture conversion by month 6 is unclear. There was not a statistically significant difference between groups in the 6MWT or the SGRQ by month 6. [2,3]

Study 312 was an open label extension of study 212 to assess the safety and tolerability of ALIS 590 mg plus GBT in MAC lung disease in patients who were refractory to conventional therapy. [2,3] The study enrolled patients who successfully completed the 6-month and end of treatment visit and had not achieved culture conversion in either group. [2,3] The results are reported in the clinical safety section below.

Several limitations of the trial design present challenges to determine the true clinical benefit of ALIS. Amikacin LIS was used as add-on therapy to a guideline-based background treatment but it was unclear if the background regimen drugs and doses were optimized for all participants, especially those with co-morbidities. In study 212, a higher percentage of comorbidities at baseline was observed in the OBR alone arm which included COPD (33% in OBR alone arm vs. 22.4% in ALIS+OBR arm), pulmonary cavitation (17% in OBR alone arm vs. 12% in ALIS+OBR arm), and dyspnea (13% OBR alone arm vs. 8% in ALIS+OBR arm). [2-4] The impact of the baseline group imbalance on efficacy and safety outcomes is unclear. For many patients, especially with nodular-bronchiectatic MAC pulmonary disease, sustained mycobacterial eradication may not be achievable and post-treatment relapses are common. Therefore, it is unclear whether antibiotic therapy duration is an adequate marker for treatment success. In Study 212, patients who did not convert to negative sputum culture at month 6 were discontinued from the study or crossed over to ALIS therapy at month 8, so there is no clear evidence to evaluate comparative efficacy beyond 6 months. A negative culture conversion does not necessarily translate into meaningful clinical improvements in physical function or health-related quality of life. Clinically relevant outcomes such as improvements in the 6MWT reported in Study 112 were not replicated in Study 212. The FDA reviewer could not determine the reasons for the discordance in the 6MWT and suggested the possibility of a chance finding.

Clinical Safety:

In all combined clinical studies with multiple amikacin LIS exposures, 646 (80.5%) patients received the FDA-approved 590 mg dose.[2,4] The exposure duration ranged from 3-20 months. [2,4] There were 32 deaths reported in the development of ALIS, and all except one occurred in studies 112, 212, and 312. [2,4] However, there was no apparent imbalance in mortality between ALIS plus OBR and OBR groups. [2,4] Roughly one-quarter to one-third of patients in the ALIS group discontinued therapy prematurely and, compared to the OBR group, most of the discontinuations were due to adverse events (16-17% vs 0-1%, respectively). [2,4] In study 212, many of the treatment emergent adverse effects (TEAEs) in the ALIS group were due to pulmonary and airway disorders (**see Table 3**). [2,4] Pre-defined adverse events of interest in the ALIS + OBR group which led to the discontinuations included bronchospasm (n=9), dysphonia (n=5), exacerbation of underlying lung disease (n=4), ototoxicity (n=4), allergic alveolitis/hypersensitivity pneumonitis (n=3), cough (n=2), hemoptysis (n=2), pneumonia (n=1) and upper airway irritation (n=1). [2-4]

Table 3. Treatment Emergent Adverse Events in Study 212 in >5% of Amikacin + OBR Treated Patients Compared to OBR Alone[2-4]

	Amikacin LIS + OBR N=223 (%)	OBR N=112 (%)
Dysphonia	105 (47.1)	1 (0.9)
Cough	87 (39)	20 (17.9)
Dyspnea	48 (21.5)	10 (8.9)
Upper airway inflammation	40 (17.9)	2 (1.8)
Hemoptysis	40 (17.9)	14 (12.5)
Musculoskeletal pain	39 (17.5)	12 (10.7)
Fatigue and asthenia	36 (16.1)	11 (9.8)
Diarrhea	29 (13)	5 (4.5)
Nausea	26 (11.7)	4 (3.6)
Headache	22 (9.9)	5 (4.5)
COPD exacerbation	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)
Rash	15 (6.7)	1 (0.9)
Vomiting	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)
Sputum change	13 (5.8)	1 (0.9)
Chest discomfort	12 (5.4)	3 (2.7)

Study 312 was an open-label extension study of Study 212 and provided limited safety evidence and no comparative efficacy data. [2-4] There were similar rates for discontinuations between groups. However, for ALIS new-starts, discontinuations due to adverse events accounted for 11 of the 15 discontinuations (73%), while discontinuation due withdrawal by subject (5/13) and discontinuation due to lack of efficacy (3/13) were the main reasons for discontinuation for those that were continued on ALIS. [2-4] Within the first 4-6 weeks after initiation, new start ALIS patients experienced a significantly higher incidence of dysphonia, cough, dyspnea and upper airway irritation than those continuing ALIS therapy.

Due to these significant adverse events experienced in clinical trials, ALIS has a FDA Boxed Warning for increased risk of, hypersensitivity pneumonitis, hemoptysis, bronchospasm, and exacerbation of underlying pulmonary disease that have led to hospitalizations in some cases. [2,4] Additional warnings and precautions include ototoxicity, nephrotoxicity, neuromuscular blockade, and embryo-fetal toxicity. [2,4]

The safety of ALIS has not been evaluated in pregnancy, breastfeeding women, pediatric patients, or patients with hepatic or renal impairment. [2,4]

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Improved survival
2) Improvement of MAC symptoms or functional capacity
3) Prevention of MAC pulmonary complications
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Change from baseline to day 84 in the semi-quantitative scale (SQS) for mycobacterial growth
2) Sputum culture conversion based on assessment of monthly sputum cultures from baseline to month 6

Table 4. Pharmacology and Pharmacokinetic Properties. [2,4]

Parameter	
Mechanism of Action	Disruption and inhibition of protein synthesis in the target bacteria by binding to the 30S ribosomal subunit.
Oral Bioavailability	Variable (Inhalation); average expected absorption is 7.42% of dose
Distribution and Protein Binding	368.6 L; ≤10% protein binding
Elimination	Renal via glomerular filtration (>90% unchanged drug in urine)
Half-Life	5.9 to 19.5 hours
Metabolism	No appreciable metabolism

Table 5. Comparative Evidence Table.[1-4]

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Oliver, et al. 2016 (Study 112) Phase 2, RCT, DB, PC followed by open-label extension phase	1. ALIS 590 mg inhalation once daily 2. placebo (sterile lipid carrier suspension) inhalation once daily 84 days randomized + 84 days open label	Demographics: Mean age: 58.5 years Race: 90-95% white Female: 88% BMI: 22 kg/m^2 Mean FEV1%: 63% Predominantly MAC: 64% CF: 19% Key Inclusion Criteria: -Adult patients with PNTM disease as defined by ATS/IDSA -Received ATS/IDSA GBT for at least 6 months prior -Persistent positive cultures for MAC or *M. abscessus* Key Exclusion Criteria: -Current smoker -FEV1 < 30% of predicted -Clinically significant cardiac, pulmonary, hepatic, or renal disease -Systemic immune deficiency -Malignancy -Hx of daily continuous oxygen supplementation	ITT: 1. 44 2. 46 mITT: 1. 44 2. 45 Attrition: 1. 9 (20.5%) 2. 0 (0%) 19 D/C study drug during open label extension phase	Primary Endpoint: Change from baseline to EOT (day 84) on SQS mycobacterial growth scale 1. 52.3% 2. 51.1% P=0.072 Secondary Endpoints: Proportion of subjects with negative sputum culture for NTM at day 84 1. 14 (32%) 2. 4 (9%) P=0.006 Tertiary Endpoints Change from baseline to day 84 in the 6MWT 1. 20.6 m 2. -25.0 m Difference: 45m P=0.0102	 NS 23%/5 N/A	Deaths: 1. 4 2. 5 D/C due to AE: 1. 9 (20.5%) 2. 0 (0%) - Infective exacerbations of underlying pulmonary disease and dyspnea 1. 7/9 (78%) 2. 0 (0%) TEAEs 1. 22 (50%) 2. 10 (22.2%) SAEs 1. 8 (18.2%) 2. 4 (8.9%) -infection and infestation 1. 11.4% 2. 6.7%	N/A for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Method of randomization/allocation not described; groups unbalanced in baseline mycobacterial load; higher percentage of females in the ALIS group (74%) compared to placebo (61%) Performance Bias: Unclear. Double blinded but no details how maintained; empty liposome placebo delivered with customized investigational nebulizer Detection Bias: Unclear. No details how/if assessors were blinded Attrition Bias: High. Greater loss in ALIS group; mITT used for analysis Reporting Bias: High. Reported endpoints that were not prespecified such as durability of sputum culture at 12 months Other Bias: Unclear. Sponsored by Insmed; multiple authors were consultants/employees of sponsor; medical writing assistance by Insmed employees **Applicability**: Patient: Subjects with refractory MAC or *M. abscessus* lung infections and included subjects with cystic fibrosis; median duration of MAC lung disease (4.5 vs. 3.3 years) Intervention: ALIS 590 mg dose likely appropriate based on prior pharmacologic studies Comparator: Placebo + GBT was appropriate for efficacy Outcomes: Surrogate endpoint with unclear link to clinical outcomes Setting: 18 US sites and 1 Canada site

2. Griffith, et al. 2018 (Study 212) Phase 3, OL, RCT	1. ALIS 590 mg once daily + OBR 2. OBR	Demographics: Mean age: 64 years old Female: 70% 1. 73.7% 2. 60.7 Multidrug regimen at screening: 90% Current smoker: 1. 11.6% 2. 8.9% Concomitant medications: Selective beta-2 receptor agonists: 1. 52.2% 2. 38.4% Fluoroquinolones: 1. 27.2% 2. 36.6% Glucocorticoids: 1. 27.7% 2. 18.8% Key Inclusion Criteria: - Age: ≥18 years - positive for NTM MAC lung infection documented by 2 cultures after 6 months of multi-drug tx - MAC-positive sputum at screening Key Exclusion Criteria: - CF, active TB, amikacin resistance, Hx of lung transplant - immunodeficiency syndromes, active malignancy, chronic steroid or anti-inflammatory therapy last 28 days - pregnancy - alcohol/substance abuse - hearing loss/or dysfunction where risk of AG toxicity outweighs the benefit - AST/ALT ≥3 x ULN, total bili ≥ 2 times ULN at screening, ANC ≤500/µL, Scr >2 x ULN - any condition that interferes with ability to safely complete study	ITT: 1. 224 2. 112 Attrition: 1. 75 (33.5%) 2. 9 (8%)	Primary Endpoint: Sputum culture conversion based on assessment of monthly sputum cultures from baseline to month 6. Converter ALIS + OBR: 65 (29%) OBR alone: 10 (8.9%) Non-converter ALIS + OBR: 159 (71%) OBR alone: 102 (91.1%) P<0.0001 Secondary Endpoint: Change from baseline in 6MWT distance at month 6 LSMD: -3.0 (95% CI, -20.6 to 14.7) P = 0.7223 Change from baseline SGRQ score: 1. 4.2 2. 0.4 LSMD: 3.8 (95% CI, 0.7 to 6.9) P = 0.0177	 20.1%/5 NS NS	Death 1. 9 (4%) 2. 5 (4.5%) D/C due to AE: 1. 39 (17.4%) 2. 1 (1%) TEAEs 1. 219 (98.2%) 2. 101 (90.2%) SAEs 1. 45 (20.2%) 2. 18 (16.1%) Subject Count of Unplanned Hospitalizations 1. 41 (18.4%) 2. 15 (13.4%) Hospitalization reasons: -Exacerbation of underlying pulmonary disease 1. 22/82 (27%) 2. 5/23 (22%) - Lower RTIs 1. 22/82 (27%) 2. 4/23 (17%)	N/A for all	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Open label; no matching placebo; interactive web response system used for randomization; patients could be excluded for any condition deemed to interfere with study outcomes Performance Bias: High. Investigators, patients not blinded to treatment. Detection Bias: High. Open label, no placebo. Data were collected by the investigators and analyzed by the sponsor. Attrition Bias: High. One-third of study population discontinued treatment mostly due to adverse effects Reporting Bias: Low. Outcomes reported as prespecified Other Bias: Unclear. Study authors received grants, personal fees, and/or consulting support from manufacturer. **Applicability**: Patient: Applies only to MAC positive patients refractory to multi-drug treatment after 6 months; extensive trial exclusions Intervention: ALIS 590 mg dose likely appropriate based on prior pharmacologic studies Comparator: Optimized background regimen (no active comparator); would have been appropriate to have placebo delivery component Outcomes: Surrogate endpoint with unclear link to clinical outcomes; tools used in the efficacy assessments (SGRQ, 6MWT) have been validated, but have not been validated in the MAC population. Setting: 127 sites in 18 countries

Abbreviations: 6MWT = six minute walk test; AG = aminoglycoside; ALIS = amikacin liposome inhalation suspension; ALT = alanine transaminase; ANC = absolute neutrophil count; ARR = absolute risk reduction; AST = aspartate aminotransferase; CI = confidence interval; CF = cystic fibrosis; DB = double blind; D/C = discontinue; EOT = end of treatment; GBT = guideline-based therapy; Hx = history; ITT = intention to treat; LSM = least squares mean; LSMD = least squares mean difference; MAC = mycobacterium avian complex; mITT = modified intention to treat; N = number of subjects; NA = not applicable;

NNH = number needed to harm; NNT = number needed to treat; NS = nonsignificant; NTM = nontuberculous MAC; OBR = optimized background regimen; OL = open label; PC = placebo controlled; PNTM = pulmonary nontuberculous mycobacteria; PP = per protocol; RTI = respiratory tract infection; SGRQ = St George's Respiratory Questionnaire; SQS = semi-quantitative scale; TB = tuberculosis; tx = treatment; ULN = upper limit of normal

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ARIKAYCE safely and effectively. See full prescribing information for ARIKAYCE.

ARIKAYCE® (amikacin liposome inhalation suspension), for oral inhalation use
Initial U.S. Approval: 2018
LIMITED POPULATION

WARNING: RISK OF INCREASED RESPIRATORY ADVERSE REACTIONS
See full prescribing information for complete boxed warning.

ARIKAYCE has been associated with a risk of increased respiratory adverse reactions, including, hypersensitivity pneumonitis, hemoptysis, bronchospasm, and exacerbation of underlying pulmonary disease that have led to hospitalizations in some cases. (5.1, 5.2, 5.3, 5.4)

----------INDICATIONS AND USAGE----------
LIMITED POPULATION: ARIKAYCE is an aminoglycoside antibacterial indicated in adults who have limited or no alternative treatment options, for the treatment of *Mycobacterium avium* complex (MAC) lung disease as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. As only limited clinical safety and effectiveness data for ARIKAYCE are currently available, reserve ARIKAYCE for use in adults who have limited or no alternative treatment options. This drug is indicated for use in a limited and specific population of patients. (1)

This indication is approved under accelerated approval based on achieving sputum culture conversion (defined as 3 consecutive negative monthly sputum cultures) by Month 6. Clinical benefit has not yet been established. (1)

Limitation of Use:
ARIKAYCE has only been studied in patients with refractory MAC lung disease defined as patients who did not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. The use of ARIKAYCE is not recommended for patients with non-refractory MAC lung disease.

----------DOSAGE AND ADMINISTRATION----------
- For oral inhalation use only. (2.1)
- Use ARIKAYCE vials only with the Lamira Nebulizer System. (2.1)
- The recommended dosage in adults is once daily oral inhalation of the contents of one 590 mg/8.4 mL ARIKAYCE vial. (2.2)
- Pre-treatment with inhaled bronchodilator should be considered in patients with a history of hyperreactive airway disease. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
ARIKAYCE is supplied as a sterile, aqueous, liposome suspension for oral inhalation in a unit-dose glass vial containing amikacin 590 mg/8.4 mL. (3)

----------CONTRAINDICATIONS----------
ARIKAYCE is contraindicated in patients with a known hypersensitivity to any aminoglycoside. (4)

----------WARNINGS AND PRECAUTIONS----------
- Hypersensitivity Pneumonitis: Reported with ARIKAYCE treatment; if hypersensitivity pneumonitis occurs, discontinue ARIKAYCE and manage patients as medically appropriate. (5.1)
- Hemoptysis: Higher frequency of hemoptysis has been reported with ARIKAYCE treatment. If hemoptysis occurs, manage the patients as medically appropriate. (5.2)
- Bronchospasm: Higher frequency of bronchospasm has been reported with ARIKAYCE treatment. Treat patients as medically appropriate if this occurs during treatment with ARIKAYCE. (5.3)
- Exacerbations of Underlying Pulmonary Disease: Higher frequency of exacerbations of underlying pulmonary disease has been reported with ARIKAYCE treatment. Treat patients as medically appropriate if this occurs during treatment with ARIKAYCE. (5.4)
- Ototoxicity: Higher frequency of ototoxicity has been reported with ARIKAYCE treatment. Closely monitor patients with known or suspected auditory or vestibular dysfunction. If patients develop tinnitus this may be an early symptom of ototoxicity. (5.5)
- Nephrotoxicity: Aminoglycosides can cause nephrotoxicity. Close monitoring of patients with known or suspected renal dysfunction may be needed when prescribing ARIKAYCE. (5.6)
- Neuromuscular Blockade: Aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts but mechanical assistance may be necessary .(5.7)
- Embryo-Fetal Toxicity: Aminoglycosides can cause total, irreversible, bilateral congenital deafness in pediatric patients exposed in utero. (5.8, 8.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥10% and higher than control) in the patients with refractory MAC lung disease were: dysphonia, cough, bronchospasm, hemoptysis, ototoxicity, upper airway irritation, musculoskeletal pain, fatigue/asthenia and exacerbation of underlying pulmonary disease, diarrhea, and nausea. (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Insmed Incorporated at 1-844-4-INSMED or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 9/2018

Amikacin Liposome Inhalation Suspension

Goal(s):

- Limit the use of amikacin liposome inhalation suspension to adult patients with limited or no alternative treatment options, for the treatment of Mycobacterium avium complex (MAC) lung disease as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy.

Length of Authorization:

- 6-month initial approval; Up to 12 months renewal

Requires PA:

- Amikacin Liposome Inhalation Suspension (ALIS)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes**: Go to **Renewal Criteria**	**No**: Go to #2
2. Is this request for treatment of an adult ≥18 years of age with Mycobacterium avium complex (MAC) lung disease verified through sputum culture?	**Yes:** Record ICD10 code. Go to #3.	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is this agent being prescribed by or in consultation with an infectious disease specialist, pulmonologist, or a specialist in the treatment of MAC lung infections?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
4. Has the patient been adherent to a 6-month course of a guideline-based 3-drug antibacterial treatment regimen including a macrolide, a rifamycin, and ethambutol within the last year?	**Yes:** List the antibiotic regimen. Go to # 5	**No:** Pass to RPh. Deny; medical appropriateness. 6-month trial of guideline-based, 3-drug antibacterial regimen is required before starting amikacin liposome inhalation suspension.
5. Will the patient be using amikacin liposome inhalation suspension as add on therapy to a guideline-based, 3-drug antibacterial MAC treatment regimen as described in question #4?	**Yes:** Approve for **6 months.** Dose not to exceed 1 vial per day (590 mg/8.4 ml vial). Renewal consideration will require documentation of monthly MAC sputum cultures and regimen adherence.	**No:** Pass to RPh. Deny; medical appropriateness. Concurrent guideline-based, 3-drug antibacterial MAC regimen is required per product labeling.

Renewal Criteria		
1. Has the patient experienced evidence of respiratory adverse effects since treatment initiation such as hypersensitivity pneumonitis, hemoptysis, bronchospasm, or exacerbation of underlying pulmonary disease?	**Yes**: Pass to RPh. Deny; medical appropriateness.	**No**: Go to #2
2. Has the patient been adherent to both amikacin LIS and guideline-based background MAC antibiotic regimen?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
3. Is there documentation of at least 3 consecutive negative monthly sputum cultures in the first 6 months of amikacin LIS therapy or a minimum of 2 consecutive negative monthly sputum cultures in the last 2 months of amikacin LIS therapy?	**Yes**: Document results of sputum culture. Approve for additional 3 months. Therapy not to exceed 12 months after converting to negative sputum status (≥3 consecutive negative MAC cultures).	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 11/19 (DE)
Implementation: TBD