ISRCTN15403905 https://doi.org/10.1186/ISRCTN15403905

A study to determine whether the study treatment amikacin liposome inhalation suspension (ALIS) can be used to successfully and safely treat patient-reported symptoms in patients newly diagnosed with MAC (Mycobacterium avium complex) lung disease who have not started treatment

Submission date
21/01/2022

Recruitment status
No longer recruiting

Registration date
07/04/2022

Overall study status
Completed

Last Edited
05/05/2022

Condition category
Infections and Infestations

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
MAC (Mycobacterium avium complex) lung disease is a serious infection. If untreated, it can cause damage to the lungs. There is a need for effective treatment options for this disease. This study is to determine whether amikacin liposome inhalation suspension (ALIS) can be used to successfully and safely treat patient-reported symptoms in patients newly diagnosed with nontuberculous mycobacterial (NTM) lung infection caused by Mycobacterium avium complex (MAC) who have not started treatment.

Who can participate?
Patients over the age of 18 years with MAC lung infection

What does the study involve?
Participants will be randomly chosen by chance (like flipping a coin) to one of the study treatment groups as follows:
1. Amikacin liposome inhalation suspension (ALIS) + azithromycin (AZI) and ethambutol (ETH)
2. Empty liposome control (ELC) (also called a placebo) + AZI and ETH
The participants will be in the study for around 17.5 months. They will be given a detailed information sheet and consent forms explaining the study and if they agree to participate they will sign the consent forms. There will be 18 visits including screening, treatment for 12 months, and visits at 1 month off treatment (month 13) and 3 months off treatment (month 15; end of study). Participants will have to attend hospital visits for assessments such as physical examination, vital signs, blood and urine sampling, lung function tests, electrocardiogram (ECG),

hearing test, sputum (a mixture of saliva and mucus coughed up from the respiratory tract), questionnaires and various other assessments. In addition, some visits do not require the participant to attend the hospital, but they will be contacted by phone and asked to produce sputum samples and send them directly to the laboratory. Globally about 250 patients will be recruited across 24 countries including the UK.

What are the possible benefits and risks of participating?
The study doctor will discuss all information regarding possible side effects of the study drug and procedures with participants during the consent process; these are detailed at length in the participant information sheet. With any medication, there is a risk of allergic reactions. The most common side effects of ALIS were mild-to-moderate hoarseness or loss of voice, cough, breathlessness, coughing up blood, feeling tired, diarrhoea, nausea, and pain in the mouth and throat. There may be serious side effects related to ALIS that may require hospitalisation: for example, worsening of chronic obstructive pulmonary disease, coughing up blood, allergic lung disorder, breathlessness, worsening of infection in bronchiectasis, and worsening of MAC infection. Possible side effects of ethambutol may include decreased vision or change in vision, including blindness which may be permanent. These changes appear to be due to nerve inflammation. Possible side effects of azithromycin may include 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. Participants will be monitored carefully during the study and asked to report any side effects to their study doctor as soon as possible. Every effort will be made to ensure that any side effects are treated promptly, and to maintain the participant's comfort and wellbeing throughout the study period. The study drug will be given through a nebuliser and participants will be trained on how to use the device correctly to avoid leakage of the study drug. The study drug may harm an unborn child or nursing infant so pregnant patients or those planning to become pregnant or breastfeeding cannot participate. During the lung function tests some patients experience dizziness, chest tightness, feel anxious, have an elevated heart rate or shortness of breath, but this is usually temporary. Blood tests may cause the participant temporary discomfort, pain, bruising, swelling and/or bleeding at the site of needle insertion for blood collection.

Where is the study run from?
Insmed Switzerland GmbH

When is the study starting and how long is it expected to run for?
April 2021 to November 2024

Who is funding the study?
Insmed Switzerland GmbH

Who is the main contact?
Prof. Michael Loebinger
M.Loebinger@rbht.nhs.uk

Contact information

Type(s)
Principal investigator

Contact name
Dr Michael Loebinger

Contact details
Sydney Street
London
United Kingdom
SW3 6NP
+44 (0)2073518337
M.Loebinger@rbht.nhs.uk

Type(s)
Scientific

Contact name
Dr Tina Molloy

Contact details
Fleming House
Strathclyde Business Park
Bellshill
United Kingdom
ML4 3NJ
+44 (0)1698575287
ukstart-upteam.sm@ppd.com

Additional identifiers

ClinicalTrials.gov (NCT)
NCT04677569

Clinical Trials Information System (CTIS)
2020-003079-16

Integrated Research Application System (IRAS)
1004406

Central Portfolio Management System (CPMS)
46440

Protocol serial number
INS-416

Study information

Scientific Title
ENCORE - a randomized, double-blind, placebo-controlled, active comparator, multicenter study to evaluate the efficacy and safety of an amikacin liposome inhalation suspension (ALIS)-based regimen in adult subjects with newly diagnosed nontuberculous mycobacterial (NTM) lung infection caused by Mycobacterium avium complex (MAC)

Acronym

ENCORE

Study objectives
To evaluate the efficacy of Amikacin Liposome Inhalation Suspension (ALIS) + background regimen [azithromycin (AZI) + ethambutol (ETH)] compared to the empty liposome control (ELC) + background regimen on patient-reported respiratory symptoms at Month 13

To evaluate the efficacy of ALIS + background regimen compared to ELC + background regimen on the following:
1. Durable culture conversion at Month 15
2. Patient-reported fatigue symptoms at Month 13
3. Culture conversion by Month 12
4. Culture conversion by Month 6
5. Culture conversion at any time during treatment
6. Time to culture conversion
7. Time to first negative culture
8. MAC isolates with amikacin minimum inhibitory concentration (MIC) ≥128 µg/ml
9. Recurrence of MAC (relapse)
10. Recurrence of MAC (new infection)
11. Within-subject meaningful change threshold estimated in respiratory symptoms from Baseline to Month 13
12. Safety and tolerability of ALIS + background regimen

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approval pending, Cambridge Central REC, REC ref: 22/EE/0033

Primary study design
Interventional

Study design
Randomized controlled double-blind parallel-group trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Nontuberculous mycobacterial (NTM) lung infection caused by Mycobacterium avium Complex (MAC)

Interventions
Eligible participants will be randomly assigned to one of the study treatment groups. To try to make sure the same number of participants are in each group, each participant will be randomly assigned to a treatment group by a computer. The study treatment they get will be chosen by chance, like flipping a coin (random).

Amikacin Liposome Inhalation Suspension (ALIS) 590 mg or empty liposome control (ELC) will be given once daily by inhalation via nebulisation over approximately 6 minutes to up to 15 minutes. ALIS or ELC will be given around the same time each day, any time of day, in the fasted

or as-fed condition. The background regimen of azithromycin 250 mg tablets and ethambutol 15 mg/kg tablets will be taken once daily by mouth, with or without food. Treatment will be given for 12 months followed by a 3 months off treatment period with a final end of study follow-up.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Amikacin, azithromycin, ethambutol

Primary outcome(s)
Respiratory symptoms measured using respiratory symptom score at baseline and month 13

Key secondary outcome(s)
1. Proportion of subjects achieving durable culture conversion at month 15
2. Fatigue symptoms measured using the fatigue symptom score at baseline and month 13
3. Proportion of subjects achieving culture conversion by month 12 (negative cultures for MAC at month 11 and month 12)
4. Proportion of subjects achieving culture conversion by month 6 (negative cultures for MAC at month 5 and month 6)
5. Proportion of subjects achieving culture conversion at any time during treatment (first two consecutive negative cultures) measured at baseline to month 12
6. Time to culture conversion (first of two consecutive negative cultures) measured from baseline to month 12
7. Time to first negative culture measured from baseline to month 12
8. Proportion of subjects who develop a MAC isolate with amikacin minimum inhibitory concentration (MIC) ≥128 µg/ml at more than one visit at any timepoint during the study, measured from baseline to month 15
9. Proportion of subjects who achieved culture conversion and subsequently have at least one MAC-positive culture in agar media or positive cultures in broth media in at least two consecutive visits that is the same species and genome as that cultured at Screening/Baseline, measured from baseline to month 15
10. Proportion of subjects who achieved culture conversion and subsequently have at least one MAC-positive culture in agar media or positive cultures in broth media in at least two consecutive visits that is different than that cultured at Screening/Baseline (different species or same species but different genome), measured from baseline to month 15
11. Proportion of subjects meeting the within-subject meaningful change threshold as reflected in PRO changes scores computed from baseline in patient-reported symptoms
12. Incidence and severity of adverse events (AEs) and treatment-emergent adverse events (TEAEs) and other safety variables (e.g., vital signs, physical examination, clinical laboratory values) from baseline to month 15

Completion date
30/11/2024

Eligibility

Key inclusion criteria

1. Male or female ≥18 years of age (19 years or older in South Korea, 20 years or older in Japan)
2. Current diagnosis of MAC lung infection. 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 the 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. COPD, bronchiectasis) have been managed according to the 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 childbearing potential (WOCBP) (i.e., fertile following menarche and until becoming postmenopausal unless permanently sterile) and fertile men (i.e., all men after puberty unless permanently sterile by bilateral orchidectomy) agree to practise 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:
11.1. True abstinence (refraining from heterosexual intercourse during the entire study)
11.2. Copper intrauterine device [IUD]
11.3. Hormonal methods (levonorgestrel-releasing intrauterine system, progestogen implant, combined oral contraceptive pill [combined with barrier method])
11.4. Exclusive homosexual relationship
11.5. Sole male partner who has undergone surgical sterilization with confirmation of azoospermia at least 3 months post-procedure
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

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex

All

Key exclusion criteria

1. Diagnosis of CF
2. History of more than three 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 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 (FEV1) < 35%, pre-bronchodilator 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. Known hypersensitivity or contraindications to the use of ALIS, aminoglycosides, or any of their excipients
19. Disseminated MAC infection
20. Positive pregnancy test or lactation at Screening. All women of childbearing potential (WOCBP) will be tested. Women not of childbearing 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 etolides), or any of their excipients per local labeling guidance

Date of first enrolment
14/10/2020

Date of final enrolment
30/11/2024

Locations

Countries of recruitment
United Kingdom

England

Scotland

Argentina

Australia

Austria

Belgium

Canada

Chile

Denmark

France

Greece

Hungary

Israel

Italy

Japan

Netherlands

New Zealand

Poland

Portugal

Spain

Taiwan

Türkiye

Study participating centre
Royal Free Hospital
Pond Street
London
United Kingdom
NW3 2QG

Study participating centre
Royal Brompton Hospital
Sydney Street
London
United Kingdom
SW3 6NP

Study participating centre
Papworth Hospital
Ermine Street South
Papworth Everard
Cambridge
United Kingdom
CB23 3RE

Study participating centre
Liverpool Heart & Chest Hospital
Broadgreen Hospital
Thomas Drive
Liverpool
United Kingdom
L14 3PE

Study participating centre

Aberdeen Royal Infirmary
Foresterhill Road
Aberdeen
United Kingdom
AB25 2ZN

Study participating centre
Ninewells Hospital
Ninewells Avenue
Dundee
United Kingdom
DD1 9SY

Study participating centre
University Hospital Birmingham
Queen Elizabeth Hospital
Edgbaston
Birmingham
United Kingdom
B15 2TH

Study participating centre
North Manchester General Hospital
Delaunays Road
Crumpsall
Manchester
United Kingdom
M8 5RB

Study participating centre
Derriford Hospital
Derriford Road
Derriford
Plymouth
United Kingdom
PL6 8DH

Sponsor information

Organisation

Insmed Switzerland GmbH

Funder(s)

Funder type
Industry

Funder Name
Insmed

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No