FULL/LONG TITLE OF THE TRIAL

A phase 2 trial of Gremubamab compared to placebo in participants with bronchiectasis and chronic *Pseudomonas aeruginosa* infection

SHORT TRIAL TITLE / ACRONYM

GRemubamab **E**r**A**dication **T**rial (GREAT-2)

PROTOCOL VERSION NUMBER AND DATE

GREAT-2 Protocol V4 19-10-23

RESEARCH REFERENCE NUMBERS

IRAS Number: 1005993

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ISRCTN Number: ISRCTN70034823

SPONSORS Number: 1-023-22

FUNDERS Number: N/A

This protocol has regard for the HRA guidance and order of content V1.2 March 2016

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the Sponsor's (and any other relevant) Standard operating Procedures, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: Patricia Burns

Date: 26.10.2023

.....

Name (please print):

Patricia Burns

Position: Senior Research Governance Manager

Chief Investigator:

Signature:

Date: 20-10-2023

Name: (please print):

Professor James Chalmers

Statistician:

Date:

19-Oct-2023

Signature: J. Stobo

Name: (please print):

Jamie Stobo

Position: Trial Statistician

KEY TRIAL CONTACTS

Chief Investigator	Prof. James Chalmers. Division of Molecular and Clinical Medicine, Level 5, Mailbox 12, Ninewells Hospital, Dundee, DD1 9SY, 01382 383642 j.chalmers@dundee.ac.uk
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I. LIST OF CONTENTS

LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse Event
AR	Adverse Reaction
AZ	AstraZeneca
BIM	Bronchiectasis Impact Measure
bPIS	brief Participant Information Sheet
CA	Competent Authority
CFU	Colony-forming unit
CI	Chief Investigator
CNORIS	Clinical Negligence and Other Risks Insurance Scheme
COPD	Chronic obstructive pulmonary disease
CTP	Clinical Trial Pharmacy
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EMBARC	European Multicentre Bronchiectasis Audit and Research Collaboration
EU	European Union
EudraCT	European Clinical Trials Database
FEV1	Forced expiratory volume in 1 second
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation (EU) 2016/679
IB	Investigator Brochure
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
IV	intravenous
NHS R&D	National Health Service Research & Development
P. aeruginosa	*Pseudomonas aeruginosa*
PI	Principal Investigator
PIS	Participant Information Sheet
PK	Pharmacokinetics
QOL-B	Quality of life bronchiectasis questionnaire
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SGRQ	St. George’s Respiratory Questionnaire
SUSAR	Suspected Unexpected Serious Adverse Reaction
TASC	Tayside Medical Science Centre
TCTU	Tayside Clinical Trials Unit
TMF	Trial Master File
TMG	Trial Management Group

TSC	Trial Steering Committee
WOCBP	women of childbearing potential
WPG	Working Practice Guidelines
w/v	weight per volume

II. TRIAL SUMMARY

Trial Title	A phase 2 trial of Gremubamab compared to placebo in participants with bronchiectasis and chronic *Pseudomonas aeruginosa* infection	
Short title	**GR**emubamab **E**r**A**dication **T**rial (GREAT-2)	
Clinical Phase	Phase 2	
Trial Design	Randomised, double-blind, placebo-controlled trial	
Trial Participants	People with Bronchiectasis chronically infected with *Pseudomonas aeruginosa*	
Planned Sample Size	60 participants	
Treatment duration	12 weeks	
Follow up duration	12 weeks	
Planned Trial Period	2 years	
	Objectives	Outcome Measures
Primary	To evaluate the efficacy of Gremubamab on *P. aeruginosa* bacterial burden in sputum at week 12	Quantitative sputum cultures
Investigational Medicinal Product(s)	Gremubamab (MEDI3902)	
Formulation, Dose, Route of Administration	Intravenous infusion, once every four weeks for a total of 3 doses on days 1, 28 and 56: • Arm 1: 1500mg • Arm 2: 500mg; • Arm 3: Placebo	

III. FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
AstraZeneca (AZ)	Drug supply and completion of PK analysis
European Respiratory Society	Financial and logistical support
European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC)	Logistical support

IV. ROLE OF TRIAL SPONSOR AND FUNDER

The roles and responsibilities of the Sponsor and Funder will be detailed in the Clinical Research Agreement.

V. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

The trial will be coordinated by a Trial Management Group (TMG), consisting of the grant holders, including the CI, collaborators, statistician, research assistant, trial manager and research nurse where appropriate. Details of membership of the TMG will be held in the Trial Master File (TMF). The TMG will meet regularly to ensure all practical details of the trial are progressing well and working well and everyone within the trial understands them. Minutes of the TMG meetings will be maintained in the TMF.

The functions of the Trial Steering Committee (TSC) will be undertaken by the TMG. No independent TSC will be convened for this trial.

A Data Monitoring Committee (DMC) will be established to oversee the safety of trial participants. The DMC will be independent from all aspects of the trial, including independent from Sponsor, trial team, collaborators and funders. The DMC will be unblinded to allocation. The DMC will meet prior to participant recruitment to decide on the frequency of DMC meetings, timings will be documented in the DMC charter. The terms of reference of the DMC are detailed in the DMC Charter and held in the TMF. Minutes of the DMC will be maintained in the TMF.

The CI will be responsible for the conduct of the trial. Site delegate(s) will oversee the trial and will be accountable to the CI. A trial-specific Delegation Log will be prepared for the trial site, detailing the duties of each member of staff working on the trial.

VI. PROTOCOL CONTRIBUTORS

Chief Investigator: Professor James Chalmers: Review and final approval

ERS Advocacy Council member: Professor Tobias Welte, review

EMBARC Steering Committee member: Professor Charles Haworth, review

TCTU Senior Trial Manager: Margaret Band: Initial draft, review

Senior Research Statistician: Professor Graeme MacLennan, review

Lead Scientist: Dr Merete Long, review

Microbiology Lead: Professor Michael Tunney, review

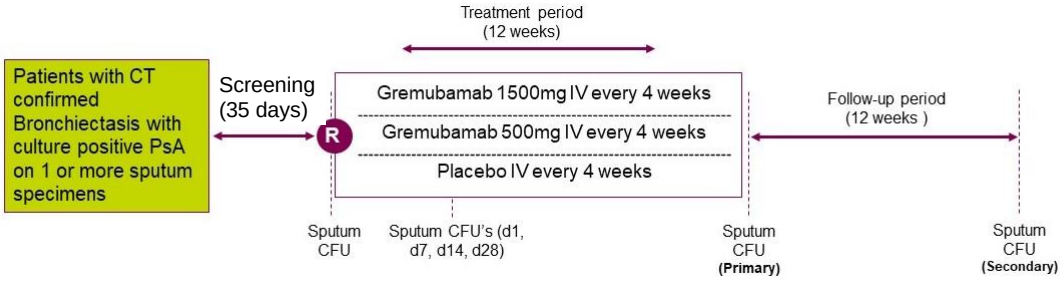
Clinical Trial Pharmacist: Shona Carson, review

TCTU Database Manager: Mel Sturgess, review

AstraZeneca: Dr Rod Hughes (AZ, MSD), Karen Cartwright (AZ, CPD), Engin Liathdale (AZ, Clinical Scientist), Sanna Rosengren (AZ, TSEM Lead)

VII. KEY WORDS: *Pseudomonas aeruginosa*, bronchiectasis, antipseudomonal treatment

VIII. TRIAL FLOW CHART



1. BACKGROUND

Bronchiectasis is a chronic respiratory disease characterised by cough, sputum production and recurrent respiratory infections.[1] Impairment of mucociliary clearance leads to increased susceptibility to lung infections and progressive decline in respiratory function.[2,3] Approximately 1/3 of patients become chronically infected with the antibiotic resistant pathogen *Pseudomonas aeruginosa (P. aeruginosa)*. This pathogen evades killing by immune cells and forms biofilms resulting in infections that persist despite treatment with antibiotics. *P. aeruginosa* infection is associated with a 7 fold increased risk of hospitalization and a 3 fold increased risk of mortality in bronchiectasis.[4–6] Current treatment options for *P. aeruginosa* are inadequate. Patients have ongoing frequent exacerbations and poor quality of life despite the availability of inhaled antibiotics, which are widely used "off label" and macrolides.[7,8] The most recent meta-analysis of inhaled antibiotic use in bronchiectasis found that on average they reduced bacterial load (primarily of *P.* aeruginosa) by 2 log units and reduced exacerbations by up to 20%.[7] The widespread use of prophylactic antibiotics carries a significant risk of antibiotic resistance.[9,10] Antibiotic treatments are not specific to respiratory pathogens and may therefore reduce the overall diversity of the airway microbiome. Low microbiome diversity is associated with increased mortality in bronchiectasis.[11] There is an urgent need for novel antipseudomonal treatments and particularly pathogen specific approaches.

This protocol describes a Proof of Principle randomized trial of Gremubamab in patients with bronchiectasis (not due to cystic fibrosis). The objective of the study will be to establish the antipseudomonal activity in vivo, investigating two doses, pharmacokinetics (PK) profile and the preliminary clinical efficacy, using the endpoints of exacerbations and quality of life, of Gremubamab in patients with bronchiectasis who are chronically infected with *P. aeruginosa*. This is an investigator initiated research study proposed by the EMBARC consortium, an international network of investigators in the field of bronchiectasis.[12]

2. RATIONALE

Widespread antibiotic resistance due to broad spectrum antibiotic use is a global problem and has stimulated the search for alternative approaches to treat difficult pathogens. Monoclonal antibody based strategies may theoretically provide a method of treating drug resistant pathogens without collateral damage to the microbiome.[13] Gremubamab (MEDI3902) is a bispecific antibody targeting two key component components of *P. aeruginosa*, PcrV, part of the type III secretion system and Psl exopolysaccharide.[13,14] These virulence factors are involved in host cell cytotoxicity, persistence and tissue adherence. Gremubamab has been shown to protect against *P. aeruginosa* infection in multiple murine and rabbit infection models.[13, 15] Studies of isolates of *P. aeruginosa* from human infections across the world have shown conservation of the targets PcrV and Psl.[14] Gremubamab has been shown to have in-vivo activity against a wide range of clinical strains of *P. aeruginosa*.[14]

In a phase 1 dose escalation study in 56 healthy subjects Gremubamab was well tolerated with infusion reactions being the most common adverse events.[16] No previous studies of Gremubamab have been performed in bronchiectasis but a phase 2 study performed in patients

with ventilator associated pneumonia, the EVADE study[22] also found Gremubamab was well tolerated and provided dose guidance for this study.

After single dose, gremubamab exhibited linear pharmacokinetics (PK) up to 1500 mg dose with relatively low inter-subject variability and a half-life of 7 to 9 days[16]. In the EVADE study, a single dose of either 500 mg or 1500 mg IV was anticipated to maintain serum exposure above the target level of 1.7 µg/mL for respectively 21 and 30 days[22] The target level of 1.7 µg/mL was derived using an acute severe pneumonia model in which an infectious dose 1-fold higher than the lethal dose 100% of a highly pathogenic *P. aeruginosa* strain was used, animals being treated with gremubamab at multiple doses. However, a 500 mg IV dose of gremubamab was able to maintain the serum concentration above the target level of 1.7 µg/mL in only 50% of the mechanically ventilated participants at Day 21. In mechanically ventilated participants, gremubamab clearance was 1.6-fold higher than in healthy participants. Altered PK in mechanically ventilated critically ill patients is well known and associated to metabolic and haemodynamic instability observed in this population. These PK changes are not expected in participants with bronchiectasis and therefore 500 mg and 1500 mg doses are anticipated to maintain serum exposure above the target level during the overall interdose period. Similar systemic exposure of gremubamab is expected after the IV administration of gremubamab in participants with bronchiectasis and healthy participants with little accumulation after multiple doses considering the half-life of 7-9 days and the interdose interval of 28 days. Therefore, the trough concentration at Day 28 after 500 mg and 1500 mg of gremubamab as multiple doses is expected to be approximately the trough concentration after a single dose of respectively 500 mg and 1500 mg.

In ex-vivo experiments we have shown that Gremubamab dose dependently increased opsonophagocytic killing of *P. aeruginosa* by neutrophils from patients with bronchiectasis. There is a need to establish whether treatment with Gremubamab can reduce *P. aeruginosa* pathogen load or achieve pathogen clearance (“eradication”) in-vivo in bronchiectasis patients. In this phase 2 study we aim to establish the preliminary efficacy and safety of Gremubamab in patients with bronchiectasis.

2.1. Assessment and Management of Risk

The experience from the phase 1 study in healthy controls and the EVADE study[22] suggests that Gremubamab treatment carries a low risk of adverse events.[16] In the phase 1 study, the most frequent adverse events were infusion reactions, which were observed in 40% of patients in the 1500mg dose group and 26.7% in the 750mg dose group. Infusion reactions were manageable with slowing of the infusion rate and pre-medication. Other adverse effects reported in 1-2 subjects were headache, dyspepsia and itch. Potential risks include, but are not limited to, anaphylaxis and serious allergic reactions (including hypersensitivity), immune complex disease and infusion related reactions

Patients will receive a total of 3 infusions. Mitigation measures including slowing infusion rates and pre-medication will be used to limit risks in this trial.[16]

Importantly this trial has been designed to allow patients to receive all background therapies recommended by international guidelines for bronchiectasis. Consequently, patients will receive

Gremubamab or placebo on a background of standard of care and there will be no risks to participants of not receiving appropriate treatment for their respiratory infection.

Evaluation of risk: Type B = Somewhat higher than the risk of standard medical care.

The assessment and management of risk is described further in Appendix 1.

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

The objective of the trial will be to establish the antipseudomonal activity in-vivo, the optimal dosing and the preliminary clinical efficacy (exacerbations and quality of life) of Gremubamab in patients with bronchiectasis who are chronically infected with *P. aeruginosa*.

3.1. Table of endpoints/outcomes

Primary Objective		
Objectives	**Outcome Measures**	**Timepoint(s)**
To evaluate the efficacy of Gremubamab on *P. aeruginosa* bacterial burden in sputum at week 12	Change from baseline (day 1) in quantitative sputum cultures (colony-forming unit (CFU))	Day 84
Secondary Objectives		
Objectives	**Outcome Measures**	**Timepoint(s)**
To evaluate the efficacy of Gremubamab on *P. aeruginosa* bacterial burden in sputum	Change from baseline in Quantitative sputum cultures	Days 7, 14, 28 and 56
To determine the persistent effects of Gremubamab on *P. aeruginosa* bacterial burden following discontinuation of treatment (week 24)	Change from baseline in Quantitative sputum cultures	Day 168
To determine if Gremubamab can achieve eradication of *P. aeruginosa* in some individuals	Eradication defined by negative sputum cultures for *P. aeruginosa* at the end of treatment	Days 84 and 168
To determine the effect of Gremubamab on health-related quality of life	Change from baseline in Quality of Life Bronchiectasis questionnaire (QOL-B), Bronchiectasis Impact Measure (BIM) questionnaire	Days 28, 56, 84 and 168
	Change from baseline in St. George's Respiratory Questionnaire (SGRQ)	Days 84 and 168

To determine the effect of Gremubamab on time to first exacerbation	Occurrence of exacerbations (as per EMBARC definition of exacerbation)	First event from visit 1 to day 84
To determine the effect of Gremubamab on pulmonary function	Change from baseline in Forced expiratory volume in 1 second (FEV1)	Day 28, 56 and 84
To assess the safety of Gremubamab in patients with bronchiectasis	Frequency of adverse events and serious adverse events between groups	Over 168 days
	Safety lab parameters.	Over 168 days
To evaluate the PK of Gremubamab	Gremubumab PK parameters through 168 days post dose	Over 168 days

Exploratory Objectives		
Objectives	**Outcome Measures**	**Timepoint(s)**
To evaluate immunogenicity of Gremubamab*	Gremubumab anti-drug antibody (ADA) response in serum through 168 days post dose	Over 168 days
To determine the effect of Gremubamab on sputum colour	Murray sputum colour chart	Days 0, 14, 28 and 56
To determine the effect of Gremubamab on total antibiotic use for exacerbation	Days of antibiotic treatment for exacerbation	Any antibiotic treatment over 84 days (treatment period) and up to day 168 (post-treatment period)
Molecular bacterial load in sputum	Change from baseline in Quantitative polymerase chain reaction for *P. aeruginosa*.	Days 7, 14, 28, 56,84 and 168
Microbiome characterisation- 16s sequencing and ITS sequencing in sputum	Change from baseline in alpha and beta diversity	Days 28, 56, 84 and 168
Neutrophil biomarkers: neutrophil elastase activity in sputum, neutrophil extracellular traps and myeloperoxidase in sputum (NETs)	Change from baseline in biomarker concentrations in sputum	Days 28, 56, 84 and 168

Mucin quantification in sputum (MUC5B and MUC5AC)	Change from baseline in biomarker concentrations in sputum	Days 28, 56, 84 and 168
Sputum proteomics	Change from baseline in sputum proteins	Day 84
P. aeruginosa isolate study*	Whole genome sequencing of P. *aeruginosa* isolates	All available timepoints where PA is isolated.
To determine the effect of Gremumab on antibiotic resistance*	Testing of P. *aeruginosa* isolates for susceptibility (minimum inhibitory concentration) to clinically relevant antibiotics	Days 0, 84 and 168
Serum antibodies against P. *aeruginosa*	Change from baseline in Anti-P. *aeruginosa* antibodies	Days 84 and 168
Systemic inflammatory markers (neutrophils, eosinophils)	Change from baseline in blood neutrophils and eosinophils)	Days 28, 56 and 84
Target engagement*	Ex-vivo assays of target engagement in blood and sputum	Days 0, 7, 28, 84 and 168

*Laboratory sample testing for these exploratory objectives may be omitted, based on emerging data from the study.

4. TRIAL DESIGN

Parallel group design.

Randomised, placebo-controlled trial.

5. TRIAL SETTING

Participants will be identified, recruited through NHS specialist respiratory services and will complete the research activities in approximately 20-30 secondary care settings within NHS trusts across the UK.

6. PARTICIPANT ELIGIBILITY CRITERIA

60 participants will be randomized across all sites.

6.1. Inclusion criteria

1. Age >18 to <86

2. Clinical diagnosis of Bronchiectasis.
3. Able to and provided informed consent.
4. Previous computerised tomography (CT) scan of the chest demonstrating bronchiectasis in 1 or more lobes
5. *P. aeruginosa* in sputum, bronchoalveolar lavage or another airway sample at least once in the 24 months prior to screening*.
6. A sputum sample that is culture or PCR positive for *P. aeruginosa* sent at the screening visit, within 35 days of randomization* †.

*a participant who does not have a positive sample for *P. aeruginosa* in the previous 24 months may submit two samples, at least 21 days apart, during the 35-day screening period. If these samples are both positive for *P. aeruginosa* then inclusion criteria 5 and 6 will be deemed met and the patient may be enrolled.

† repeat sputum samples may be provided during the screening period, if the sample taken during the screening visit is negative for *P. aeruginosa*.

6.2. Exclusion criteria

1. Known hypersensitivity to Gremubamab or any excipient of the investigational product
2. Known clinical diagnosis of Cystic fibrosis
3. Immunodeficiency requiring replacement immunoglobulin.
4. Active tuberculosis or nontuberculous mycobacterial infection (currently under treatment or requiring treatment in the opinion of the investigator).
5. Active allergic bronchopulmonary aspergillosis (receiving treatment with corticosteroids and/or antifungal medication).
6. Recent significant haemoptysis (a volume requiring clinical intervention, within the previous 4 weeks prior to screening).
7. Treatment with long term inhaled, systemic or nebulized anti-pseudomonal antibiotics which are newly initiated within the previous 3 months prior to screening[a].
8. Chronic treatment with cyclical doses of inhaled or nebulized antibiotics e.g 28 days on and 28 days off at the time of screening.
9. Receipt of antipseudomonal antibiotics for an exacerbation during the screening period[b].
10. Treatment with immunosuppressives within previous 6 months prior to screening.
11. Participants with a primary diagnosis of Chronic obstructive pulmonary disease (COPD) associated with >10 pack years smoking history[c].
12. Participants with a primary diagnosis of asthma or asthma which is considered to be poorly controlled at screening[c].
13. Participants with FEV_1 <25% predicted value at screening.
14. Glomerular filtration rate (eGFR) below 25ml/min/1.73m^2 or requiring dialysis. This will be determined at screening.
15. Use of any investigational drugs within five times of the elimination half-life after the last dose or within 30 days, whichever is longer.
16. Unstable co-morbidities (e.g., cardiovascular disease, active malignancy) which in the opinion of the investigator would make participation in the trial not in the participant's best interest.
17. Pregnant or lactating females.

18. Women of child baring age or male partners of women of child baring age and not practicing a method of acceptable birth control[d]

[a] Participants who are receiving stable chronic inhaled/nebulized antibiotics with no planned changes to treatment during the trial are eligible. Treatment with systemic macrolide or other oral prophylactic antibiotics are allowed, providing a stable dose, and initiation of treatment. at least 3 months prior to screening and maintained throughout the study.

[b] Patients receiving antipseudomonal antibiotics during the screening period may prolong the screening period to a maximum of 60 days and may be randomized provided they have a positive sputum sample for *P. aeruginosa* following cessation of antibiotic therapy. All eligibility criteria must be met prior to randomisation, re-screening procedures to assess eligibility may be required.

[c]Asthma and COPD are common co-diagnoses in patients with bronchiectasis. Where a patient has a diagnosis of bronchiectasis plus either asthma or COPD, they may be enrolled in the trial if the clinician performing the screening assessment determines that bronchiectasis is the primary clinical diagnosis, i.e where the patient's symptoms and exacerbations are primarily due to bronchiectasis in the opinion of the investigator.

[d] See section 8.11 for details

7. TRIAL PROCEDURES

All trial procedures will be carried out as per Schedule of Procedures, Appendix 4.

7.1. Recruitment

Anonymised information on participants who are not randomised will be collected for CONSORT reporting and includes:

- age,
- gender,
- ethnicity (if applicable),
- whether the patient is randomised or not randomised,
- the reason not eligible for trial participation, or if they are eligible but declined

7.1.1. Participant identification

Identification of potentially eligible trial participants may make use of any or all of the following

- From secondary care via contact with participants at specialist respiratory clinics or pulmonary rehabilitation classes. Clinic lists and rehabilitation class participant lists will be reviewed by a member of the clinical care team or trial teams, after approval of the clinical care team, and medical records checked to identify suitable participants. Potential participants will then either be approached and given the brief Participant Information Sheet (bPIS) when they attend clinic or class or will be posted an invite letter and bPIS. Contact at clinic or class will be by a member of the clinical care team. Postage of invitation letters and bPIS will be carried out by the clinical care team or aa member of the trial team after approval from the clinical care team.

- From local Bronchiectasis databases where participants have given prior consent to be contacted for future research projects, e.g., EMBARC registry, or local registers such as TAYBRIDGE, BRONCH-UK, or similar databases with appropriate approval in other NHS Boards/TRuSTs as defined locally. Local PI or delegated member of the clinical care or trial teams will send out invite letters with bPIS to individuals who may be suitable to take part.
- Recruitment of participants registered via the Scottish Health Research Register (SHARE)
- From primary care via the Primary Care Networks. These participants will be sent out an invitation letter and bPIS from the GP practice. GP practices will also be asked to display trial posters and bPIS in their waiting rooms.

When first contact is via letter a bPIS will be sent which gives a general overview of the trial. Participants will be asked to contact the trial team if they are interested in the trial. When first contact is in a hospital clinic, they will be given a bPIS and will be asked to either return an expression of interest in a stamped addressed envelope or to contact a member of the trial team by telephone or email; trial staff may also arrange a convenient time to call the participant. Contact details will be provided on the bPIS.

Should individuals express an interest in taking part in the trial, the PI or delegate will contact the individual and ask for permission to check their medical notes. Individuals who returned a reply slip may have provided this permission on the slip in which case further contact with them would not be required prior to accessing their medical notes. Participants will receive a full Participant Information Sheet.

Recruitment may also utilise publicity materials including posters, information leaflets and advertisements.

The local PI will be responsible for recruitment but may delegate to other named individuals within the trial team.

7.1.2. Screening

At the screening visit, Visit 1, the procedures as detailed in the Schedule of Procedures, Appendix 4, will be carried out.

Where the participant does not have a record of *P. aeruginosa* in sputum, bronchoalveolar lavage or another airway sample at least once in the 24 months prior to screening, a sputum sample will be taken for culture at the screening visit, a further sample will be collected at least 21 days after screening. Both of these samples must have evidence of *P. aeruginosa* growth for eligibility.

In cases where the sputum sample collected at visit 1 screening is negative for *P. aeruginosa,* repeat sputum samples may be provided during the screening period. Each participant requires one positive sputum sample at the screening visit or during the screening period, within 35 days of randomization, to be eligible.

Assessment of eligibility will be carried out by the PI or other medically qualified delegate. Eligibility will be assessed at Visit 2, randomisation/baseline, once all blood and sputum results have been reviewed.

Details of all participants consented to the trial and screened for eligibility will be recorded on the Enrolment and Randomisation Log, this will detail if a participant fails screening or goes on to be randomised.

Where an ineligible participant's medical condition, including ineligibility due to a recent infection, or concomitant medications change sufficiently so that they are deemed potentially eligible for the trial they may be rescreened one further time. All screening procedures will be repeated, and eligibility checked.

7.1.3. Ineligible participants

Where an individual is found to be ineligible for trial participation, will be thanked and the reasons for the ineligibility fully explained. Any queries or questions will be answered by an appropriate member of the trial team. If ineligibility is related to an incidental finding (IF) which is considered to be clinically significant, it will be reported to the participant's healthcare provider e.g. GP in the UK and/or consultant by the site PI, with the consent of the individual.

7.1.4. Payment

Reasonable travel expenses for any visits additional to normal care will be given to participants.

7.2. Consent

The PI retains overall responsibility for the conduct of research at their site. This includes the taking of informed consent of participants at their site. They will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of GCP and Declaration of Helsinki.

Where a participant requests to speak with a physician from the trial team the consent process will not be completed until the participant has spoken to the physician and had all their questions answered to their satisfaction.

For adults who lose capacity their previous wishes will remain legally binding and this will remain valid unless the protocol changes significantly. If this occurs and further consent is required from a participant who has lost capacity, the participant's legal representative or if not contactable a professional legal representative will be asked for their consent.

In all cases the PI or delegate will consult with carers and take note of any signs of objection or distress from the participant – the participant will be withdrawn if they raise objection. Where appropriate the participant will be withdrawn from any further clinical intervention and agreement will be sought from a carer to allow data collection.

7.2.1. Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Blood and sputum will be stored for future biomarker and molecular microbiology research in labs at the University of Dundee for future research. This is likely to include biomarker measurement, microbiome research and antibiotic resistance research. Specimens may be used for submission to ethically approved research tissue banks for future unspecified research held within Tayside and will be registered with NHS Tayside Biorepository. Future use of those

specimens will be governed by the NHS Tayside Biorepository and access committee. Not allowing sputum and blood samples to be used for future research will not affect their participation in the trial. An EDTA blood sample for future genetic research will be obtained and patients will give optional consent for future genetic studies. A Paxgene tube will be obtained for potential future transcriptomic research.

Participants will be asked at consent if they are willing for blood and sputum samples to be stored for future research, including commercial research. Consent from participants will be gained for:

- use of their specimens in future research unrelated to the clinical condition under trial
- use of their specimens in genetic research
- contact by trial staff for further ethically approved future research

Where a participant subsequently rescinds their consent for this data, specimens and/or future contact, all data and specimens collected for these reasons will be destroyed. Any data collected to the point of withdrawal will be retained for reasons of public interest in the area of public health (Article 9(2)(i) GDPR).

7.3. The randomisation scheme

Participants will be allocated to receive trial treatment infusions once every 4 weeks for a total of 3 doses on days 1, 28 and 56 of either Gremubamab 1500mg (IV), Gremubamab 500mg or placebo (IV), all in addition to standard of care. Randomisation will be 1:1:1, Gremubamab 1500mg:Gremubamab 500mg:placebo.

Randomisation will be stratified by inhaled antibiotic use.

7.3.1. Method of implementing the randomisation/allocation sequence

After successful completion of screening the participant will be assessed for eligibility for randomization. This will be documented in the participant's medical notes and electronic Case Report Form (eCRF).

Participants will be randomised by the PI or delegate to one of the two treatment regimens as noted in Section 8.1.

The PI or delegate will use a centrally controlled web based GCP compliant randomisation system, Tayside Randomisation System (TRuST), run by the UK Clinical Research Collaboration registered Tayside Clinical Trials Unit (TCTU). TRuST is provided by the Health Informatics Centre, University of Dundee. TCTU use a validated randomisation program and will securely backup both the randomisation seed and the randomisation allocation.

Unblinded staff will randomise the participant using TRuST. The randomisation allocation will be emailed to the person completing the randomisation and Clinical Trials Pharmacy only.

Access to be able to randomise a participant will only be given after completion of appropriate training.

7.4. Blinding

The trial will be blinded to participants and research staff carrying out trial assessments.

The active/placebo IMP will not be matched, see section 8, randomisation and preparation of the IMP will be carried out by an unblinded member of the trial team. Unblinded members of the trial team will only carry out randomisation and preparation of the IMP and will not carry out any other trial activities. (The decision to randomise [or not] each individual patient must be made by blinded staff.) This will allow the staff carrying out trial assessments to be blinded to treatment allocation. The Delegation Log will detail the tasks delegated to individual members, when delegating tasks, the PI will ensure staff delegated to randomise and prepare the IMP will not be delegated other roles within the trial. The exception to this will be that unblinded delegated medical staff will be allowed to carry out the physical exam, review blood, sputum and ECG results and assess for eligibility at Visit 1 only, prior to randomisation.

Participants will not be able to request to be unblinded, participants will be informed of the results of the trial and their treatment allocation once the trial results have been published.

7.5. Emergency Unblinding

TCTU will provide each PI with a login to the interactive web-based randomisation system, Tayside Randomisation System (TRuST), for 24-hour emergency unblinding at their site only. The Chief Investigator (CI) will also have access to unblind participants at all sites. The date, reason and result will be documented and signed by the person carrying out the unblinding. This will be stored in a sealed envelope in the ISF. Disclosure of the unblinding result will be to individuals involved in the participant's care only. Where possible, the participant will remain blinded and remain in the trial and continue with the trial procedures. The Sponsor will be notified of any emergency unblinding occurring.

In addition, a paper copy of the allocation will be stored securely in NHS Tayside Clinical Trials Pharmacy. Unblinding will only be carried out where a physician considers that it is necessary for clinical safety.

7.6. Baseline data

Baseline data will be collected at day 1 as per Schedule of Procedures, Appendix 4, and as described below, section 7.7.

7.7. Trial assessments

Trial assessments will be performed according to the Schedule of Procedures, Appendix 4. Where trial assessments identify any clinically significant incidental findings, these will be communicated to the participant's GP, with the participant's consent.

Trial assessments will be carried out according to trial specific Working Practice Guidelines (WPG).

Missed trial assessments or visits completed outside the visit window will not be reported as breaches where this is due to participant choice or a clinical decision.

Medical history: Focused medical history, taken from medical records and participant reporting, including the following information:

- History of chronic medical conditions related to inclusion and exclusion criteria
- Medication allergies

Review concomitant medications and therapies taken from medical records and participant reporting

Review of adverse events: participants will be asked about the occurrence of any adverse events since the previous visit, medical records will also be reviewed.

Physical examination: A detailed physical examination will be performed at screening to exclude participants with co-morbidities or other clinical disorders that would constitute an exclusion from the trial. This will include the following systems:

- Respiratory
- Cardiovascular
- Abdominal
- Neurological
- Dermatological

Height & weight: as per WPG

Vital signs: Blood Pressure, pulse, temperature, oxygen saturation as per WPG

Electrocardiogram (ECG): as per WPG, will be reviewed by a doctor prior to randomisation

Blood samples: Collected, processed, and stored as per laboratory manual. Full blood count, urea and electrolytes, liver function tests will be analysed by the local NHS laboratory. Samples will also be taken for exploratory outcomes. The PK and ADA samples may also be used by AZ to develop their PK and ADA analytical methods. Additional blood samples will be taken for future biomarker and molecular microbiology research, see section 7.2.1. A maximum of 50 ml of blood will be obtained at each visit.

Sputum sample: A sputum sample will be collected, processed divided and stored as per laboratory manual. Participants will be asked to bring a spontaneous early morning sputum sample with them to visits, from day 1 visit. Where a participant is unable to produce a sputum sample at a visit a hierarchical approach to obtaining sputum samples will be used:

1. spontaneous sputum sample produced at the visit
2. spontaneous early morning sputum brought from home on the day
3. spontaneous early morning sputum brought in within the following 48 hours after the scheduled visit.
4. Induced sputum in sites able to perform induced sputum according to local protocols.

Sputum colour will be assessed using the Murray Sputum Colour Chart. Sample will also be taken for exploratory outcomes. Additional sputum sample will be taken for future biomarker and molecular microbiology research, see section 7.2.1.

Standard spirometry: post bronchodilator spirometry at visits will be carried out as per WPG using American Thoracic Society/European Respiratory Society's guidelines[17]. FEV1 forced vital capacity (FVC) and Forced Expiratory Flow at 25-75% (FEF25-75) will be measured.

Severity of bronchiectasis will be evaluated using the Bronchiectasis Severity Index and MRC dyspnoea score. Exacerbation assessment will use the EMBARC definition of exacerbation.[18]

Pregnancy test: will be carried out for women of childbearing potential (WOCBP), as described in section 6.2. Where required, the initial test at the screening visit will be by serum analysis, urine pregnancy test will be carried out prior to administration of IMP at follow-up visits and at the final visit. See also notes in the exclusion criteria section 6.2, regarding contraception.

7.8. Long term follow-up assessments

Nil

7.9. Quality of life assessments

Will be evaluated using the QOL-B[19], the SGRQ[20], and the BIM questionnaire.[21] The SGRQ has a 3-month recall period and will therefore be performed at baseline and 3 months. The QOL-B and BIM questionnaire have a shorter recall period and will be performed monthly. An end of treatment qualitative questionnaire will be completed at visit 7 to collect participant experiences of the infusion.

7.10. Withdrawal criteria

Participants are free to withdraw at any time and are not obliged to give reason(s). The CI, PI or delegate will make a reasonable effort to ascertain the reason(s), both for those who express their right to withdraw and for those lost to follow up, while fully respecting the individual's rights.

The investigator may withdraw a patient at any time if it is in the best interest of the participant and treatment continuation would be detrimental to the participant's wellbeing. The Investigator will make a clinical judgment as to whether or not an adverse event (AE) is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant should, if required, be offered an end-of-trial assessment.

A full explanation will be provided. As the trial is being conducted on an intention to treat basis, if the participant has been randomised and given one or more dose of IMP, s/he will be asked to complete trial visits as per the protocol, to allow for an intention to treat analysis - but will be censored in the per-protocol analysis. Participants are free to refuse to do so. Withdrawn participants will not be prescribed IMP.

In addition, the trial drug will be discontinued in the following circumstances:

- Pregnancy
- If an allergic reaction assessed as ≥ grade 3 using the Common Terminology Criteria for Adverse Events, including anaphylaxis, assessed as related to the trial drug occurs, the trial drug will be stopped immediately, and treatment will be initiated as appropriate.

Those withdrawn, including those lost to follow-up, will be identified and a descriptive analysis of them provided, including the reasons for their loss, if known, and its relationship to treatment and outcome.

7.11. Storage and analysis of clinical samples

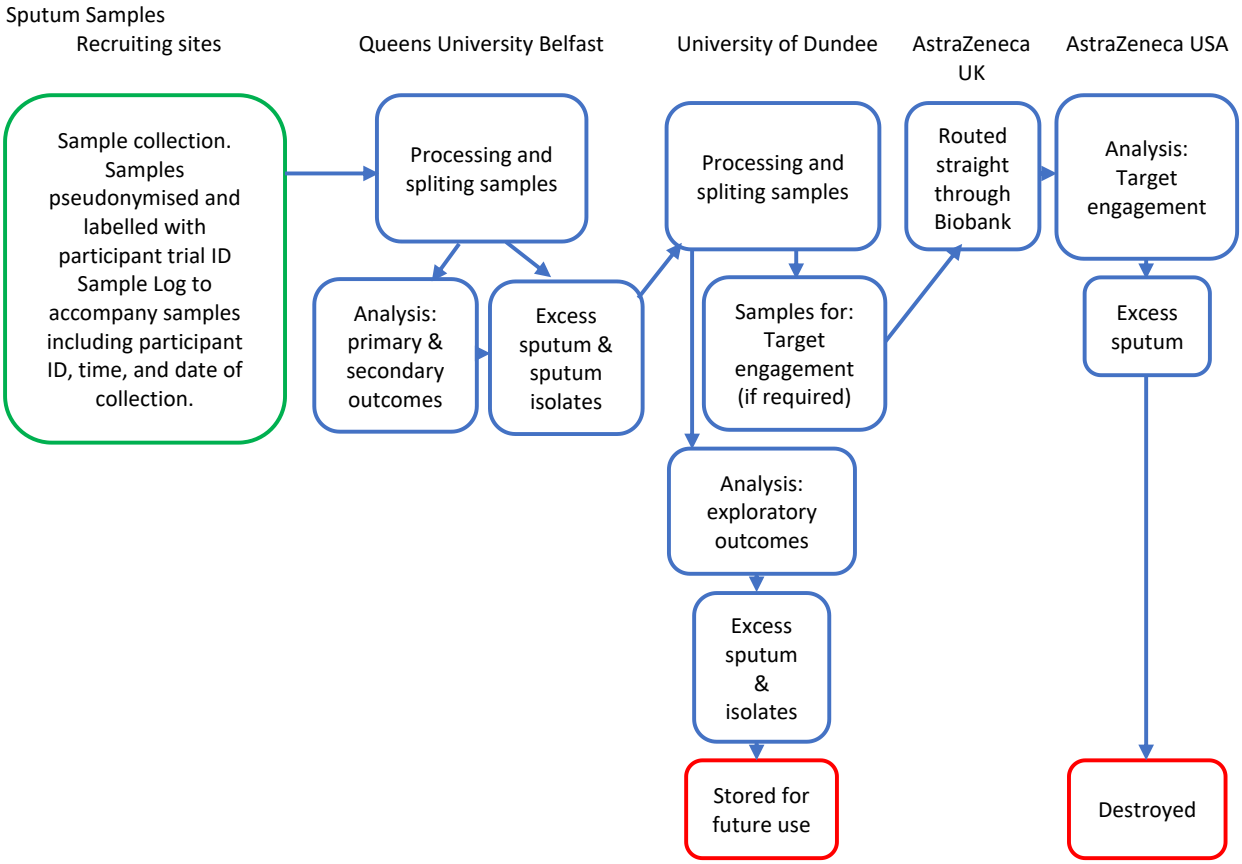
Sputum samples required for outcome measures will be transferred to Queen's University Belfast (QUB), Evolve Laboratory. QUB will carry out bacterial load analysis and store samples until the end of the trial. At the end of the trial sputum samples will be transferred to University

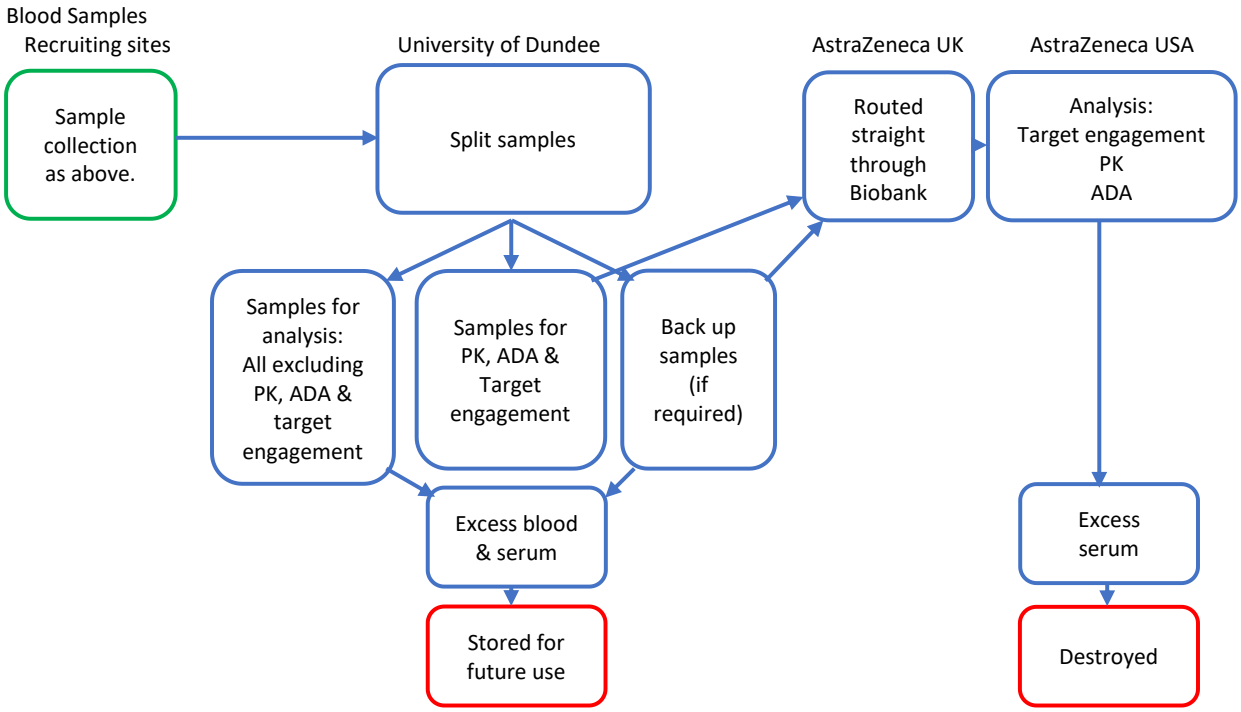
of Dundee (UoD), Division of Cardiovascular Medicine where samples will be split with some being transferred to AZ Biobank, Cambridge, UK. AZ will be responsible for the chain of custody of these samples. The target engagement analysis will be completed on behalf of AZ by PPD Development, North Carolina, USA. Any remaining sputum samples, including those collected for future use will remain at the UoD, Division of Cardiovascular Medicine, for analysis. Excess samples and samples collected for future use will be stored in UoD, Division of Cardiovascular Medicine, under the control of the CI for future research use.

Blood samples will be transferred to UoD, Division of Cardiovascular Medicine at the end of the trial. Samples required for PK and ADA analysis will be transferred from UoD to AZ Biobank, Cambridge, UK. AZ will be responsible for the chain of custody of these samples. PK and ADA samples will be analysed by AZ laboratory, Gaithersburg, Maryland USA. Excess samples and samples collected for future use will be stored in UoD, Division of Cardiovascular Medicine, under the control of the CI for future research use.

The collection, processing and storage of samples will be detailed in the Laboratory Manual. The analysis of samples will be detailed in the Laboratory Analytical Plans and/or agreements with external laboratories (AZ/QUB).

7.11.1. Summary of sample transfers


Sputum Samples
Recruiting sites
Queens University Belfast
University of Dundee
AstraZeneca UK
AstraZeneca USA
Sample collection. Samples pseudonymised and labelled with participant trial ID Sample Log to accompany samples including participant ID, time, and date of collection.
Processing and spliting samples
Analysis: primary & secondary outcomes
Excess sputum & sputum isolates
Processing and spliting samples
Samples for: Target engagement (if required)
Analysis: exploratory outcomes
Excess sputum & isolates
Stored for future use
Routed straight through Biobank
Analysis: Target engagement
Excess sputum
Destroyed


Blood Samples
Recruiting sites
University of Dundee
AstraZeneca UK
AstraZeneca USA
Sample collection as above.
Split samples
Samples for analysis: All excluding PK, ADA & target engagement
Samples for PK, ADA & Target engagement
Back up samples (if required)
Excess blood & serum
Stored for future use
Routed straight through Biobank
Analysis: Target engagement PK ADA
Excess serum
Destroyed

7.12. End of trial

The end of trial at all Sites is defined as last participant last visit. The Sponsor, CI and/or the TSC have the right at any time to terminate the trial for clinical or administrative reasons.

The end of the trial will be reported to the Sponsor, Research Ethics Committee (REC)/ Institutional Review Board (IRB), Competent Authority (CA) and National Health Service Research & Development (NHS R&D) Office(s)/equivalent within 90 days, or 15 days if the trial is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A final clinical trial report will be submitted to the CA within 1 year of the end of the trial and will also be provided to the Sponsor and REC/IRB.

7.13. Managing Exacerbations (and worsening of bronchiectasis not meeting definition of exacerbations)

Exacerbations and worsening of bronchiectasis should be treated in accordance with local standard of care and investigator judgment. Patients experiencing an exacerbation or worsening of bronchiectasis should only be withdrawn from the study by the investigator if the withdrawal criteria are met (see section 7.10).

8. TRIAL TREATMENTS

8.1. Name and description of investigational medicinal product(s)

	IMP	Dosage, form and strength	Placebo	Dosage, form and strength
Arm 1	Gremubamab	1500 mg intravenous infusion (reconstituted and diluted to a total volume of 250 mL)	Liquid buffer in saline	Intravenous infusion of 30 mL (as supplied, and diluted to a total volume of 250 mL)
Arm 2	Gremubamab	500 mg intravenous infusion (reconstituted and diluted to a total volume of 250 mL)	Liquid buffer in saline	Intravenous infusion of 30 mL (as supplied, and diluted to a total volume of 250 mL)

8.1.1. Investigational Medicinal Product

Gremubamab, previously known as MEDI3902, is a bivalent, bispecific human immunoglobulin G1 kappa monoclonal antibody.

Gremubamab is a lyophilized product. Following reconstitution with 4 mL sterile water for injection, the investigational product is further diluted into 0.9% (weight per volume [w/v]) saline to a total volume of 250 mL for intravenous (IV) infusion.

Supplied as a sterile white to off white, lyophilized powder in a clear 20 mm 10R glass vial at a nominal fill volume of 4 mL (post reconstitution), stoppered with a siliconized 20 mm chlorobutyl rubber stopper, and sealed with flip-off cap Overseal.

8.1.2. Placebo

The placebo is a liquid product intended for IV administration.

The placebo is supplied as a sterile, colourless to slightly yellow, clear to slightly opalescent liquid, free from visible particles, in a 20 mm 10R glass vial at a nominal fill volume of 4 mL, stoppered with a siliconized 20 mm chlorobutyl rubber stopper, and sealed with a flip-off cap overseal, and is further diluted into 0.9% (w/v) saline to a total volume of 250 mL for IV infusion.

8.2. Regulatory status of the drug

No Marketing Authorisation held.

The IMP has been used previously trials of healthy adults[16] and in mechanically ventilated adults colonised with *Pseudomonas aeruginosa*[20].

8.3. Product Characteristics

The reference safety information (RSI) is described in Section 9.4.

8.4. Drug storage and supply

IMP and placebo vials will be supplied to Clinical Trial Pharmacies (CTP). To be stored at 2-8^{O}C.

Water for injection for reconstitution of the IMP will be procured by site CTP

0.9% Sodium Chloride for infusion to be supplied by TCTU.

Further details will be provided in the Pharmacy Manual.

8.5. Preparation and labelling of Investigational Medicinal Product

IMP and placebo vials will be supplied to Clinical Trial Pharmacies over labelled with annex 13 compliant labels.

After randomisation the IMP/placebo will be prepared:

IMP – to be reconstituted with 4ml water for injection. Diluted with 0.9% Sodium Chloride for infusion and supplied in infusion bag. Annex 13 compliant labels will be applied to infusion bags.

Placebo - Diluted with 0.9% Sodium Chloride for infusion and supplied in infusion bag. Annex 13 compliant labels will be applied to infusion bags.

Labelling of infusion bags will ensure blinding of staff administering infusion to participant.

Further details will be supplied in the Pharmacy Manual supplied to sites.

8.6. Accountability Procedures

All IMP will be supplied by AZ and over labelled, QP released and distributed to sites by Sharp Clinical Services. Trial medication will be received by a delegated person at the trial site Clinical

Trial Pharmacy, handled and stored safely and properly, and kept in a secured location as detailed in the Pharmacy Manual. All trial clinical supplies will be dispensed only in accordance with the protocol.

The PI or delegated trial staff will maintain an accurate record of the receipt and dispensing of the IMP within TRuST. Monitoring of drug accountability will be performed as per Sponsor Monitoring Plan.

8.7. Dosage schedules

Participants will receive IMP/placebo as described in section 7.3.

8.7.1. Description and justification of route of administration

IMP/placebo will be given by intravenous infusion through a 0.20 micron or 0.22 micron low protein binding filter via IV pump.

8.7.2. Frequency of administration

IMP/placebo will be given once every 4 weeks for a total of 3 doses on days 1, 28 and 56.

8.7.3. Infusion rate

IMP/placebo will be infused at a rate of ≤ 62.5 mL/hr. (This is equivalent to ≤ 6.25 mg/minute for the higher dose of Gremubamab).

8.7.4. Missed doses

If a participant misses a treatment dose, they will continue with further treatment doses as per protocol.

8.8. Dosage modifications

No modifications to dose will be made during the trial

8.9. Known drug reactions and interaction with other therapies

Infusion reactions are relatively common (40% in the phase 1 study) and can be managed by slowing the infusion rate.[15] These potential risks include, but are not limited to, anaphylaxis and serious allergic reactions (including hypersensitivity), immune complex disease and infusion related reactions. Details of mitigation of risk are detailed in Appendix 1.

Participants will be pre-medicated with an antihistamine prior to being dosed with the trial drug (see section 8.12).
Participants will be observed for at least 30 minutes after completion of infusion of trial medication. Participants will be given contact information for the trial team in case they experience symptoms later.

There are no known drug interactions.

8.10. Concomitant medication

Details of all concomitant medications will be recorded on the trial eCRF on a concomitant-medications log. Where possible patient's regular treatments received for the management of bronchiectasis should remain stable throughout the study period.

New long-term inhaled or oral anti-pseudomonal antibiotics should not be newly initiated during the study. There are no other prohibited medications.

8.11. Trial restrictions

WOCBP must be willing to have pregnancy testing prior to trial entry and prior to each administration of trial medication dose.

A woman is considered of childbearing potential, i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause (including use of hormone replacement therapy).

In addition, WOCBP must be willing to use a form of a medically approved birth control method throughout the trial (and for minimum of 16 weeks after last dose), which include:

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
    - oral
    - injectable
    - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence, when this is in line with the preferred and usual lifestyle of the participant, abstinence is acceptable only as true abstinence. Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Men who are sexually active with WOCBP will also be required to use a form of medically approved birth control method as listed above throughout the trial (and for minimum of 16 weeks after last dose) and will be requested to inform the trial team of any pregnancy occurring.

Participants will be informed that they should not give blood during their trial participation.

8.12. Assessment of compliance with treatment

The administration of IMP will be recorded in the eCRF and clinical trial database, this information will be made available to the trial statistician at the end of the trial. The failure of the participant to receive IMP at the appropriate visit will be reported to the Sponsor as a breach of protocol unless this is due to the participant's refusal to receive IMP or a clinical decision that it is not appropriate for the participant to receive the IMP. See section 8.7.5 for dealing with missed doses and restarting treatment. Participants who do not receive all doses of IMP will be encouraged to continue in the trial and complete all visits and visit assessments.

8.13. Name and description of each Non-Investigational Medicinal Product (NIMP)

Antihistamine

All subjects will be premedicated with antihistamine prior to each dose of IMP, for example, 10 mg chlorpheniramine IV, 50 mg diphenhydramine IV, clemastine 2 mg IV, or dexchlorpheniramine 5 mg IV (or another antihistamine preparation utilised in routine clinical practice for management of acute allergic reactions). Where a participant is already taking antihistamines then the pre-dose antihistamine should not be given.

9. PHARMACOVIGILANCE

9.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product (IMP) which is related to any dose administered to that participant. The phrase "response to an IMP" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. Adverse events that may be related to the IMP are listed in the Investigator's Brochure (IB) for each product.
Serious Adverse Event (SAE)	A SAE is any AE that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Term	Definition
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A SAR, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information, see section 9.4:

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

9.2. Operational definitions for (S)AEs

Worsening of bronchiectasis during the trial will not be classed as an AE but is defined as an outcome. Hospitalisations resulting from worsening of bronchiectasis are common events for patients with bronchiectasis and therefore will be recorded but not classed as SAEs. The exception to this is when, in the opinion of the investigator, there is a causal relationship between the trial drug and the hospitalisation for bronchiectasis, or if death occurs.

An abnormal laboratory finding, that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant, will be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition will be reported (e.g., renal failure, haematuria) not the laboratory abnormality. Abnormal laboratory values that are not, in the investigator's opinion, medically significant and do not require intervention will not be reported as AEs

A non-clinically significant, in the opinion of the investigator, worsening of a pre-existing condition during the trial will not be classed as an AE. Pre-specified elective hospitalisations for treatment planned prior to randomisation will not be considered as an AE. However, any AEs occurring during such hospitalisations will be recorded.

9.3. Recording and reporting of AEs, SAEs, SARs AND SUSARs

All AEs will be recorded on the AE Log in the eCRF. Details of AEs will be recorded in the medical record. AEs will be assessed for severity by the PI. AEs will be recorded from the time a participant consents to join the trial until the participant’s last trial visit. Any SUSAR, that the investigator becomes aware of, will be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.

An AE may be classified as a SAE or AR.

Participants with unresolved AEs/SAEs at end of trial will be followed up until 30 days after participant’s last visit. SUSARS will be followed until resolution, where a participant agrees to this.

The CI, PI or delegate will ask about the occurrence of AEs and hospitalisations at every visit during the trial. SAEs will be submitted on an SAE form to the Sponsor Pharmacovigilance

Section tay.pharmacovigilance@nhs.scot within 24 hours of becoming aware of the SAE. Site PIs will also notify the CI when submitting an SAE.

The evaluation of expectedness will be made based on the knowledge of the reaction and the relevant safety information (RSI) see Section 9.4. The Sponsor will make the definitive assessment on expectedness for the purposes of SUSAR reporting.

The Sponsor is responsible for reporting SUSARs to the appropriate CA, and the REC/IRB. Fatal or life-threatening SUSARs will be reported within 7 days and non-fatal and non-life threatening SUSARs within 15 days.

Reporting of safety data to the funders will be as detailed in the funding agreement.

9.4. Reference Safety Information

The current version, of the IB will be held in the Trial Master File (TMF) - specifically in Pharmacy Site File, Investigator Site File (ISF) and Sponsor File. Section 6 Investigator Brochure (IB) contains the Reference Safety Information for IMP and is detailed below. The IB will be reviewed at least annually and where there have been any changes to the Reference Safety Information which may impact on the trial the protocol will be reviewed and a substantial amendment submitted for regulatory approvals.

There are no expected events

9.5. Responsibilities

CI/PI or delegated staff:

- Checking for AEs and ARs when participants attend for treatment / follow-up.

CI/PI or medically qualified delegate:

- Confirmation of eligibility criteria
- Using medical judgement in assigning seriousness, causality and whether the event/reaction was using the Reference Safety Information approved for the trial.
- Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.

CI:

- Central data collection of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database.
- Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.
- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
- Immediate review of all SUSARs.
- Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.

- Periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis
- Preparing the clinical sections and final sign-off of the Development Safety Update Report (DSUR).
- Reporting safety information to funder and AZ as per contract.

Sponsor:

- Expedited reporting of SUSARs to the CA and REC/IRB within required timelines.
- The unblinding of a participant for the purpose of expedited SUSAR reporting.
- Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
- Preparing standard tables and other relevant information for the Development Safety Update Reports (DSUR) in collaboration with the CI and ensuring timely submission to the CA and REC/IRB.

AstraZeneca:

- Responsible for maintaining IB and the manufacturing/preparation documentation.

9.6. Notification of deaths

All deaths occurring during the trial, will be reported to the sponsor irrespective of whether the death is related to disease progression, the IMP, or an unrelated event. Deaths will be reported to Sponsor as SAEs as per Section 9.3.

9.7. Pregnancy reporting

Pregnancy itself is not considered an AE or SAE, unless there is a congenital abnormality or birth defect. Any unexpected pregnancy occurring during the trial and the outcome of the pregnancy, will be recorded on a Tayside Medical Science Centre (TASC) Pregnancy Notification Form and submitted to the Sponsor Pharmacovigilance Section pharmacovigilance.tayside@nhs.scot within 24 hours of becoming aware of the pregnancy and the outcome of the pregnancy. The pregnancy will be followed up until the end of the pregnancy. If the trial participant is a male, informed consent for follow up will be sought from his female partner.

9.8. Overdose

An overdose is defined as receipt of over 3000mg of Gremubamab, the highest dose tested in the phase 1 study, given as a single dose. An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE section in the eCRF. Any dose administered other than prescribed dose for that participant will be reported to the Sponsor as a protocol breach.

If an overdose of study drug occurs in the course of this study, then the Investigator or other site personnel will inform the appropriate sponsor representatives immediately, or no later than 24 hours after becoming aware of it. The designated sponsor representative will work with the Investigator to ensure that all relevant information is provided to the sponsor's Pharmacovigilance Committee.

9.9. Reporting urgent safety measures

The PI or other trial physician will take appropriate immediate urgent safety measures in order to protect the participants against any immediate hazard to their health or safety. The CA, REC/IRB and Sponsor will be notified in writing within three days.

9.10. The type and duration of the follow-up of participants after adverse reactions.

All adverse reactions will be recorded as per section 9.3. Where adverse reactions occur, assessment of clinical condition and appropriate treatment will be instigated by a delegated doctor and will continue until the symptoms resolve or the condition stabilises.

9.11. Development safety update reports

The following reports will be submitted each year as a condition of the regulatory authorisation to undertake a clinical trial or as a condition of a favourable opinion from a REC.

The DSUR will be prepared jointly by the Sponsor Pharmacovigilance Section and CI and submitted by the Sponsor to the CA on the anniversary of date of Clinical Trial Authorisation.

The DSUR and reports of SUSARs will be sent to REC/IRB by the Sponsor Pharmacovigilance Section. Any other safety reports, for example, reports of a DMC, will be sent by the CI to REC/IRB, with a Safety Report Form, and to the Sponsor.

10. STATISTICS AND DATA ANALYSIS

10.1. Sample size calculation

The sample size calculation assumes that Gremubamab will be at least as effective as inhaled antibiotic treatment at reducing bacterial load in sputum. The meta-analysis by Laska[7] was used to estimate the appropriate effect size, where the mean difference between antibiotic treatment and placebo/control was -2.32 log units. Data from the ORBIT-3 and ORBIT-4 trials[23] suggest a standard deviation for the change of around 2.6. It is assumed that the change will be shown on the highest antibody dose, but there is evidence that antibodies do not follow the standard dose-effect curve. Therefore, only one change is considered despite testing more than one dose.

The target sample size is 60 patients total, randomised 1:1:1 (Gremubamab 1500mg: Gremubamab 500mg: placebo). Each Gremubamab dose arm is compared to placebo separately; the placebo arm is shared. 20 patients per arm for the comparison of Gremubamab 1500mg against placebo, and 20 patients per arm for the comparison of Gremubamab 500mg against placebo, provides high power (>93%) for each of these comparisons at the 1-sided 10% significance level to detect a large difference of the magnitude in Laska[7] (a standardised difference of 0.89), but also provides good power if the true difference is smaller. For example, the power to detect a difference of 1.84 log units (a standardised difference of 0.71) is >82%. See Table 10.1.1.

There has been a lengthy delay to the start of recruitment, approximately halving the original 12-month recruitment period (see section 10.2). Table 10.1.1 also shows the power for a range of scenarios, illustrating that even if recruitment is less than planned, power to detect a difference in line with Laska[7] is reasonable (total recruitment as low as 30 patients would give almost 75%

power for each Gremubamab dose arm vs placebo comparison; 36 patients total would give approximately 80% power).

Table 10.1.1: Power for each Gremubamab dose vs placebo comparison, for a given sample size and "true" difference in means.

Total recruitment	Sample size per arm for the Gremubamab 1500mg vs placebo and Gremubamab 500mg comparisons	Power for each Gremubamab dose arm vs placebo comparison			
		Target diff: -1.59 (SD=2.60)	Target diff: -1.84 (SD=2.60)	Target diff: -2.00 (SD=2.60)	Target diff: -2.32 (SD=2.60)
60	20	73.6%	82.4%	87.0%	93.4%
45	15	64.4%	73.5%	78.6%	87.0%
30	10	52.2%	60.4%	65.5%	74.8%
15	5	35.8%	41.3%	44.9%	52.2%

10.2. Planned recruitment rate

Recruitment was originally planned to take 1 year in approximately 20-30 sites.

Recruitment will stop end December 2023 due to the IMP/placebo expiry date. No extension to recruitment will be given. Due to delays within the approval process, the trial was unable to start recruitment in early 2023 as planned. Justification of the trial feasibility with the reduced recruitment period is given in section 10.1.

10.3. Statistical analysis plan

A statistical analysis plan will be finalised prior to data lock.

The statistical analysis plan will detail the summary of baseline data and flow of patients, primary and secondary outcome analysis, subgroup analyses, adjusted analysis, participant population and, procedure(s) to account for missing or spurious data.

10.4. Interim analysis and criteria for the premature termination of the trial

There will be no interim analysis.

10.5. Economic evaluation

No economic evaluation will be performed.

11. DATA MANAGEMENT

11.1. Data collection tools and source document identification

Medical records will be used as source data. The questionnaires will be completed by the participants and act as source data, the completed form will be filed in the medical notes. All trial data relevant to a participant's general medical history will be recorded in the medical record. The medical record will be flagged to state that the patient is participating in the GREAT-2 trial.

The PI or delegate will maintain source documents for each participant in the trial, consisting of hospital medical records containing demographic and medical information, laboratory data, electrocardiograms, trial questionnaires and the results of any other tests or assessments.

An eCRF, using CASTOR Electronic Data Capture system, will be provided by TCTU. The trial system will be based on the protocol for the trial. Development and validation of the trial database and quality control will be done according to TCTU procedures.

The eCRF will not collect more information than is required to meet the aims of the trial and to ensure the eligibility and safety of the participant.

The PI may delegate eCRF data entry but is responsible for completeness, plausibility and consistency of the eCRF. Delegated trial staff will enter the data required by the protocol into the eCRFs following training in the definitions and methods used in completing the eCRF. Any queries will be resolved by the PI or delegated member of the trial team. On completion of data collection, the PI must certify that the data entered into the eCRFs are complete and accurate.

Data verification and cleaning and extraction of data will be performed as per TCTU local procedures and detailed in the Data Management Plan.

General laboratory data methods and results will be documented in laboratory notebooks and then analysed and written up for publication for dissemination to the scientific community (Tayside only). All electronic data will be stored on secure University of Dundee or cloud-based servers which have restricted access and have disaster recovery systems in place.

11.2. Data handling and record keeping

The data management system will be Castor, as approved by Sponsor.

The data management system will be based on the protocol for the trial and individual requirements of the investigators. The eCRF will collect only information that is required to meet the aims of the trial and to ensure the eligibility and safety of the participant. The database is managed in line with all applicable principles of medical confidentiality and UK law on data protection, namely, the Data Protection Act 2018, which brought UK law into line with the European Union (EU) Data Protection Directive. The Data Controller will be the University of Dundee and the Data Custodian will be the CI.

Development and validation of the trial database, quality control and extraction of data will be managed by TCTU. Details will be documented in a Data Management Plan.

11.3. Access to Data

The CI, PIs and all institutions involved in the trial will permit trial related-monitoring, audits, REC/IRB review, and regulatory inspection. In the event of an audit, the CI and/or PI will allow the Sponsor, representatives of the Sponsor or regulatory authorities direct access to all trial records and source documentation.

AZ are the primary beneficiary of the trial data, intellectual property, and inventions as detailed in the contract with ERS/AZ/University of Dundee. AZ have a contractual right to examine and audit the trial data. The University of Dundee and the CI have a right to use the trial data for internal research. There are no rights for academic collaborators or rights for CI to use the trial data with third parties.

11.4. Archiving

Archiving of trial documents will be as detailed in the archiving plan, in compliance with Sponsor Standard Operating Procedures. All trial documentation, electronic and paper, will be kept for 25 years. Medical records will be maintained in compliance with local NHS policy on retention of medical records. The CI will be responsible for arranging the archiving of the TMF and ensuring that research data is archived in a way that will permit accurate reconstruction of the research. Sites will be responsible for archiving local trial records including the ISF and Pharmacy Site File. Sponsor will be responsible for archiving the Sponsor file.

12. MONITORING, AUDIT & INSPECTION

12.1. Monitoring

A trial risk assessment is carried out by the Sponsor prior to Sponsorship approval being granted. The Sponsor has determined the appropriate extent and nature of monitoring for the trial and will appoint appropriately qualified and trained monitors independent to the trial team. A Monitoring Plan will be developed by the Sponsor based on the trial risk assessment which may include on site monitoring. The Monitoring Plan will be reviewed regularly using a risk-based approach and up-dated as required. The Monitoring Plan will detail the procedures and anticipated frequency of monitoring, processes reviewed. Sites must have access to source data for purposes of remote monitoring and assist the Sponsor in monitoring of the trial. In recognition that source data may come from different sources at each site, sites shall ensure that a source data identification list is supplied to the Monitoring Team in advance of any monitoring review and ensure they have this data is available on the agreed date and time to facilitate the review

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Research Ethics Committee (REC) review & reports

Before the start of the trial in each participating country, approval will be sought from an independent REC/IRB for that country for the trial protocol, Informed Consent Form and other relevant documents.

Substantial amendments that require review by REC/IRB will not be implemented until the REC/IRB grants a favourable opinion for the trial.

All correspondence with the REC/IRB will be retained in the TMF.

A progress reports will be submitted to the REC/IRB according to REC/IRB approval conditions in each country. It is the CI's responsibility to produce the REC/IRB reports as required.

The CI will notify the REC/IRB in each country of the end of the trial. If the trial is ended prematurely, the CI will notify the REC/IRB in each country, including the reasons for the premature termination. The CI will submit a final report with the results, including any publications/abstracts, according to REC/IRB approval conditions in each country.

A copy of all REC/IRB reports will be submitted to the Sponsor.

13.2. Peer review

This trial has been funded the European Respiratory Society who have reviewed the grant application. The trial has also been peer reviewed by AZ The protocol has been reviewed and approved by the Sponsor Committee.

Resulting publications will be reviewed by the referees of the journal to which the paper will be submitted.

13.3. Public and Patient Involvement

Lay person review of the Participant Information Sheet and Informed Consent Form has been completed by the European Lung Foundation Bronchiectasis Patient Advisory Group. Feedback from the group has been adopted throughout these documents. Two patient partners were involved in the development of the end of treatment qualitative questionnaire. We will also involve the European Lung Foundation, a European patient group, in dissemination of research results.

13.4. Regulatory Compliance

The trial will not commence in each country until a Clinical Trial Authorisation is obtained from the appropriate CA and favourable REC/IRB opinion. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments in the UK and appropriate equivalents in other participating countries.

Before any site can enrol participants into the trial, the CI, PI or delegate will ensure that appropriate approvals from participating organisations are in place.

For any amendment to the trial, the CI, PI or delegate, in agreement with the sponsor, will submit information to the appropriate body in order for them to issue approval for the amendment. The CI, PI or delegate will work with sites (so they can put the necessary approvals and arrangements in place to implement the amendment to confirm their support for the trial as amended.

13.5. Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed, e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol. Trial staff will not implement deviations to the protocol except where necessary to eliminate an immediate hazard to trial participants.

Accidental protocol breaches can happen at any time. They will be adequately documented on the relevant forms and reported to the CI and Sponsor using the TASC Breach Reporting Form. If there is a breach of the protocol, the nature of and reasons for the breach will be recorded in the TMF and documented in the trial Breach Log. Breaches from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

13.6. Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree –

a) the safety or physical or mental integrity of the participants of the trial; or
b) the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor of a clinical trial will notify the licensing authority in writing of any serious breach of

a) the conditions and principles of GCP in connection with that trial; or
b) the protocol relating to that trial, as amended from time to time.

If a serious breach of the protocol or GCP is suspected, this will be reported to the Sponsor immediately using the TASC Breach Reporting & Form and will be recorded in the eCRF and documented in the trial Breach Log.

If a breach necessitates a subsequent protocol amendment, this will be submitted as per section 13.10.

13.7. Data protection and patient confidentiality

The CI and trial staff will comply with the requirements of the General Data Protection Regulation (EU) 2016/679 (GDPR) and the UK Data Protection Act 2018 or any subsequent amendment or replacement thereof with regard to the collection, storage, processing and disclosure of personal data and will uphold the principles of GDPR in Article 5.

The CI and trial staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or local equivalent.

All trial records and data will be managed in a manner designed to maintain participant confidentiality. All records, electronic or paper, will be kept in a secure storage area with access limited to appropriate trial staff only. Computers used to collate data will have limited access measures via usernames and passwords. Age, gender and ethnicity will be the only personal identifiable details held on CASTOR Electronic Data Capture system. Date of Birth will be held on the TRuST system to allow for the identification of participants where emergency unblinding is required, date of birth is not shared outside of TRuST.

Personal data or data concerning health will not be released without the existence of a legal basis for processing under Articles 6 and 9 of GDPR, such as official authority 6(1)e or substantial public interest 9(2)g. The CI and trial staff will not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the Sponsor will be required for the disclosure of any said confidential information to other parties.

Access to collated participant data will be restricted to AZ, the CI and appropriate delegated trial staff. AZ will not have access to personal identifiable details other than those held on the electronic data capture system.

The transfer of data to AZ will be as described in the Clinical Research Agreement.

Published results will not contain any personal data that could allow identification of individual participants.

13.8. Financial and other competing interests

The CI has received fees for consulting from the trial funder, AstraZeneca. and holds research grants from AstraZeneca. The CI is Chief Editor of the European Respiratory Journal which is funded by the European Respiratory Society. His institution receives compensation from the European Respiratory Society for this work. Any conflict of interest declared by site staff shall be notified to the Sponsor and retained in the TMF.

AZ will benefit directly from the trial by owning the trial data, intellectual property and n=any developed technologies.

13.9. Indemnity

The University of Dundee and Tayside Health Board are Co-Sponsoring the trial.

Insurance. – The University of Dundee will obtain and hold Clinical Trials Insurance cover for legal liabilities arising from the trial.

Tayside Health Board will maintain its membership of the Clinical Negligence and Other Risks Insurance Scheme (CNORIS) which covers the legal liability of Tayside in relation to the trial.

Where the trial involves University of Dundee staff undertaking clinical research on NHS participants, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

Indemnity. The Co-Sponsors do not provide trial participants with indemnity in relation to participation in the Trial but have insurance for legal liability as described above.

Where other Scottish Health Boards are participating as trial sites, those other Scottish Health Boards will maintain membership of CNORIS to cover their liability in relation to their conduct of the trial.

Other participating sites will maintain membership of a scheme similar to CNORIS.

13.10. Amendments

Amendments to the protocol will be conducted in compliance with Sponsor Standard Operating Procedures. The decision to amend the protocol will lie with the CI after consultation with the TMG and trial statistician. The CI will seek Sponsor approval for any amendments to the Protocol or other approved trial documents. The Sponsor will decide whether an amendment is substantial or non-substantial. The CI will be responsible for submitting the amendment to the appropriate regulatory authorities and communicating amendments to sites. Amendments to the protocol or other trial documents will not be implemented without approval from the Sponsor and subsequent approval from the appropriate REC/IRB and/or CA, as appropriate, and appropriate site approvals The amendment history will be detailed in an Amendment Log.

13.11. Post-trial care

Following the end of trial, participants should be continued, started or restarted on the appropriate treatment for their bronchiectasis. No provision for continuation of trial medications will be made by the trial team or Sponsor

13.12. Access to the final trial dataset

The CI and Trial Statistician will have access to the final trial dataset. Access to the final trial dataset to others will be approved by the CI.

14. DISSEMINATION POLICY

14.1. Dissemination policy

Details of the trial and clinical trial final report will be published on the European Clinical trials Database (EudraCT) database and ISCTRN Registry, no later than 12 months after the end of trial. Trial results will be available to the public via the EU Clinical Trial Register and ISCTRN Registry. The report will be made available to the Funder. The report can be used for publication and presentation at scientific meetings. Trial investigators have the right to publish orally or in writing the results of the trial.

Participants in the trial will be notified of the results via a Results Letter.

14.2. Authorship eligibility guidelines

ERS, the university of Dundee and the CI have the rights to publish the results of the trial. Other academic collaborators will not have the right to publish the results of the trial. AZ will only publish results after permission from the UoD has been sought.

AZ are the primary beneficiary of the trial data, intellectual property, and inventions as detailed in the contract with ERS/AZ/UoD. AZ have a contractual right to examine and audit the trial data. On completion of the trial, the trial data will be analysed and tabulated, and a clinical trial final report will be prepared. The criteria for authorship will follow the criteria of The International Committee of Medical Journal Editors. The CI will be responsible for authorship of the final report.

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16. APPENDICIES

16.1. Appendix 1-Risk

Risks associated with trial interventions

☐ A ≡ Comparable to the risk of standard medical care

☒ B ≡ Somewhat higher than the risk of standard medical care

☐ C ≡ Markedly higher than the risk of standard medical care

Justification: The IMP has been tested previously in healthy adults[16] and in mechanically ventilated adults colonised with *Pseudomonas* aeruginosa. Potential and identified risks are stated in Section 9.4. However, this is the first use of the medication in this patient population, hence there is the *possibility* of additional unknown risks.

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		How will these risks be minimised?		
IMP/ Intervention	Body system/ Hazard	Activity	Frequency	Comments
IMP/ Placebo	Infusion related reaction	Participant will be premedicated with an antihistamine prior to being dosed with the IMP.	Prior to each infusion	
		Maximum infusion rate is limited	Each infusion	
		Infusion rate will be slowed in the occurrence of a non-severe (grade 1 or 2) reaction using the Common Terminology Criteria for Adverse Events, as determined by the local PI (or delegate). Continuation of further doses of IMP will be decided by the PI in discussion with the participant.	Each infusion	
		The infusion will be stopped in the occurrence of a severe reaction, as determined by local PI (or delegate).	Infusion causing severe reaction.	
IMP/ Placebo	Anaphylaxis and serious allergic reactions (including hypersensitivity)	Site must have drugs/equipment to treat acute anaphylactic reactions plus personnel trained to recognize and treat anaphylaxis.	Each infusion	

		Participant's vital signs will be monitored and observed throughout each IMP infusion and for at least 30 mins post infusion.	Each infusion	
		If an allergic reaction assessed as ≥ grade 3 using the Common Terminology Criteria for Adverse Events, including anaphylaxis, assessed as related to the trial drug occurs, the trial drug will be stopped immediately, and treatment will be initiated as appropriate. The participant will be withdrawn from further IMP treatments.	Infusion causing hyper-sensitivity	
IMP/ Placebo	Immune complex disease	Urea and electrolytes will be monitored for any evidence of deteriorating renal function.	Every 4 weeks	The Investigator will make a clinical judgment as to whether the severity requires the participant's removal from treatment.
Outline any other processes that have been put in place to mitigate risks to participant safety (e.g., DMC, independent data review, etc.) Participant safety will be reviewed periodically by the independent DMC.				
Outline any processes (e.g., IMP labelling +/- accountability +/- trial specific temperature monitoring) that have been simplified based on the risk adapted approach.				

16.2. Appendix 2 - Trial management / responsibilities

Responsibilities will be detailed the co-sponsorship and participating site agreements.

16.2.1. Participant registration/randomisation procedure

TCTU TRuST web-based randomisation system will be used. Sites will be provided with a randomisation guide detailing the web-based randomisation system process. Prior to recruitment individuals delegated this task and on completion of training will be given a username and password.

16.2.2. Data management

Data management will be overseen by TCTU Data Management Team.

Local sites will be expected to enter data directly on to the eCRF. Worksheets will be provided to facilitate this process, but their use is not mandatory. Worksheets, where used, will not record source data and will not be used for monitoring purposes.

All data from participants should be entered on the eCRF within 7 days of the last data collection point for that participant.

Data queries will be generated by the Data Management Team and emailed to sites, return of queries should be within 2 weeks.

16.2.3. Preparation and submission of amendments

TCTU Trial Management Team will be responsible for working with the CI to submit any amendments.

16.2.4. Preparation and submission of Annual Reports

TCTU Trial Management Team will be responsible for liaising with the CI to submit REC/IRB annual reports. The Sponsor Pharmacovigilance Team will be responsible for liaising with the CI to submit Annual Safety Reports.

16.2.5. Data protection/confidentiality

The CI and trial staff will comply with the requirements of the Data Protection Act 2018, GDPR or EU General Data Protection Regulation and the Data Protection Act 2018, as applicable in each country, or any subsequent amendment or replacement thereof with regard to the collection, storage, processing and disclosure of personal data. The CI and trial staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or local equivalent.

16.2.6. Trial documentation and archiving

Archiving trial site data will be the responsibility of individual sites. Payment for archiving will be provided as per site agreement.

16.3. Appendix 3 – Authorisation of participating sites

16.3.1. Required documentation

The following data should be made available to TCTU Trial Management Team prior to site initiation:

- PI CV, signed and dated
- PI GCP certificate
- Protocol signature page, signed and dated by PI
- Copy of signed Participating Site Agreement
- Copy of NHS R&D confirmation of capacity and capability

The following data should be made available and held within the ISF/Pharmacy Site File prior to site initiation:

- CV, signed and dated for all trial staff listed on Delegation Log
- GCP certificate for all trial staff listed on Delegation Log

16.3.2. Procedure for initiating/opening a new site

Site Initiation will be performed by Sponsor monitors and TCTU Trial Management Team and may be on site or remote.

TCTU Trial Management Team will initiate release of trial drug to the site after NHS R&D confirmation of capacity and capability.

16.3.3. Principal Investigator responsibilities

The PI's legal responsibilities will be listed in the Participating Site Agreement a summary is given below:

- Attendance at the site initiation meeting,
- Training of new members of trial staff in the protocol and its procedures,
- Ensuring that the ISF is accurately maintained,
- Dissemination of important safety or trial related information to all stakeholders within their site
- Safety reporting within the required timelines
- Ensuring data entry to eCRF and responses to data clarification queries are completed within the required timelines.
- Certify data entered on eCRF is correct and complete.
- Ensuring any trial staff coming into contact with participants have the appropriate Personal Protective Equipment and training in its use.
- Archiving of site trial data.

16.4. Appendix 4 – Schedule of Procedures

Type of visit	Screening V1	Baseline and randomization V2	Treatment phase V3	Treatment phase V4	Treatment phase V5	Treatment phase V6	End of Treatment Assessments V7	Post treatment assessment 1 V8	Post treatment assessment 2 V9	Unscheduled visit Assessments
Timeline	-35 days prior to baseline	Day 1 Up to 35 days after V1	Day 7 ±2	Day 14 ±2	Day 28 ±2	Day 56 ±2	Day 84 ±2	Day 112 ±4 Phone call	Day 168 ±4	As Required
Informed Consent	X									
Inclusion/Exclusion Criteria Check	X	X								
Medical History	X									
Record Concomitant Medications	X	X	X	X	X	X	X		X	X
Physical Examination	X									X
Height & weight	X									
Check Vital Signs [a]	X	X	X	X	X	X	X		X	X
ECG	X									
Pregnancy Test - serum (if applicable)	X									
Pregnancy Test - urine (if applicable)		X			X	X			X	
Full blood count	X				X	X	X		X	
Urea & electrolytes, creatinine, eGFR	X				X	X	X		X	
Liver function tests	X				X	X	X		X	
EDTA blood sample for genetics	X									

Type of visit	Screening V1	Baseline and randomization V2	Treatment phase V3	Treatment phase V4	Treatment phase V5	Treatment phase V6	End of Treatment Assessments V7	Post treatment assessment 1 V8	Post treatment assessment 2 V9	Unscheduled visit Assessments
Timeline	-35 days prior to baseline	Day 1 Up to 35 days after V1	Day 7 ±2	Day 14 ±2	Day 28 ±2	Day 56 ±2	Day 84 ±2	Day 112 ±4 Phone call	Day 168 ±4	As Required
Paxgene tube for transcriptomics		X			X		X		X	
Biomarker Blood Sample [b]	X	X			X	X	X		X	X
Target engagement blood sample		X	X		X		X		X	
PK Blood Sample		X Predose & post infusion [c]	X	X	X Predose & post infusion [c]	X Predose & post infusion [c]	X		X	
ADA Blood Sample		X Predose				X Predose			X	
Sputum sample for P. *aeruginosa* testing	X[D]									
Sputum sample for outcome analysis		X	X	X	X	X	X		X	X
Sputum sample for storage		X	X	X	X	X	X		X	X
Sputum colour assessment		X		X	X	X				
Standard Spirometry	X				X	X	X		X	
Quality of life bronchiectasis questionnaire		X		X	X	X	X		X	X
SGRQ		X					X		X	
BIM		X		X	X	X	X		X	X
Qualitative end of treatment questionnaire							X			

Type of visit	Screening V1	Baseline and randomization V2	Treatment phase V3	Treatment phase V4	Treatment phase V5	Treatment phase V6	End of Treatment Assessments V7	Post treatment assessment 1 V8	Post treatment assessment 2 V9	Unscheduled visit Assessments
Timeline	-35 days prior to baseline	Day 1 Up to 35 days after V1	Day 7 ±2	Day 14 ±2	Day 28 ±2	Day 56 ±2	Day 84 ±2	Day 112 ±4 Phone call	Day 168 ±4	As Required
Bronchiectasis severity index and components e.g MRC dyspnoea score	X									
Exacerbation recording		X	X	X	X	X	X		X	
Administration of trial medication [e]		X			X	X				
Vital signs [a f] during administration of trial medication		X			X	X				
Record Adverse Events		X	X	X	X	X	X	X	X	X
Randomisation		X								

If, at any point after randomisation, a patient is, in the opinion of the investigator, too unwell to attend visit 5 or 6 and to receive trial medication (e.g. hospitalized) within the ordinarily permitted window, then the visit may be delayed by up to 7 days. If this occurs, then the timing of subsequent visits should be calculated from the delayed visit to maintain the correct separation between subsequent visits. Where a delay of more than 7 days occurs, the scheduled visit should take place, but the trial medication will not be given. Subsequent visits will take place as originally scheduled.

Missed trial assessments or trial medication, or visits completed outside the visit window, will not be reported as breaches, where this is due to participant choice or a clinical decision.

[a] Vital Signs: Blood pressure, pulse, temperature, oxygen saturation
[b] Biomarker blood samples will be stored and analysed at the end of the trial
[c] to be collected from the opposite arm to the infusion
[d] a participant who does not have a positive sample for *P. aeruginosa* in the previous 24 months may submit two samples, at least 21 days apart, during the 35-day screening period. If these samples are both positive for *P. aeruginosa* then inclusion criteria 5 and 6 will be deemed met and the patient may be enrolled.
.[e] including pre-medication with antihistamine (see section 8.13)
[f] Vital signs will be recorded during infusion at 5, 30, 60, 120 and 240 mins after the start of the infusion and 30 minutes after end of infusion.

16.5. Appendix 5 – Safety Reporting Flow Chart

Activity	Responsibility	Timing	Comments
Review medical records and questioning of participant for evidence of AEs at all visits.	Trial staff	All visits	Recorded on eCRF system.
Review of recorded AEs for causality and seriousness	PI (or delegate)	Within 24 hour of recording	Recorded on eCRF and/or medical records.
Reporting SAEs - All SAEs need to be assessed and signed off by the PI or delegated doctor.	PI (or delegate)	Within 24 hours of becoming aware of SAE	SAE form: https://www.ahspartnership.org.uk/tasc/for-researchers/sops/safety-and-pharmacovigilance Reported to: Tay.pharmacovigilance@nhs.scot j.chalmers@dundee.ac.uk
Reviewing of SAEs	Sponsor	Within 24 hours of receiving SAE form	
Reporting of SUSARs to CA	Sponsor	Within 7 days if life threating or fatal. Within 15 days for others	

16.6. Appendix 6 – Amendment History

Amendment No.	Protocol version no.	Date	Author(s) of changes
N/A	2	05-05-23	M Band, J Chalmers
Details of changes made Inclusion of changes requested from MHRA, REC and Lead R&D review: Section IV: Clarification that DMC is independent and of frequency of DMC reviews Section IX: correction of typographical error in screening timeframe Section 2: Rationale to justify the selection of doses used Section 6.2: Removal of Foot note b for exclusion criteria 8 Section 7.1.1: Clarification of who was completing participant identification and sending out invitation letters Section 7.2: Clarification of who the “appropriate person” is for taking consent if participant loses capacity. Section 7.10: Clarification that participants will not be able to withdraw data and tissue Section 9.4: Clarification of risk Section 16.4: Clarification that eGFR is used for eligibility			
AM08	3	28-09-23	M Band, J Chalmers, J Stobo
Details of changes made: Key trial Contacts: updated with new trial statistician and data manager Sections III, 6, 10.1 Sections III, 7.3, 8.7.2: Clarification of timing of doses, requested by MHRA Sections 2, 2.1: Provision of reference for now published data Section 3.1 clarification of timing of outcome measures Sections 6.1, 7.1.2. Screening: clarification that additional sputum samples can be collected for eligibility during the screening period. Section 7.4: Clarification that administration of trial treatment will be by a member of the team blinded to trial treatment allocation Section 7.7: additional explanation of what blood samples may be used for Sections 7.9, 13.3, 16.4: addition of end of treatment qualitative questionnaire. Sections 7.10, 16.1: Clarification of assessment of allergic reaction grading Section 7.11: Clarification of where storage and analysis of samples will take place Section 8.4: Change to non-IMP supply Sections 8.4, 8.5, 8.6: Correction of associated document name (Pharmacy Manual)			

Section 8.6: Clarification of IMP and placebo accountability procedures
Section 9.2: Clarification of recording hospitalisations resulting from worsening bronchiectasis
Section 9.7: Correction of email for pregnancy reporting
Section 9.8: Clarification of definition of overdose
Section 10.1: Revision of sample size calculation.
Section 10.2: Clarification of shortened recruitment window
Section 13.7: Clarification that date of birth will be held within the IWRS
Section 14.1: Addition of reporting via ISCTRN
Section 16.4: Clarification of sputum sample collection
Throughout correction of typographical errors