GREAT-2
GRemubamab ErAdication Trial

Introduction

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

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

GREAT-2 website https://sites.dundee.ac.uk/great-2/

CI: Professor James Chalmers, University of Dundee

Trial Management: Tayside Clinical Trials Unit, University of Dundee

Sponsor: University of Dundee & NHS Tayside

BACKGROUND

- Bronchiectasis is a debilitating chronic respiratory disease characterised by cough, sputum production and associated with a vicious cycle of lung inflammation, and infection.
- Approximately one third of people with bronchiectasis become infected with a bacteria called *Pseudomonas aeruginosa* (*P. aeruginosa*).
  - Often becomes resistant to antibiotics.
  - Associated with a 7 fold increased risk of hospitalization and 3 fold increased risk of mortality
- The purpose of this trial is to test whether an intravenous infusion containing a new monoclonal antibody called Gremubamab can reduce the amount of infection with *P. aeruginosa*.

OBJECTIVE

- 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*.

GREMUBAMAB

- Monoclonal antibody therapy is a form of immunotherapy that uses monoclonal antibodies to bind specifically to certain cells or proteins.
- The objective is that this treatment will stimulate the patient's immune system to attack those cells
- Monoclonal antibody therapy is expected to work with the immune system to eliminate *P. aeruginosa* infection.
- New medication being developed by AstraZeneca.
- Previous trials:
  - Phase I trial (healthy volunteers) well tolerated, infusion reactions being the most common adverse events
  - Phase II trial (patients with ventilator associated pneumonia) well tolerated, provided dose guidance for GREAT-2
  - Ex-vivo experiments have shown Gremubamab dose dependently increased opsonophagocytic killing of *P. aeruginosa* by neutrophils from patients with bronchiectasis.
- Administered as intravenous infusion 4-weekly

PRIMARY OBJECTIVE

To evaluate the **efficacy of Gremubamab on *P. aeruginosa* bacterial burden** in sputum at week 12

Outcome Measure:
Change from baseline to end of treatment in sputum cultures (colony-forming unit)

Timepoint(s)
Baseline and day 84

Secondary Objectives	
Objectives	Outcome Measures
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 **pharmokinetics** of Gremubamab	Gremubamab pharmokinetics parameters through 168 days post dose. Over 168 days

Exploratory Objectives	
Objectives	Outcome Measures
To evaluate immunogenicity of Gremubamab	Gremubumab anti-drug antibody (ADA) response in serum through 168 days post dose
To determine the effect of Gremubamab on sputum colour	Murray sputum colour chart. Days 0, 7, 14, 28, 56 and 84
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

Treatment allocation

Participants will be randomised to one of three treatment arms:

		Dosage, form and strength	Frequency
Arm 1	Gremubamab	1500 mg intravenous infusion (reconstituted and diluted to a total volume of 250 mL)	Once every 4 weeks for total of 3 infusions
Arm 2	Gremubamab	500 mg intravenous infusion (reconstituted and diluted to a total volume of 250 mL)	
Arm 3	Placebo	Intravenous infusion of 30 mL (as supplied, and diluted to a total volume of 250 mL)	