ARISE - A Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Multicenter Study to Validate Patient-Reported Outcome Instruments in Adult Subjects with Newly Diagnosed Nontuberculous Mycobacterial (NTM) Lung Infection Caused by Mycobacterium avium Complex (MAC)

Published: 27-10-2020
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Primary ObjectiveTo generate evidence demonstrating the domain specification (via modern psychometric methods), reliability, validity, and responsiveness (within-subject meaningful change) of the patient-reported outcome (PRO) endpoints Secondary…

Ethical review	Approved WMO
Status	Completed
Health condition type	Respiratory tract infections
Study type	Interventional

Summary

ID

NL-OMON51951

Source
ToetsingOnline

Brief title
INS415

Condition

- Respiratory tract infections

Synonym
Nontuberculous Mycobacterial Lung Infection, NTM

Research involving
Human

Sponsors and support

Primary sponsor: Insmed Incorporated
Source(s) of monetary or material Support: Insmed Incorporated

Intervention

Keyword: ALIS, Amikacin Liposome Inhalation Suspension, Mycobacterium avium Complex, Nontuberculous Mycobacterial Lung Infection

Outcome measures

Primary outcome

Primary Endpoint

Findings on psychometric validation optimized and reported for:

1) Cross-sectional validation (modern psychometrics, internal consistency,

concurrent validity, and known-groups validity) at Baseline.

2) Test-retest reliability between Screening and Baseline among subjects

reporting no change on Patient Global Impression of Severity (PGI-S) between

Screening and Baseline. PGI-S anchors will be PRO specific, with a respiratory

and fatigue PGI-S applied to the Quality of Life - Bronchiectasis (QOL-B)

respiratory domain and Patient-Reported Outcome Measurement Information System

- Fatigue-Short Form 7a (PROMIS F-SF 7a), respectively.

3) Within-subject meaningful change estimated via anchor-based methods and

validated via empirical cumulative distribution functions (eCDFs) and

probability density functions (ePDFs) between Baseline and End of Study (EOS)

(Month 7).

Secondary outcome

Proportion of subjects achieving culture conversion by Month 6 (negative cultures for MAC at Month 5 and Month 6).

Change from Baseline to Month 7 in respiratory symptom score.

Change from Baseline to Month 7 in fatigue symptom score.

Time to culture conversion (first of 2 consecutive negative cultures) of Baseline to EOT assessments.

Time to first negative culture of Baseline to EOT assessments.

Proportion of subjects who develop a MAC isolate with amikacin MIC >= 128 µg/mL at more than 1 visit at any timepoint during the study.

Proportion of subjects who achieved culture conversion and subsequently have at least 1 MAC positive culture in agar media or positive cultures in broth media in at least 2 consecutive visits that is the same species and genome as cultured at Screening/Baseline.

Proportion of subjects who achieved culture conversion and subsequently have at least 1 MAC positive culture in agar media or positive cultures in broth media in at least 2 consecutive visits that is different than cultured at Screening/Baseline (different species or same species but different genome).

Incidence and severity of adverse events (AEs) and treatment-emergent adverse events (TEAEs) and other safety variables (eg, vital signs, physical examination, clinical laboratory values) from Baseline through the end of study (EOS).

Study description

Background summary

Nontuberculous mycobacterial lung disease caused by MAC is a potentially life-threatening and progressively destructive disease. If left untreated, MAC lung disease can be progressive, and has a fiveyear mortality rate of 33.3%. The current treatment of NTM lung disease is a multidrug therapy, but the optimal treatment has yet to be established. There remains an unmet medical need for patients with non-cavitary lung disease with newly diagnosed MAC lung infections.
A significant proportion of this patient population treated with currently available multidrug therapy do not achieve treatment success. Previous studies showed that in a total of 16 studies involving 1,462 patients, the rate of treatment success with ALIS was 60% as defined by culture conversion. This study aims to validate a patient-reported outcome instrument to evaluate symptoms in patients with MAC lung disease. The instrument validated in this study will be used for the assessment of the clinical benefit in a separate study.

Study objective

Primary Objective
To generate evidence demonstrating the domain specification (via modern psychometric methods), reliability, validity, and responsiveness (within-subject meaningful change) of the patient-reported outcome (PRO) endpoints

Secondary Objectives:
To evaluate the effect of each treatment arm (amikacin liposome inhalation suspension [ALIS] + background regimen (azithromycin [AZI] + ethambutol [ETH]) and empty liposome control (ELC) + background regimen on the following:
1. Culture conversion by Month 6
2. Patient-reported respiratory symptoms at Month 7
3. Patient-reported fatigue symptoms at Month 7
4. Time to culture conversion
5. Time to first negative culture
6. MAC isolates with amikacin minimum inhibitory concentration (MIC) >= 128 µg/mL
7. Recurrence of MAC (relapse)
8. Recurrence of MAC (new infection)
9. Safety and tolerability of ALIS +background regimen

Study design

This is a randomized, double-blind, placebo-controlled, active comparator study

in eligible subjects with a new diagnosis (initial or subsequent; see Figure 2) of MAC lung infection. Subjects will be randomized at Baseline in a 1:1 ratio to receive one of the two treatment regimens: ALIS + AZI + ETH or ELC + AZI + ETH for 6 months.

Randomization will be stratified by region and history of MAC lung infection (initial or subsequent). After Baseline, subjects will return to the study site for in-clinic visits at Months 1, 3, 5, 6/EOT, and 7/ EOS.

Visits at Months 2 and 4 do not require in-clinic appointments. At these non-in clinic visits, AEs and concomitant medications will be assessed and subjects will be required to produce and ship sputum samples. At the Month 6/EOT visit, subjects will discontinue all study treatments and will be followed for a 1 month off treatment period, during which initiation of any new medical or non medical therapies for MAC lung infection should be avoided.

At Month 7/EOS, subjects will complete all protocol-specified assessments and EOS procedures in specific order as provided below.

Intervention

ALIS 590 mg or ELC will be administered once daily (QD) by inhalation via nebulization over approximately 6 minutes to up to 15 minutes. Study drug may be administered around the same time each day, any time of day, in the fasted or as-fed condition but should be administered consistently around the same time each day.

Azithromycin 250 mg tablets and ethambutol 15 mg/kg tablets will be taken QD by mouth, with or without food.

Study burden and risks

The study medicines may have side effects.

The most common side effects (occurs in 1 in 10 people or more) seen with ALIS given once daily were: mild-to-moderate hoarseness or loss of voice, cough, breathlessness, coughing up blood, fatigues, diarrhea, nausea (feeling of having to vomit), and pain in the mouth and throat.

ETH, taken once daily, may cause decreased vision or change in vision, including blindness which may be permanent. These changes appear to be due to nerve inflammation.

AZI, taken once daily, may cause allergic reactions which can, rarely, be fatal. It may also cause abnormal heart rhythm and gastrointestinal symptoms

including decreased appetite, constipation, upset stomach, gas, vomiting and diarrhoea.

Tell the study doctor and study staff if you have any of the above symptoms, or any other side effects, during the study.

The study procedures may also cause side effects.

Despite recent advances in the treatment of Non-tuberculous mycobacterial lung disease caused by MAC, there is still a need for an effective treatment. The sponsor believes that the side effects and burden of participating are proportional, given the positive effects that participation in the trial may have on the progression of the patient's disease.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Subjects 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 South Korea)
2. Current diagnosis of MAC lung infection (initial, second, or third infection event). MAC or mixed infection with MAC as the dominant species 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. Subjects 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 (eg, 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] (ie, fertile following menarche and until becoming post-menopausal unless permanently sterile) and fertile men (ie, all men after puberty unless permanently sterile by bilateral orchidectomy) agree to practice a highly effective method of birth control from Day 1 to at least 90 days after the last dose. Examples of such birth controls are:
• true abstinence (refraining from heterosexual intercourse during the entire study),
• copper intrauterine device [IUD],
• hormonal methods (levonorgestrel-releasing intrauterine system, progestogen implant, combined oral contraceptive pill [combined with barrier method]),
• exclusive homosexual relationship, or
• sole male partner who has undergone surgical sterilization with confirmation of azoospermia at least 3 months post procedure while participating in the study.
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
14. Men with partners who are WOCBP (pregnant or non-pregnant) agree to use

condoms and non-pregnant partners should practice a highly effective method of birth control

Exclusion criteria

Subjects 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 MAC lung infection, 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 MAC lung infection, defined as positive sputum culture for MAC <= 6 months of cessation of prior successful treatment 6. MAC isolate with MIC for liposomal 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 (eg, 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 (FEV1) < 35%, prebronchodilator use
14. Current smoker
15. History of lung transplantation
16. Use of inhaled or systemic aminoglycosides with activity against MAC (eg, amikacin, kanamycin, or streptomycin) during Screening
17. Prior exposure to ALIS (including clinical study)
18. 18. Known hypersensitivity to aminoglycosides 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. Women not of child-bearing potential are defined as postmenopausal (ie, amenorrheic for 12 months without an alternative medical cause or confirmed by more than one follicle stimulating hormone [FSH] measurement), or naturally or

surgically sterile through bilateral oophorectomy, hysterectomy, or bilateral salpingectomy. For women under the age of 45 years , confirmatory testing with FSH should be considered.)
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

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	16-08-2022

Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Amikacin liposome inhalation suspension (ALIS)
Generic name:	Amikacin sulfate
Product type:	Medicine
Brand name:	EMB-Fatol
Generic name:	Ethambutol
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Zithromax
Generic name:	Azithromycin dihydrate
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	27-10-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-12-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-12-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-12-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	01-04-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-04-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-08-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-09-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-002545-42-NL
ClinicalTrials.gov	NCT04677543
CCMO	NL74702.091.20

Study results

Date completed:	09-05-2023
Results posted:	11-06-2024

First publication
24-05-2024