Trial Conduct, Baseline Characteristics, and Symptom Burden of Patients in the ARISE Study

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SUPPLEMENTARY MATERIALS

Table S1 Detailed inclusion/exclusion criteria

Inclusion criteria	Exclusion criteria
Patients must satisfy all of the following criteria to be included in the study: 1. Male or female ≥ 18 years of age (19 years or older in the Republic of Korea) 2. Current diagnosis of MACLD. MAC or mixed infection with MAC as the dominant species is allowed, with MAC as the intended organism for treatment 3. Positive sputum culture for MAC within 6 months prior to screening 4. Positive sputum culture for MAC at screening 5. A chest computed tomography (CT) scan, read locally, within 6 months prior to screening to determine presence and size of pulmonary cavities. Patients who do not have a chest CT scan within 6 months prior to screening will be required to obtain a chest CT scan, read locally, during screening 6. In the Investigator's opinion, documented respiratory signs/symptoms at screening that are attributable to the current MAC lung infection 7. An average QOL-B Respiratory Domain score of ≤ 85 based on scores at screening and on the day of enrollment prior to randomization 8. In the Investigator's opinion, underlying lung disease (e.g., chronic obstructive pulmonary disease [COPD], bronchiectasis) have been managed according to best local standard of care, and on stable maintenance therapy for a minimum of 4 weeks prior to randomization 9. Willingness and ability to adhere to prescribed study treatment during the study 10. Ability to produce (spontaneously or with induction) approximately 2 mL of sputum for mycobacteriology at screening 11. Women of child-bearing potential [WOCBP] (i.e.. fertile following menarche and until becoming post-menopausal unless permanently sterile) and fertile men (i.e., all men after puberty unless permanently sterile by bilateral orchidectomy) agree to use a highly effective method of birth control from day 1 to at least 90 days after the last dose 12. Provide signed informed consent prior to administration of study drugs or performing any study related procedure 13. Be able to comply with study drugs use, study visits, and study procedures as defined by the protocol	Patients who meet any of the following criteria will be disqualified from entering the study: 1. Diagnosis of cystic fibrosis (CF) 2. History of more than 3 MAC lung infections 3. Received any mycobacterial antibiotic treatment for current MAC lung infection 4. Refractory MACLD, defined as having positive MAC cultures while being treated with a multidrug mycobacterial antibiotic treatment regimen for a minimum of 6 consecutive months and no documented successful treatment, defined as negative sputum culture for MAC and cessation of treatment 5. Relapse of prior MACLD, defined as positive sputum culture for MAC ≤ 6 months of cessation of prior successful treatment 6. MAC isolate with MIC for amikacin ≥ 128 µg/mL at screening 7. Evidence of any pulmonary cavity ≥ 2 cm in diameter, as determined by chest CT scan, read locally, within 6 months prior to screening 8. Radiographic finding of new lobar consolidation, atelectasis, significant pleural effusion, or pneumothorax during routine clinical care within 2 months prior to screening 9. Active pulmonary malignancy (primary or metastatic) or any malignancy requiring chemotherapy or radiation therapy within 1 year prior to screening or anticipated during the study 10. Active pulmonary tuberculosis requiring treatment during screening 11. Hospitalization for underlying lung disease during screening 12. Acute pulmonary exacerbation (e.g., COPD or bronchiectasis) requiring treatment with antibiotics, or corticosteroids (IV or oral), within 4 weeks prior to and during screening 13. Predicted forced expiratory volume in 1 second (FEV_1) < 35%, pre-bronchodilator use 14. Current smoker 15. History of lung transplantation 16. Use of inhaled or systemic aminoglycosides with activity against MAC (e.g., amikacin, kanamycin, or streptomycin) during screening 17. Prior exposure to ALIS (including clinical study)

14. Men with partners who are WOCBP (pregnant or non-pregnant) agree to use condoms and non-pregnant partners should use a highly effective method of birth control	18. Known hypersensitivity or contraindications to use to ALIS, aminoglycosides, or any of their excipients 19. Disseminated MAC infection 20. Positive pregnancy test or lactation at screening. All WOCBP will be tested. 21. Administration of any investigational drug within 8 weeks prior to screening 22. Known or suspected acquired immunodeficiency syndromes (HIV-positive, regardless of CD4 counts). Other immunodeficiency syndromes that may interfere with study participation in the opinion of the Investigator 23. Significant (as determined by the Investigator) hearing loss, vestibular dysfunction, neuromuscular weakness or a diagnosis of myasthenia gravis, where the potential risk of aminoglycoside toxicity outweighs the potential benefit 24. Aspartate aminotransferase or alanine aminotransferase ≥ 3 times the upper limit of normal (ULN) or total bilirubin ≥ 1.5 times ULN at screening 25. Absolute neutrophil count ≤ 500/μL at screening 26. Serum creatinine > 2 times ULN at screening 27. Current alcohol, medication, or illicit drug abuse 28. Any condition that, in the opinion of the Investigator, interferes with ability to safely complete the study or adhere to study requirements 29. Known and active COVID-19 infection 30. MAC isolate with MIC for clarithromycin ≥ 32 μg/mL at screening 31. Known hypersensitivity or contraindications to use to ethambutol, azithromycin (including other macrolides or ketolides), or any of their excipients per local labeling guidance
ALIS amikacin liposome inhalation suspension, *CF* cystic fibrosis, *COPD* chronic obstructive pulmonary disorder, *CT* computed tomography, *FEV_1* forced expiratory volume in 1 second, *FSH* follicle stimulating hormone, *HIV* human immunodeficiency virus, *MAC Mycobacterium avium* complex, *MACLD Mycobacterium avium* complex lung disease, *MIC* minimum inhibitory concentration, *QOL-B* Quality of Life–Bronchiectasis questionnaire, *ULN* upper limit of normal, *WOCBP* women of child-bearing potential	