ISRCTN17596258 https://doi.org/10.1186/ISRCTN17596258

AIR-NET- Testing anti-inflammatories for the treatment of bronchiectasis

Submission date 02/08/2024	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol
Registration date 23/10/2024	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 06/11/2024	**Condition category** Respiratory	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol
Background and study aims
AIR-NET- Testing anti-inflammatories for the treatment of bronchiectasis

Who can participate?
Adults over 18 years, with bronchiectasis.

What does the study involve?
Not provided at time of registration

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration
Risks:
This trial is categorised as: Type B, Somewhat higher than the risk of standard medical care. The trial treatments are all repurposed drugs already approved for use in conditions other than bronchiectasis.
Arm 1: Usual care
Arm 2: Disulfiram
Disulfiram is an alcohol deterrent compound licensed for use as an adjuvant in the treatment of drinking problems. The most common adverse reaction (AR) reported during treatment is alcohol reaction. Disulfiram–ethanol reactions often develop within 15 minutes after exposure to ethanol; symptoms usually peak within 30 minutes to 1 hour, and then gradually subside over the next few hours. Symptoms may be severe and life-threatening. Participants will be informed of the reaction risk and must agree to abstain from alcohol during treatment and for up to 14 days after discontinuation.
Arm 3: Dipyridamole
Dipyridamole is licensed for use in secondary prevention of ischaemic stroke and transient ischaemic attacks and as an adjunct to oral anti-coagulation for prophylaxis of thromboembolism associated with prosthetic heart valves. The most commonly reported adverse effects are headache, dizziness, diarrhoea, nausea (very common, ≥1/10) and angina pectoris, vomiting, rash, myalgia (common, ≥ 1/100 < 1/10).
Arm 4: Doxycycline

Doxycycline is licensed for use in the treatment of a variety of infections caused by susceptible strains of Gram-positive and Gram-negative bacteria and certain other micro-organisms. The most common adverse effects observed in patients receiving tetracyclines, including doxycycline, are hypersensitivity, headache, nausea/vomiting, photosensitivity reaction rash including maculopapular and erythematous rashes (common, ≥ 1/100 < 1/10).

Adverse events, medications, exacerbations and vital signs will be reviewed at each visit. Regular safety bloods will be performed to assess full blood count, urea and electrolytes and liver function tests.
The data monitoring committee will perform a safety review of each active treatment arm. Each safety review will take place after 10 participants have completed treatment in the active arm.

Where is the study run from?
University of Dundee (UK)

When is the study starting and how long is it expected to run for?
July 2024 to February 2027

Who is funding the study?
LifeArc (UK)

Who is the main contact?
airnet-tm@dundee.ac.uk
Professor James Chalmers, j.chalmers@dundee.ac.uk

Contact information

Type(s)
Principal Investigator

Contact name
Prof James Chalmers

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Type(s)
Public, Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1010124

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
1-027-24, CPMS 62256

Study information

Scientific Title
A randomised, open-label, multifactorial, multicentre, platform trial using a range of repurposed anti-inflammatory treatments to improve outcomes in patients with bronchiectasis not due to cystic fibrosis, within the EMBARC international clinical research network.

Acronym
AIR-NET

Study objectives
Primary objective:
To evaluate the effect of a range of interventions compared to usual care on the activity of NE in sputum

Secondary objectives:
1. To evaluate the effect of a range of interventions compared to usual care on the activity of NE in sputum
2. To evaluate the effect of a range of interventions compared to usual care on time to onset of first bronchiectasis exacerbation
3. To evaluate the effect of a range of interventions compared to usual care on quality of life
4. To evaluate the effect of a range of interventions compared to usual care on clinical benefits
5. To evaluate the effect of a range of interventions compared to usual care on walking distance
6. To evaluate the safety of a range of interventions compared with usual care
7. To evaluate the effect of a range of interventions on peripheral blood neutrophil function

Ethics approval required
Ethics approval required

Ethics approval(s)

Approved 21/10/2024, London-Central Research Ethics Committee (3rd Floor 3 picadilly Place, London Road, Manchester, M1 3BN, United Kingdom; +44 (0)207 104 8061; londoncentral.rec@hra.nhs.uk), ref: 24/LO/0679

Study design
Interventional double blind randomized parallel group controlled trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

Participant information sheet

Health condition(s) or problem(s) studied
Bronchiectasis

Interventions
Participants will be randomised using the online Tayside Randomisation System (TRuST) to one of the trial arms:
Arm 1: Usual care
Arm 2: Disulfiram 200 mg, two tablets taken orally, once daily
Arm 3: Dipyridamole 200 mg, one capsule taken orally, twice daily
Arm 4: Doxycycline 100 mg, one capsule taken orally, once daily
Trial treatment will be for 28 days, with a 28 day follow up period.

Intervention Type
Drug

Pharmaceutical study type(s)
Therapy

Phase
Phase II

Drug/device/biological/vaccine name(s)
Disulfiram, dipyridamole, doxycycline

Primary outcome measure
Activity of sputum Neutrophil elastase. Day 0 and 28

Secondary outcome measures

Current secondary outcome measures as of 06/11/2024:
1. Activity of sputum Neutrophil elastase. Days 0, 7, 14 and 56
2. Time to first pulmonary exacerbation (EMBARC definition). Days 0 to 28
3. Quality of life-bronchiectasis (QOL-B) respiratory symptom scale, Bronchiectasis Impact Measure (BIM) questionnaire. Days 0, 7, 14, 28 and 56
4. Distance covered during a 6-minute walk. Days 0 to 28
5. Frequency of adverse events (AEs) and serious adverse events (SAEs). Day 0, 28
6. Phagocytosis of bacteria; Reactive oxygen species generation; Degranulation; Ex-vivo formation of neutrophil extracellular traps; Mass cytometry (endpoints may vary depending on the experimental arm). Days 0 to 56

Tertiary outcome measures:
1. Frequency of pulmonary exacerbations (EMBARC definition). Days 0 to 28; Days 0 to 56
2. Measure the concentration of MMPs and NETs in sputum, as well as other biomarkers e.g. proteomics, bacterial load, microbiome. Days 0, 7, 14, 28 and 56
3. Measure serum biomarkers of inflammation and redox status. Days 0, 7, 14, 28 and 56
4. Peripheral blood neutrophil proteomics performed on isolated cells. Days 0 and 28

Previous secondary outcome measures:
1. Activity of sputum Neutrophil elastase. Days 0, 7, 14 and 56
2. Time to first pulmonary exacerbation (EMBARC definition). Days 0 to 28
3. Quality of life-bronchiectasis (QOL-B) respiratory symptom scale, Bronchiectasis Impact Measure (BIM) questionnaire. Days 0, 7, 14, 28 and 56
4. Distance covered during a 6-minute walk. Days 0 to 28
5. Frequency of adverse events (AEs) and serious adverse events (SAEs). Day 0, 28
6. Phagocytosis of bacteria; Reactive oxygen species generation; Degranulation; Ex-vivo formation of neutrophil extracellular traps; Mass cytometry (endpoints may vary depending on the experimental arm). Days 0 to 56

Tertiary outcome measures:
1. Frequency of pulmonary exacerbations (EMBARC definition). Days 0 to 28; Days 0 to 56
2. Measure the concentration of MMPs and NETs in sputum, as well as other biomarkers e.g. proteomics, bacterial load, microbiome. Days 0, 7, 14, 28 and 56
3. Measure serum biomarkers of inflammation and redox status. Days 0, 7, 14, 28 and 56
4. Peripheral blood neutrophil proteomics performed on isolated cells. Days 0 and 28
5. Label-free liquid chromatography/mass spectrometry sputum identification and relative quantification of proteins. Day 0 and 28
6. Peripheral blood transcriptomics. Day 0 and 28
7. Nasal brushing transcriptomics. Day 0 and 28

Sub-study outcome measures:
1. Change in skin perfusion with iontophoresis of acetylcholine and sodium nitroprusside using laser Doppler perfusion imaging. Days 0, 28 and 56
2. Change in arterial stiffness index. Days 0, 28 and 56
3. Change in pulse wave velocity. Days 0, 28 and 56

Overall study start date
31/07/2024

Completion date
28/02/2027

Eligibility

Key inclusion criteria
1. ≥18 years
2. Able to provide informed consent.
3. Capable of complying with all trial procedures and of completing the trial, in the opinion of the investigator.
4. Bronchiectasis, confirmed by computed tomography (CT), showing bronchiectasis in 1 or more lobes.
5. Normally produces sputum daily.
6. Able to provide a sputum sample at the screening visit or between screening and randomisation.
7. Active neutrophilic inflammation at screening/baseline indicated by a positive NEATstik (Neutrophil Elastase Airways Test) result.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
168

Key exclusion criteria
1. Enrolled previously in the trial 3 times.
2. Respiratory infection or bronchiectasis exacerbation 4 weeks prior to screening and/or between screening and randomisation
3. Antibiotic or corticosteroid 4 weeks prior to screening and/or between screening and randomisation
4. Active allergic bronchopulmonary aspergillosis (defined by International Society for Human and Animal Mycology criteria) on steroids and/or anti-fungals,
5. Nontuberculous mycobacterial infection on antibiotic therapy
6. Immunodeficiency on immunoglobulin replacement
7. A primary diagnosis of COPD or asthma (a secondary diagnosis of COPD or asthma is permitted)
8. Cystic fibrosis
9. Active malignancy except non-melanoma skin cancer
10. Currently taking brensocatib
11. Use of any investigational drugs within five times of the elimination half-life after the last dose or within 30 days, whichever is longer. Current enrolment in non-interventional, observational studies will be allowed

12. Currently pregnant or breast-feeding
13. Women of childbearing age and not practicing an acceptable method of birth control
14. Additional exclusion criteria for individual treatment arms are described in the protocol

Date of first enrolment
18/11/2024

Date of final enrolment
01/03/2026

Locations

Countries of recruitment
United Kingdom

Study participating centre
-
United Kingdom
-

Sponsor information

Organisation
University of Dundee

Sponsor details
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Sponsor type
University/education

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ROR
https://ror.org/03h2bxq36

Funder(s)

Funder type
Research organisation

Funder Name
LifeArc

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Peer reviewed scientific journals
Conference presentation
Submission to regulatory authorities
Other
Consent will be sought for data to be shared for the purposes of research. Any information which identifies the participant will be removed prior to sharing.

Intention to publish date
28/02/2028

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from the Chief Investigator (Professor James Chalmers, j.chalmers@dundee.ac.uk). Approval of requests will be at the discretion of the Chief Investigator. Data will be available after the primary publication of the relevant experimental arm; there is no end date for requests. Data will be transferred using an appropriate secure method (e.g. encrypted email, file transfer system, or similar), and will be limited to only data required to perform the proposed analysis. Data will be anonymised or pseudonymised as appropriate. Patient consent for data sharing will be obtained at trial entry. The full details and terms of the transfer will be set out in a data sharing agreement.

IPD sharing plan summary
Available on request