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# Amikacin liposome inhalation suspension in treating non-tuberculous mycobacterial pulmonary diseases

**Keywords:** pulmonary diseases, amikacin liposome, non-tuberculous mycobacteria, mycobacterium avium complex, chronic obstructive pulmonary disease

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## Introduction

Pulmonary infectious disease caused by non-tuberculous mycobacteria (NTM) is more prevalent after the age of sixty where the incidence and prevalence are approximately 2.6 and 26.7 per 100,000 persons, respectively. Mycobacterium avium complex (MAC) is about 80% of the causes of pulmonary NTM disease. Hypothetically, NTM are not transmitted from person to person, but they are acquired from the environment. The diagnosis of pulmonary NTM disease requires respiratory or constitutional symptoms, positive cultures from two sputum specimens or one bronchoalveolar lavage (BAL), pulmonary nodules, and cavities, or bronchiectasis. Characteristically, treating pulmonary MAC disease includes the combination of a rifamycin, ethambutol, and a macrolide and continues for 12 months after becoming negative sputum cultures with treatment success rates of 20 %-90%. Unfortunately, if the reports include patients with treatment interruption, relapse, required surgery, or died, the cure rate is about 40%. The variability of the treatment success rates depends on whether treatment success was calculated based on intension-to-treat analyses and whether relapses were included as failures or failures were included as relapses. The mean direct expenditure per patient with pulmonary NTM disease and hospitalizations are four-fold and three times higher than that of controlled population. In a previous study, the mortality rates in patients with pulmonary NTM disease who received antimicrobials and who were prescribed macrolide monotherapy were 22.4% and 6.0%, respectively. With concomitant chronic obstructive pulmonary disease (COPD), the mortality rate was increased to 41.5%.

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. Amikacin targets the 30S ribosomal subunit of the 16S rRNA and disrupts protein synthesis in bacteria, including NTM. Mutations in the rrs gene of the 16S rRNA may contribute to the resistance mechanisms and resulting in minimum inhibitory concentration (MICs) of at least 64µgm/mL. In rats, inhaled ALIS increased amikacin concentrations in pulmonary macrophages by 5- to 8-fold at 2, 6, and 24 hours post-dose and retained more amikacin at 24 hour in airways and pulmonary tissues relative to inhaled free amikacin. Various amikacin-containing treatment regimens with the dosage of amikacin varying from 500 mg to 600 mg, the administrative period ranging from 15 days to 500 days and at least one treatment cycle have been studied in the patent application publication proposed by Eagle *et al*. in 2015. They concluded that there was a change from baseline on semiquantitative scale for mycobacterial culture for a treated patient, and/or NTM culture conversion to negative during or after the administration period. Currently, randomized phase 3 trial ALIS for treatment-refractory NTM pulmonary disease caused by MAC in adult patients is ongoing. A drug company announced that the United States Food and Drug Administration (US FDA) ' s Antimicrobial Drug Advisory Committee voted in favor (12-2) for the safety and efficacy of ALIS for adults with NTM pulmonary disease caused by MAC who have no treatment or limited options. The US FDA is not bound by the Committee's recommendations but takes them into consideration for approval. The Prescription Drug User Free Act (PDUFA) target the date on September 28, 2018 for consideration. If approved, ALIS would be the first treatment in the US for patients with pulmonary NTM disease caused by MAC.

## Conclusion

In several clinical trials, ALIS delivered amikacin to pulmonary macrophages, airways, and pulmonary tissues better than free amikacin given by either intravenous or inhalation administration. The mechanism of improved delivery into pulmonary macrophages and retention within airways and pulmonary tissues has been demonstrated to effectively treat refractory NTM pulmonary disease and represents a promising novel therapeutic approach for patients.

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## Conflict of interest

Author declares there is no conflict of interest in publishing the article.