GREAT-2 SIV training presentation

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)	

Training:

- TRuST IMP Accountability
- Randomisation: options to delegate to pharmacy or unblinded team
- IMP preparation
- Breach reporting

This presentation is a summary to highlight key points for the SIV

Please view each individual presentation for more details

And record in your individual Trial Training Log (filed in ISF)

Contact the Trial Manager if you have any queries Great-2-TM@dundee.ac.uk

IMP/Placebo Accountability for Clinical Trial Pharmacy

Requirements

- Delegated on Delegation Log
- TRuST training completed – this presentation
- TRuST log-in
- Printer

- For the GREAT-2 trial, the clinical trial pharmacy team are **unblinded** to treatment allocation.

TRuST Randomisation & Drug Accountability System

- Recording drugs received
- Dispensing/releasing drugs
- Recording drug returns
- Recording drugs disposal
- Recording damaged drugs
- Recording expired drugs
- Quarantining drugs
- Drug accountability

- TRuST can be accessed directly: https://hicservices.dundee.ac.uk/TRuST or from the GREAT-2 website https://sites.dundee.ac.uk/great-2/
- Login details will be sent out after training has taken place. If not received, click on “Forgotten Password” and enter your email as your username

- Login with your details; on first login you will be asked to change your password

If you forget your password click the forgotten password link and your new password will be emailed to you

If you have multiple projects using TRuST you will need to select the GREAT-2 trial from the dropdown menu.

Main Menu


trust
Tayside Randomisation SysTem
Project: GREAT-2 Test
TEST SITE
Site: Tayside
PHARMACY
Scan in Drugs
Release Drugs
Drug Returns
Drugs Disposal
Drug Accountability
Drugs on Shelf
Damaged Drugs
Discontinued Study Drugs
Expired Drugs
Quarantine

Recording drugs received (1)

Acknowledgement of Receipt of Clinical Trial Material

Study Name		**GREAT-2 Test**			
EudraCT	**2022-003215-28**	CTA		IRAS	**1005993**
Delivered to:		**01 - Tayside**			

Email a copy of the form within 7 working days to Tricia Mepham/tricia.mepham@sharpclinical.com

Please find enclosed the following supplies. Please check the quantity and condition of the supplies, complete the last 2 columns in the table below, sign and date to acknowledge receipt.

Please remember to scan in the individual pack IDs on the TRuST system within the next 7 days

Pack ID(s)	Batch	Expiry	Received (√ or x)	Comment? (e.g. item damaged/missing)
0200	321	01/04/2025		
0201	321	01/04/2025		
0202	321	01/04/2025		
0249	321	01/04/2025		
Total Quantity	**50**			

Packed By:		Date:	

Received By:		Date:	
Designation:			

SHARP CLINICAL, Unit 28, Heol Klockner, Heads of the Valley Ind. Estate, Rhymney, Tredegar, NP22 5RL, United Kingdom

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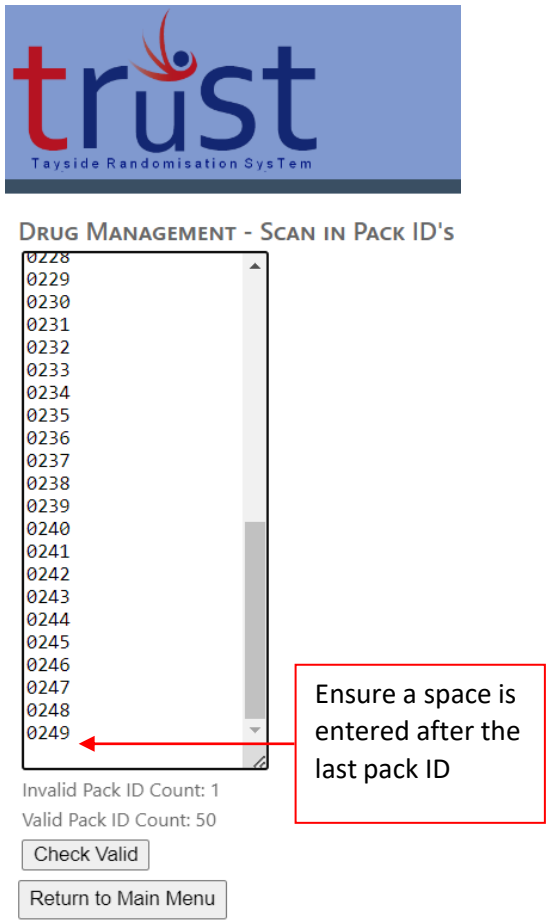
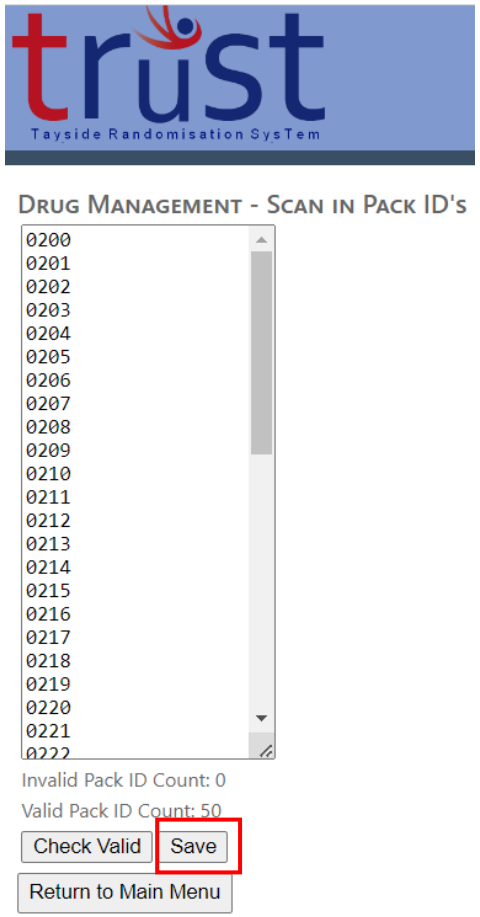
To be completed by SHARP Clinical Services Ltd:
Acknowledgement of receipt signed, dated and returned. Filed in Clinical Trial Folder.

- Acknowledgement of Receipt of Clinical Trial Material Form
  - Confirm receipt on form: complete “Received” column by placing a tick in each box.
  - If any packs are missing or damaged, documented under “Comments” column
  - Sign and date form under “Received By” (see next slide)
  - Email signed form to SHARP & file in PSF

Recording drugs received (2)
Scan in drugs





- Click “Scan in Drugs” from main Menu
- Enter pack IDs manually – one per line
- Ensure there is a space entered after the last pack ID
- Click “Check Valid”
- Remove any invalid bottle IDs added accidently
- When all pack IDs are valid, click “Save”
- Drug Accountability and Drugs on Shelf will be updated

Randomisation

Randomisation: Blinding

- The GREAT-2 trial requires both blinded & unblinded study team members
- If the site team are unable to have both blinded & unblinded team members, the role of randomisation may be delegated to the clinical trial pharmacist team
- Please see GREAT-2 site randomisation flow chart for responsibilities for both options
- Let the trial manager know who will be performing randomisation at your site

Role	Blinded or Unblinded
Person performing randomisation	Unblinded
Person completing page 1 of clinical trial release form	Unblinded
Trial doctor who signs IMP request form (unless using blinded IMP request form)	Unblinded
Person preparing IMP or placebo IV bag	Unblinded
Person who administers treatment & completes page 2 of Clinical Trial Release Form	Blinded
Person who performs trial assessments	Blinded

Clinical Trial Request Form – Blinded (Visit 2)

GREAT-2 GRemubamab ErAdication Trial

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

CLINICAL TRIAL REQUEST FORM FOR PHARMACY BLINDED

EudraCT	2022-003215-28	Sponsor	University of Dundee and NHS Tayside
IRAS	1005993	Protocol No.	1-023-22

Chief Investigator	Prof James Chalmers	Tel No	01382 386 131
Principal Investigator		Tel No	

To be completed by blinded trial team when pharmacy are carrying out randomisation:

Participant trial ID:			
Participant Name:			
Date of Birth:		CHI/hospital number:	
Visit Number:		Visit Date:	

Gender	Male / Female
A sputum sample that is culture or PCR positive for *P. aeruginosa* sent at the screening visit and within 35 days of randomization?	YES/NO
FEV1% at screening	
eGFR ml/min	
Inhaled Antibiotic Use?	YES/NO
Has the CI/PI signed CRF to confirm eligibility of participant?	YES/NO
Does the participant meet eligibility criteria?	YES/NO

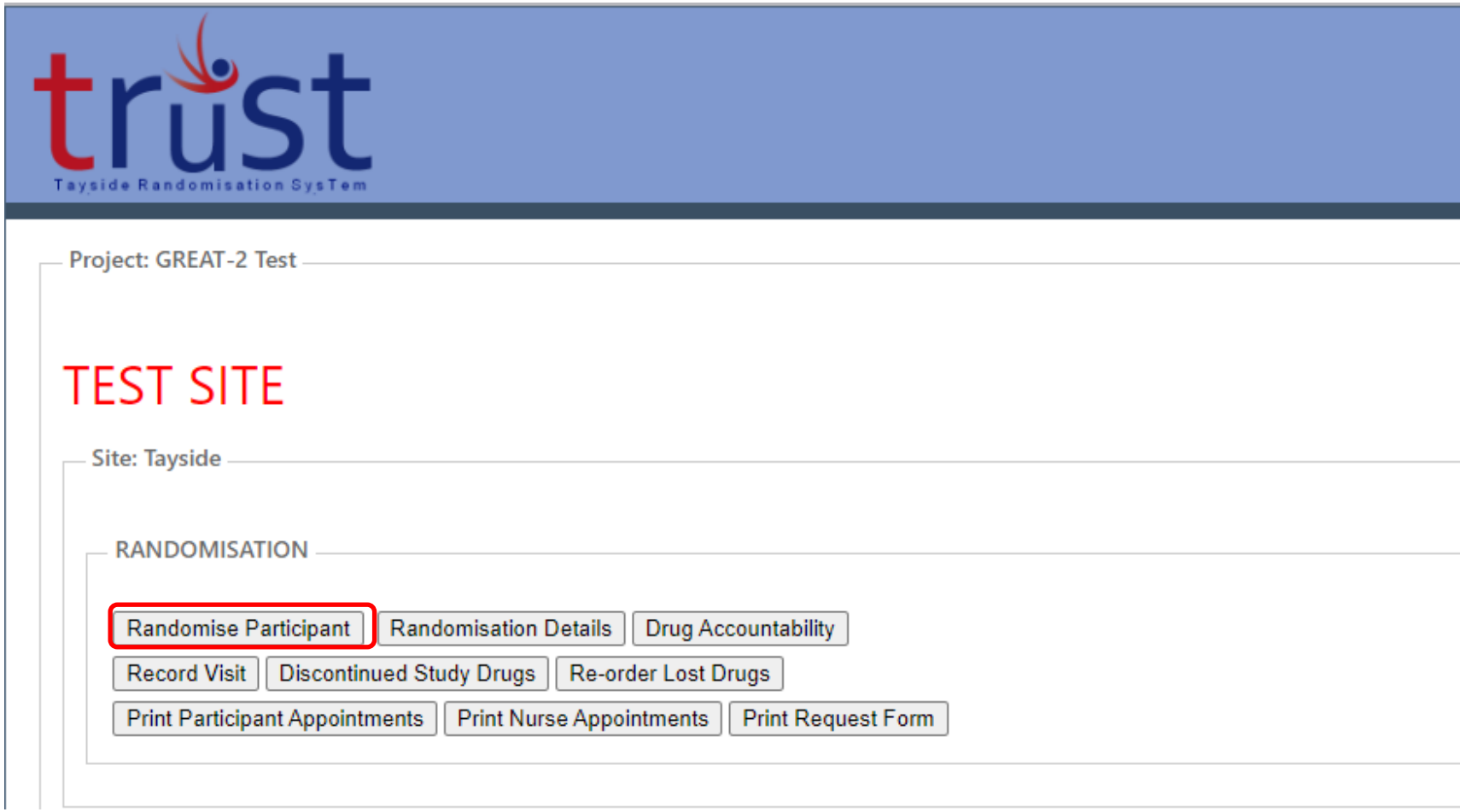
Please Supply	Gremubamab 1500mg / Gremubamab 500mg / Placebo
Total volume to be infused:	250 ml
Rate of infusion:	62.5 ml/hour

Delegate doctor's signature:	Date:
Print name:	

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

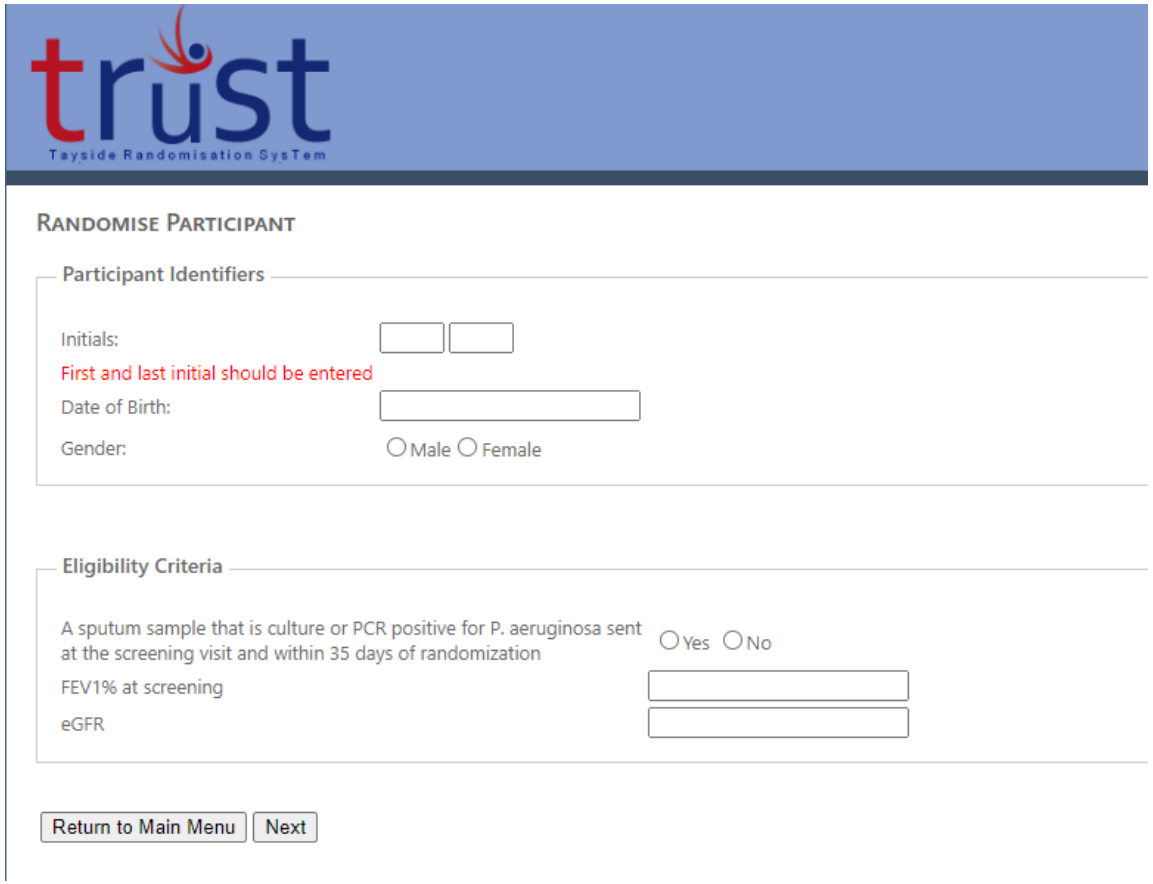
- This form is not generated by TRuST
- If pharmacy or unblinded team are delegated randomisation then the trial doctor can sign a **blinded** clinical trial request form if the site does not have an unblinded doctor
- Blinded research nurse should complete the participant details & eligibility questions
- The trial doctor and research nurse will remain blinded
- Take the completed Blinded Request Form to the person who is performing randomisation
- The clinical trial request form should be filed in the PSF

Randomising a participant



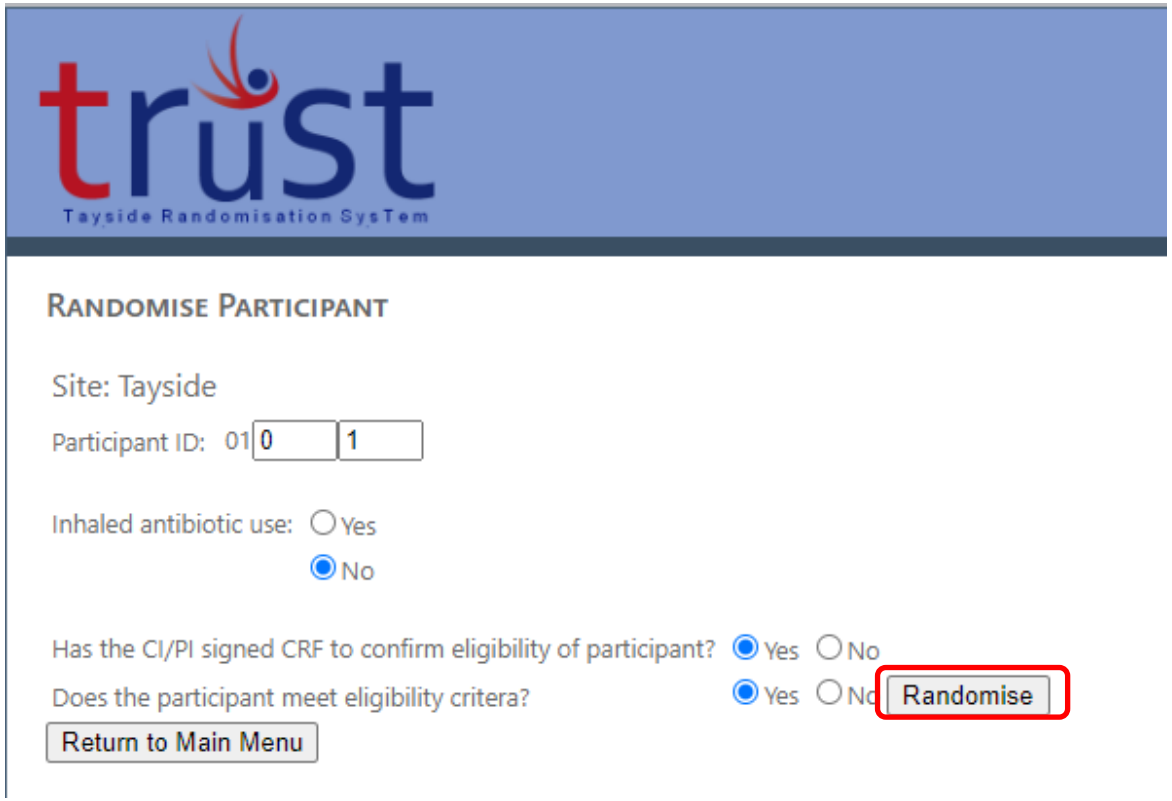
- Main menu.
- Click randomise participant.

Randomising a participant



- Enter participant identifiers
- Complete eligibility criteria questions
- Click next

Randomising a participant

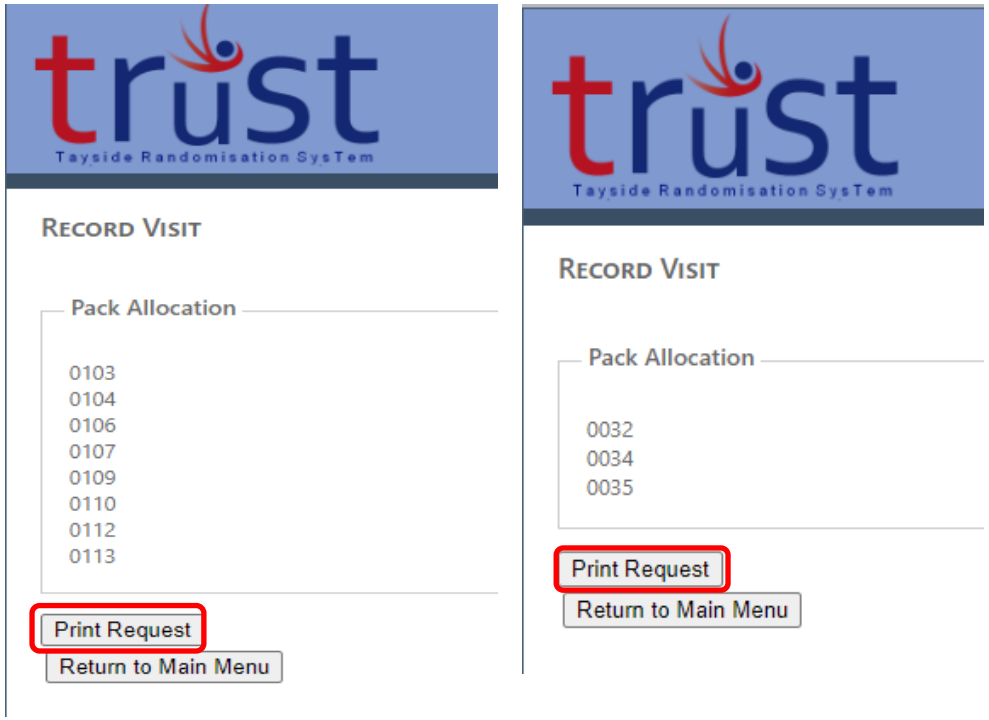


- Enter participant ID. The first number is provided and is the site number. Enter the 2 further digits. E.g. for the first patient consented enter “01”.
- To confirm what Participant IDs have already been used at your site, go back to main menu and click “randomisation details”.
- Complete randomisation questions
- **It is an MHRA and GCP requirement that a medical doctor confirms eligibility prior to randomisation.**
- Click randomise button

Randomising a participant

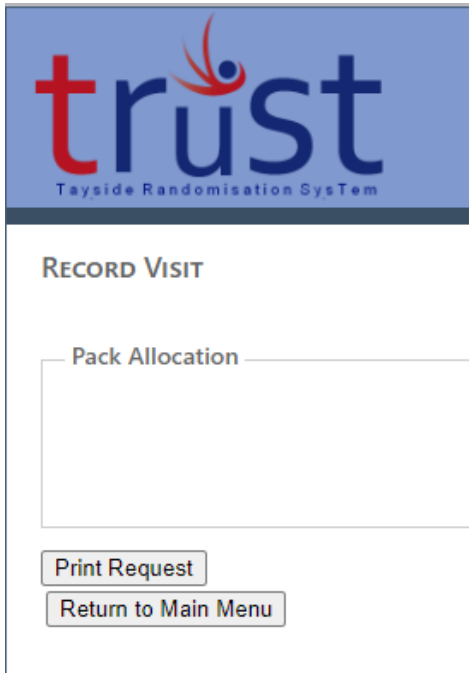
- Randomisation notification will be displayed
- You will receive an email confirming this allocation
- Click “Record Visit” to display the pack ID allocation.

Print Clinical Trial Request Form



- After clicking “Record Visit”, the pack ID allocation will be displayed
- The number of pack IDs allocated to a visit depends on the treatment allocation:
- 8 pack IDs are allocated for Gremubamab high dose
- 8 pack IDs are allocated for placebo treatment allocation
- 3 pack IDs are allocated for Gremubamab low dose
- Click on “Print Request” to generate the Clinical Trial Request Form for Pharmacy.

Insufficient IMP stock



- If the Pack Allocation box does not display any pack IDs, this indicates that your site has no remaining stock for that treatment allocation.
- If the number of pack IDs listed under Pack Allocation is less than the correct amount for the treatment, this indicates that your site has insufficient stock of the randomised treatment.
- **Do not proceed with the randomisation and contact the trial manager immediately.**

Clinical Trial Request Form - Unblinded

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

CLINICAL TRIAL REQUEST FORM FOR PHARMACY

EudraCT	2022-003215-28	Sponsor	University of Dundee and NHS Tayside
CTA		Protocol No.	1-023-22
IRAS	1005993	Local CTP ID	

Chief Investigator	Prof James Chalmers	Tel No	01382 386131
Principal Investigator	Prof James Chalmers	Tel No	01382 386131

Participant ID:	0119		
Participant Name:			
Date of Birth:	17/03/1971	Hospital Number/CHI:	
Visit Number:	2	Visit Date:	04/04/2023

Randomised to	Placebo
Total volume to be infused	250 ml
Rate of infusion	62.5 ml/hour
Please Supply	
Sodium chloride 0.9% (250ml/500ml)	1 bag
Gremubamab 200mg/Placebo 4ml	8 vials
Water for injection	0 ml

Please Supply	Gremubamab 1500mg/Gremubamab 500mg/Placebo					
Dose	200mg for Gremubamab per pack/4ml for Placebo per pack					
Pack ID						
0138	0141	0144	0147	0150	0153	0156
0159						

Investigator's or delegate's Signature:		Date:
Research Nurse's Signature:		Date:

FOR TRuST Validation:			
Barcodes			
0138	0141	0144	0147
0150	0153	0156	0159

- This form is generated by TRuST
- Complete the GREAT-2 Clinical Trial Request Form by filling in the participant name and hospital number/CHI.
- Ensure the form is signed by an **unblinded** study doctor who is delegated this task on the Delegation Log (this cannot be the PI) and take this to Pharmacy
- If the unblinded Clinical Trial Request Form (Visit 2) has been signed by a blinded doctor, then the IMP Request Form generated by TRuST does not need to be signed
- Take Request Form to the Clinical Trial Pharmacy and collect trial drugs as per usual local practice
- Clinical trial request form will be filed in the PSF

Clinical Trial Release Form – page 1

- Clinical Trial Pharmacy (CTP) or unblinded team members will prepare the IV bag with the IMP or placebo vials, according to the pharmacy manual
- When the vials of IMP/Placebo are released from clinical trial pharmacy, TRuST will generate a **Clinical Trial Release Form**

Important: page 1 of the Clinical Trial Release Form contains unblinded information. Only page 2 of the clinical trial release form should be given to the blinded team member along with the trial medication infusion. Ensure that the Clinical Trial Release Form is printed on 2 separate pages.

Clinical Trial Release Form – page 2

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

This sheet ONLY to be given with IMP infusion to blinded Research Nurse

EudraCT	**2022-003215-28**	Sponsor	**University of Dundee and NHS Tayside**
CTA		Protocol No.	**1-023-22**
IRAS	**1005993**	Local CTP ID	

Chief Investigator	**Prof James Chalmers**	Tel No	**01382 386131**
Principal Investigator	**Prof James Chalmers**	Tel No	**01382 386131**

Participant ID:	**0110**		
Participant Name:			
Date of Birth:	**21/08/2023**	Hospital Number/CHI:	
Visit Number:	**2**	Visit Date:	**04/04/2023**

Randomised to	**Gremubamab 1500mg or Gremubamab 500 mg or placebo**
Total volume to be infused	**250 ml**
Rate of infusion	**62.5 ml/hour**
Infusion made up by (signature)	
Date	
Time	
Print name	
Checked by (signature)	
Print name	
Infusion given by (signature)	
Date	
Start time	
Print name	
Checked by (signature)	
Print name	

- The blinded nurse giving the infusion to the participant must also sign, date and document the start time of the infusion. This information must be checked & signed by another team member (orange bracket)
- After the treatment has been completed, file signed infusion sheet in the ISF
- Infusion preparation should be completed as close as possible to the time of treatment administration.
- **The time between preparation of the dose to administration should not exceed 4 hours at room temperate.**
- If storage time exceeds this, a new dose must be prepared using new pack IDs and the Trial Manager must be informed.

Randomisation & IMP preparation for sites who have both unblinded research nurses & unblinded doctor
Randomisation is performed by unblinded research nurse

Randomisation

- Blinded research nurse provides the randomisation details to the unblinded research nurse via an unsigned blinded Clinical Trial Request Form (Visit 2)
- Randomisation is performed by unblinded research nurse on TRuST
- The Unblinded Clinical Trial Request Form is generated from TRuST with randomisation allocation and pack IDs

Clinical Trial Request Form

- The Clinical Trial Request Form is generated on TRuST. This must be printed and signed by an unblinded research nurse & unblinded trial doctor
- The unblinded research nurse takes the signed Clinical Trial Request Form to Clinical Trial Pharmacy (CTP)
- The signed unblinded Clinical Trial Request Form must be filed in the PSF

IMP Release

- Clinical Trial Pharmacy release pack IDs on TRuST
- The Clinical Trial Release Form is generated on TRuST and printed
- Pack IDs are released to CTP staff or delegated unblinded team member to prepare IMP infusion
- Page 1 of the Clinical Trial Release Form is signed by CTP staff who released the IMP & the unblinded person collecting the IMP packs for preparation

IMP Preparation

- CTP or delegated unblinded team member prepare IMP with the IV bags provided
- Part of page 2 of Clinical Trial Release Form is completed by the unblinded team member who prepared the infusion
- Infusion is labelled with blinded IV bag labels that have been provided, IV bags are covered with coloured sleeves to protect from light
- The prepared IV bag & page 2 of the Clinical Trial Release Form are given to blinded research nurse to administer infusion
- The last section of page 2 of Clinical Trial Release Form is completed by the blinded person who administered the infusion. This must be filed in ISF.

Randomisation & IMP preparation for sites who have unblinded research nurses but do not have unblinded doctors

Randomisation is performed by unblinded research nurse

Clinical Trial Request Form

- A blinded Clinical Trial Request Form (Visit 2) is completed by blinded research nurse
- The blinded Clinical Trial Request Form is signed by a blinded research nurse & blinded trial doctor
- The blinded Clinical Trial Request Form is provided to the unblinded research nurse

Randomisation

- Randomisation is performed by unblinded nurse on TRuST, entering details from the blinded Clinical Trial Request Form
- Clinical Trial Request Form (unblinded) is generated from TRuST, this should be printed and filed in PSF alongside the signed blinded Clinical Trial Request Form
- The unblinded Clinical Trial Request Form does not require to be signed by a doctor as the blinded form has already been signed

IMP Release

- Clinical Trial Pharmacy release the pack IDs detailed on the unblinded Clinical Trial Request Form
- The Clinical Trial Release Form is generated on TRuST and printed
- Pack IDs & the Clinical Trial Release Form are provided to a delegated unblinded team member to prepare IMP infusion
- Page 1 of the Clinical Trial Release Form must be signed by CTP staff who released the IMP & the unblinded team member who will prepare IMP

IMP Preparation

- CTP or delegated unblinded team member prepare IMP infusion
- Part of page 2 of Clinical Trial Release Form is completed by the unblinded team member who prepared the infusion
- Infusion is labelled with blinded IV bag labels that have been provided, IV bags are covered with coloured sleeves to protect from light
- The prepared IV bag & page 2 of the Clinical Trial Release Form are given to blinded research nurse to administer infusion
- The last section of page 2 of Clinical Trial Release Form is completed by the blinded person who administered the infusion. This must be filed in ISF.

Randomisation & IMP preparation for sites who do not have unblinded research nurses
Randomisation is performed by clinical trial pharmacy

Clinical Trial Request Form

- A blinded Clinical Trial Request Form (Visit 2) is completed by blinded research nurse
- The blinded Clinical Trial Request Form is signed by a blinded research nurse & blinded trial doctor
- The blinded Clinical Trial Request Form is provided to Clinical Trial Pharmacy (CTP)

Randomisation

- Randomisation is performed by unblinded CTP staff on TRuST, entering details from the blinded Clinical Trial Request Form
- Clinical Trial Request Form (unblinded) is generated from TRuST, this should be printed and filed in PSF alongside the signed blinded Clinical Trial Request Form
- The unblinded Clinical Trial Request Form does not require to be signed by a doctor as the blinded form has already been signed

IMP Release

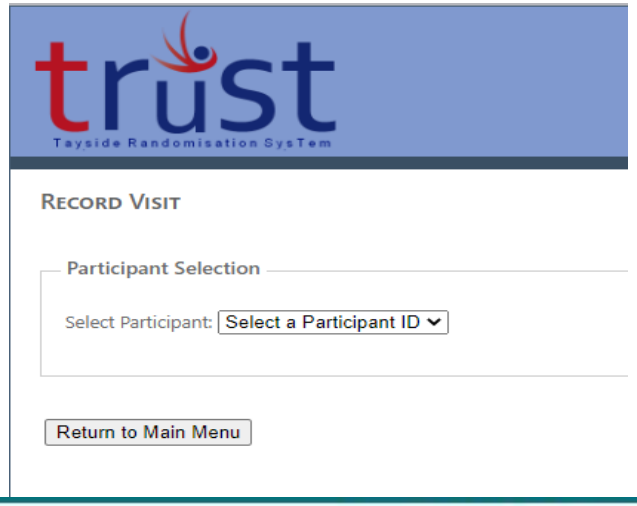
- Clinical Trial Pharmacy release the pack IDs detailed on the unblinded Clinical Trial Request Form
- The Clinical Trial Release Form is generated on TRuST and printed
- Pack IDs & the Clinical Trial Release Form are provided to a delegated unblinded team member to prepare IMP infusion
- Page 1 of the Clinical Trial Release Form must be signed by CTP staff who released the IMP & the unblinded team member who will prepare IMP

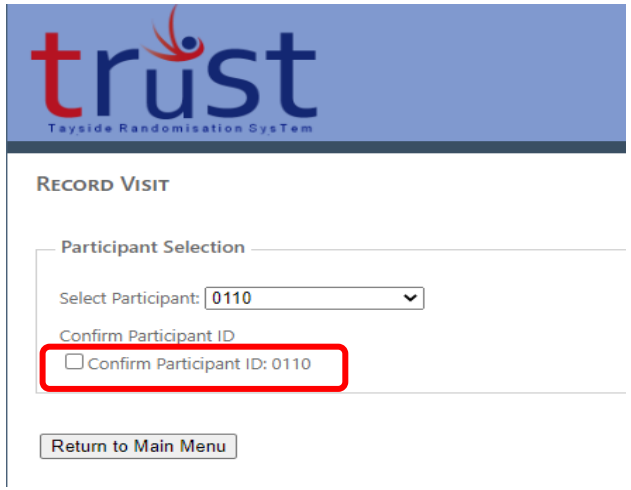
IMP Preparation

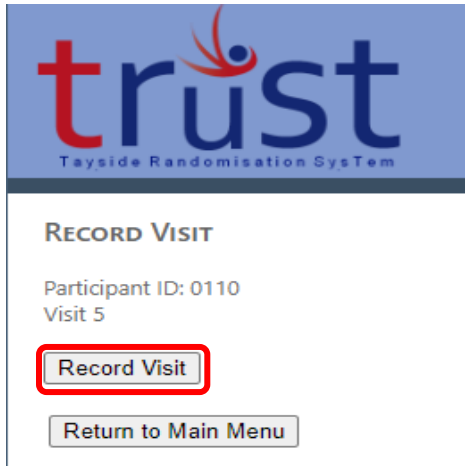
- CTP or delegated unblinded team member prepare IMP infusion
- Part of page 2 of Clinical Trial Release Form is completed by the unblinded team member who prepared the infusion
- Infusion is labelled with blinded IV bag labels that have been provided, IV bags are covered with coloured sleeves to protect from light
- The prepared IV bag & page 2 of the Clinical Trial Release Form are given to blinded research nurse to administer infusion
- The last section of page 2 of Clinical Trial Release Form is completed by the blinded person who administered the infusion. This must be filed in ISF.

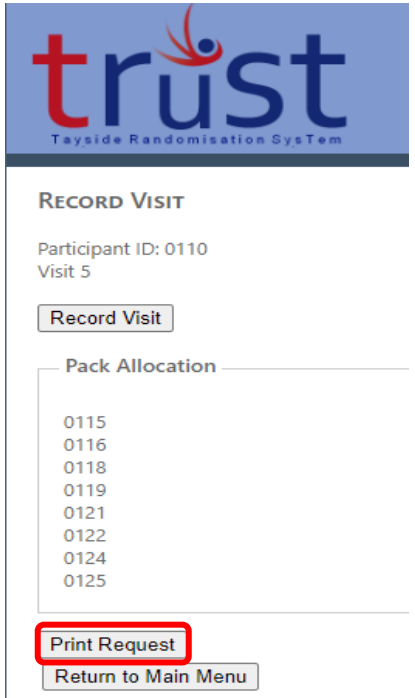
Printing Clinical Trial Request Form for visit 5 & visit 6

- From “Main Menu”, click on “Record Visit”
- Select participant ID from dropdown list:
- Tick “Confirm Participant ID”
- Click “Record Visit”
- Click “Print Request”, download & print.









Releasing IMP

Randomisation & allocation of pack IDs

If RN is performing the randomisation:

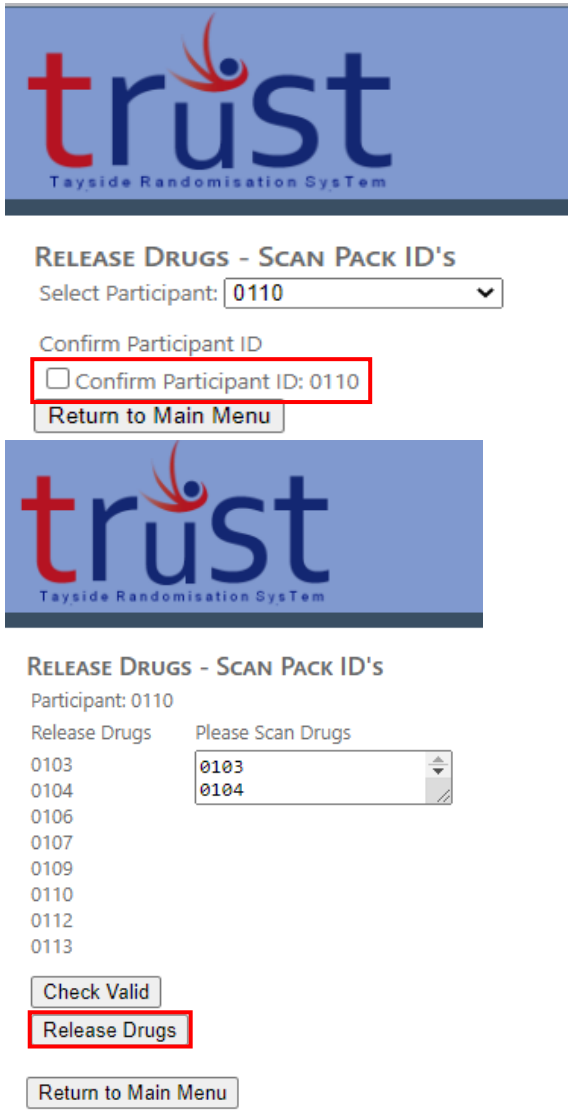
You will receive a hard copy of the Unblinded IMP Request Form from the Research Nurse after randomisation. This will list the allocated pack IDs for the participant. Either the Unblinded IMP Request Form or the Blinded IMP Request Form (visit 2) must be signed by a trial doctor.

If pharmacy is performing the randomisation:

Clinical Trial Pharmacy will receive a hard copy of the Blinded IMP Request Form before randomisation

A member of clinical trial pharmacy will perform the randomisation and this will allocate pack IDs to the participant

Dispensing/Releasing drugs (1)



- Click “Release Drugs” on Main Menu
- Select participant ID from the Clinical Trial Request Form
- Tick “Confirm Participant ID”
- Check pack IDs listed on TRuST match the pack IDs listed on the Clinical Trial Request Form
- Enter pack IDs listed on the Request Form in the “Please Scan Drugs” box - one pack ID per line, ensure there is a space entered after the last pack ID
- Click “Check Valid”
- If all pack IDs entered as valid, the Release Drugs button will appear
- Click “Release Drugs” to generate the Clinical Trial Release Form
- Print Clinical Trial Release Form
- Drug Accountability will be updated

Dispensing/Releasing drugs (1)
Clinical Trial Release Form Page 1

GREAT-2
GRemubamab ErAdication Trial

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

CLINICAL TRIAL RELEASE FORM

EudraCT	**2022-003215-28**	Sponsor	**University of Dundee and NHS Tayside**
CTA		Protocol No.	**1-023-22**
IRAS	**1005993**	Local CTP ID	

Chief Investigator	**Prof James Chalmers**	Tel No	**01382 386131**
Principal Investigator	**Prof James Chalmers**	Tel No	**01382 386131**

Participant ID:	**0105**

Randomised to	**Placebo**
Total volume to be infused	**250 ml**
Rate of infusion	**62.5 ml/hour**
Please Supply	
Sodium chloride 0.9% (250ml/500ml)	**1 bag**
Gremubamab 200mg/Placebo 4ml	**8 vials**
Water for injection	**0 ml**

Please Supply	**Gremubamab 1500mg/Gremubamab 500mg/Placebo**					
Dose	**200mg for Gremubamab per pack/4ml for Placebo per pack**					
Expiry	**13/02/2024**					
Quantity	**1 vial per pack**					
Pack ID						
0054	**0057**	**0072**	**0075**	**0102**	**0105**	**0108**
0111						

Released By:		Date:
Checked By:		Date:
Collected By:		Date:

FOR TRuST Validation:			
Barcodes			
0054	**0057**	**0072**	**0075**
0102	**0105**	**0108**	**0111**

Ensure that the Clinical Trial Release Form is printed on 2 separate pages.

Important: page 1 of the Clinical Trial Release Form contains unblinded information.

Page 1:

- Signed by the person releasing the pack
- Checked & signed by another member of the pharmacy team
- Signed by the person collecting the packs

Dispensing/Releasing drugs (2)
Clinical Trial Release Form Page 2

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This sheet ONLY to be given with IMP infusion to blinded Research Nurse

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Principal Investigator	**Prof James Chalmers**	Tel No	**01382 386131**

Participant ID:	**0105**		
Participant Name:			
Date of Birth:	**14/09/1955**	Hospital Number/CHI:	
Visit Number:	**2**	Visit Date:	**17/03/2023**

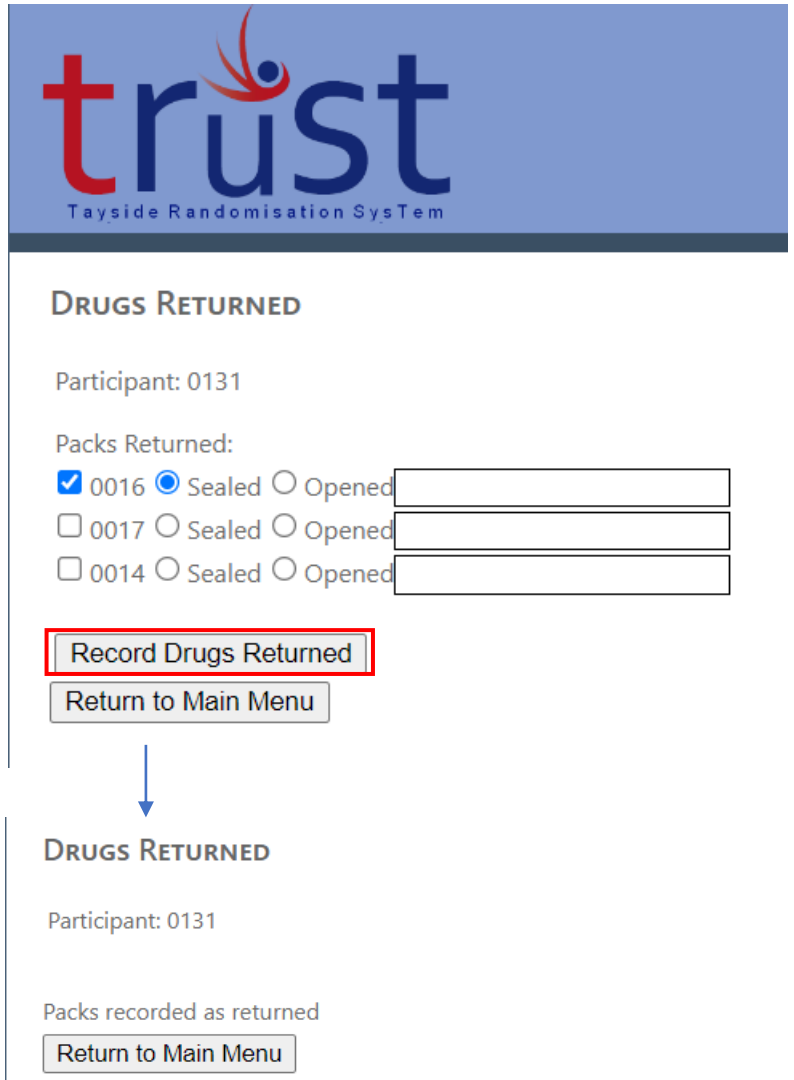
Randomised to	**Gremubamab 1500mg or Gremubamab 500 mg or placebo**
Total volume to be infused	**250 ml**
Rate of infusion	**62.5 ml/hour**
Infusion made up by (signature)	
Date	
Time	
Print name	
Checked by (signature)	
Print name	
Infusion given by (signature)	
Date	
Start time	
Print name	
Checked by (signature)	
Print name	

- Unblinded team member to prepare the IV infusion according to the IMP Management Plan
- IV infusion should be prepared as close as possible to when the treatment will be given.

Page 2:

- Sign “Infusion made by”
- Add date and time of infusion preparation
- Checked & signed by another member of the pharmacy team
- **Only** Page 2 to be given to the blinded team member and record of administration of infusion completed
- To be filed in ISF

Recording Drug Returns

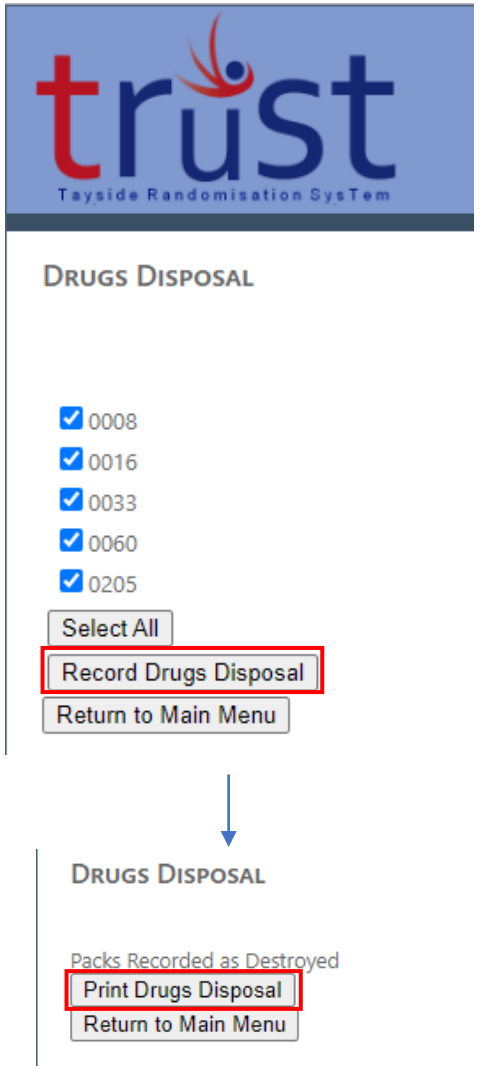


- Click “Drug Returns” on Main Menu
- Select and confirm the participant ID which the pack is allocated to
- Tick pack IDs which are being returned
- Select “Sealed” or “Opened”
- In the textbox, if you have selected “opened” enter the number of vials (e.g. “1”)
- Click “Record Drugs Returned”
- Drug Accountability will be updated

Clinical trial pharmacy should not record drug returns on TRuST for the ½ unused vial that will be remaining from each infusion. This should be documented locally as per local procedure.

Drug returns should only be recorded where a vial is not used due to other circumstances and the whole vial is unused.

Recording Drugs Disposal (1)



All drug returns may be disposed of immediately, there is no need to request permission from Trial Manger

At the end of the trial, wait until CTP have been requested by Trial Manager to dispose of any remaining drugs

- Click “Drug Disposal” on Main Menu
- This will list all of the pack IDs that have been marked as returned
- Tick the appropriate pack IDs
- Click “Record Drug Disposal”
- Print Clinical Trial Disposal Form
- Drug Accountability will be updated

Recording Drugs Disposal (2)

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CLINICAL TRIAL DISPOSAL FORM

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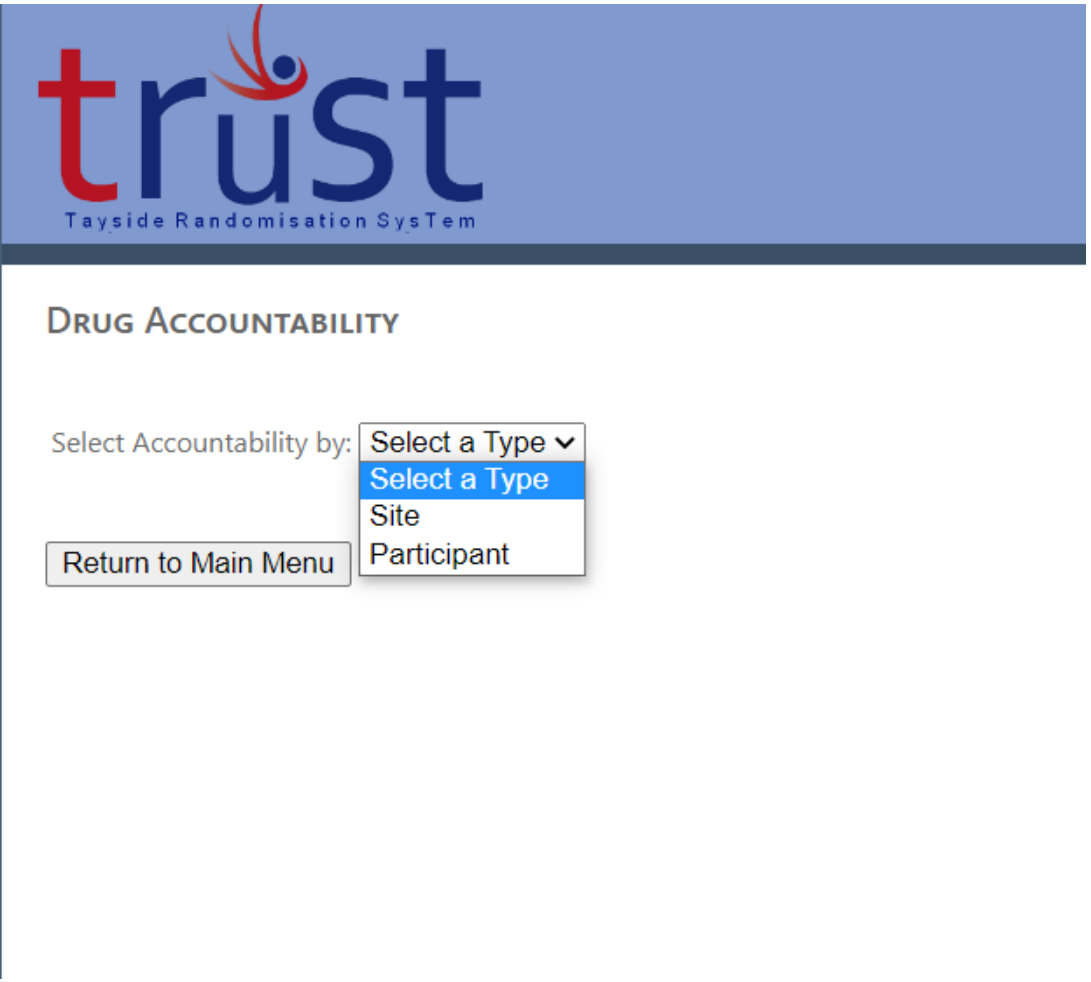
FOR PHARMACY USE:	
Pack ID:	**Quantity of Unused (vial per pack)**
0008	**1**
0016	**1**
0033	**1**
0060	**1**
0205	**1**

Disposed as CTP Policy by	
Date of Disposal	

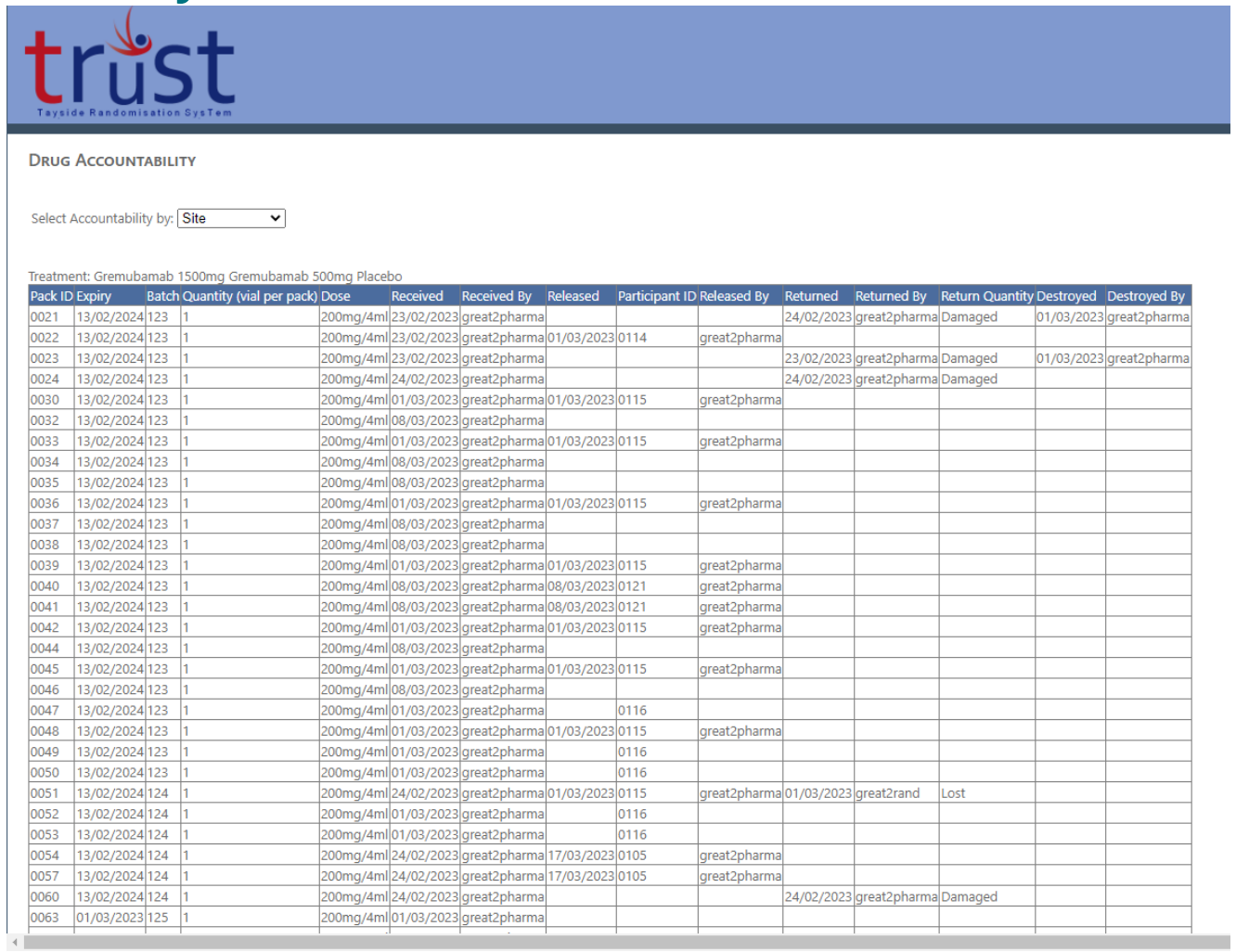
- Dispose of drugs as per local procedure
- Complete Clinical Trial Disposal Form
- File in PSF

Drug Accountability (1)



- Drug Accountability can be viewed as either a whole site or for individual participants.
- Drug accountability displays pack IDs and does not display which treatment each participant has been allocated to.
- Click “Drug Accountability” on Main Menu
- Select type of accountability to view
- Drug accountability can be viewed by site or by participant

Drug Accountability (2)
By Site



trust
Tayside Randomisation SysTem

DRUG ACCOUNTABILITY

Select Accountability by: Site

Treatment: Gremubamab 1500mg Gremubamab 500mg Placebo

Pack ID	Expiry	Batch	Quantity (vial per pack)	Dose	Received	Received By	Released	Participant ID	Released By	Returned	Returned By	Return Quantity	Destroyed	Destroyed By
0021	13/02/2024	123	1	200mg/4ml	23/02/2023	great2pharma				24/02/2023	great2pharma	Damaged	01/03/2023	great2pharma
0022	13/02/2024	123	1	200mg/4ml	23/02/2023	great2pharma	01/03/2023	0114	great2pharma					
0023	13/02/2024	123	1	200mg/4ml	23/02/2023	great2pharma				23/02/2023	great2pharma	Damaged	01/03/2023	great2pharma
0024	13/02/2024	123	1	200mg/4ml	24/02/2023	great2pharma				24/02/2023	great2pharma	Damaged		
0030	13/02/2024	123	1	200mg/4ml	01/03/2023	great2pharma	01/03/2023	0115	great2pharma					
0032	13/02/2024	123	1	200mg/4ml	08/03/2023	great2pharma								
0033	13/02/2024	123	1	200mg/4ml	01/03/2023	great2pharma	01/03/2023	0115	great2pharma					
0034	13/02/2024	123	1	200mg/4ml	08/03/2023	great2pharma								
0035	13/02/2024	123	1	200mg/4ml	08/03/2023	great2pharma								
0036	13/02/2024	123	1	200mg/4ml	01/03/2023	great2pharma	01/03/2023	0115	great2pharma					
0037	13/02/2024	123	1	200mg/4ml	08/03/2023	great2pharma								
0038	13/02/2024	123	1	200mg/4ml	08/03/2023	great2pharma								
0039	13/02/2024	123	1	200mg/4ml	01/03/2023	great2pharma	01/03/2023	0115	great2pharma					
0040	13/02/2024	123	1	200mg/4ml	08/03/2023	great2pharma	08/03/2023	0121	great2pharma					
0041	13/02/2024	123	1	200mg/4ml	08/03/2023	great2pharma	08/03/2023	0121	great2pharma					
0042	13/02/2024	123	1	200mg/4ml	01/03/2023	great2pharma	01/03/2023	0115	great2pharma					
0044	13/02/2024	123	1	200mg/4ml	08/03/2023	great2pharma								
0045	13/02/2024	123	1	200mg/4ml	01/03/2023	great2pharma	01/03/2023	0115	great2pharma					
0046	13/02/2024	123	1	200mg/4ml	08/03/2023	great2pharma								
0047	13/02/2024	123	1	200mg/4ml	01/03/2023	great2pharma		0116						
0048	13/02/2024	123	1	200mg/4ml	01/03/2023	great2pharma	01/03/2023	0115	great2pharma					
0049	13/02/2024	123	1	200mg/4ml	01/03/2023	great2pharma		0116						
0050	13/02/2024	123	1	200mg/4ml	01/03/2023	great2pharma		0116						
0051	13/02/2024	124	1	200mg/4ml	24/02/2023	great2pharma	01/03/2023	0115	great2pharma	01/03/2023	great2rand	Lost		
0052	13/02/2024	124	1	200mg/4ml	01/03/2023	great2pharma		0116						
0053	13/02/2024	124	1	200mg/4ml	01/03/2023	great2pharma		0116						
0054	13/02/2024	124	1	200mg/4ml	24/02/2023	great2pharma	17/03/2023	0105	great2pharma					
0057	13/02/2024	124	1	200mg/4ml	24/02/2023	great2pharma	17/03/2023	0105	great2pharma					
0060	13/02/2024	124	1	200mg/4ml	24/02/2023	great2pharma				24/02/2023	great2pharma	Damaged		
0063	01/03/2023	125	1	200mg/4ml	01/03/2023	great2pharma								

Official Trial Accountability Log – paper copy not required during trial

- Select Accountability by Site
- At end of trial the Trial Manager will inform CTP to dispose of any remaining drugs
- Drug Accountability Log must be printed after all remaining drugs and drug returns have been recorded and disposed of

Drug Accountability (3)
Current Stock

trust
Tayside Randomisation SysTem

CURRENT STOCK

Pack ID	Expiry	Batch	Quantity	Received	Received By
0003	13/02/2024	123	1	12/04/2023	great2pharma
0006	13/02/2024	123	1	12/04/2023	great2pharma
0009	13/02/2024	123	1	12/04/2023	great2pharma
0010	13/02/2024	123	1	12/04/2023	great2pharma
0011	13/02/2024	123	1	12/04/2023	great2pharma
0012	13/02/2024	123	1	12/04/2023	great2pharma
0013	13/02/2024	123	1	12/04/2023	great2pharma
0014	13/02/2024	123	1	12/04/2023	great2pharma
0015	13/02/2024	123	1	12/04/2023	great2pharma
0016	13/02/2024	123	1	12/04/2023	great2pharma
0017	13/02/2024	123	1	12/04/2023	great2pharma
0018	13/02/2024	123	1	12/04/2023	great2pharma
0019	13/02/2024	123	1	12/04/2023	great2pharma
0020	13/02/2024	123	1	12/04/2023	great2pharma
0025	13/02/2024	123	1	12/04/2023	great2pharma
0026	13/02/2024	123	1	12/04/2023	great2pharma
0027	13/02/2024	123	1	12/04/2023	great2pharma
0028	13/02/2024	123	1	12/04/2023	great2pharma

- Displays the current available stock
- Lists pack IDs which have been received on TRuST but have not been allocated to a participant yet.

Notes

Documents to be filed in PSF:

- Signed Acknowledgement of Receipt of Clinical Trial Material
- Signed Clinical Trial Request Forms
- Signed Clinical Trial Release Forms (page 1 only)
- Signed Drug Disposal Forms – at end of trial
- Complete Drug Accountability Form – at end of trial only

- Please document this training to your ‘Trial Training log’ held in the PSF

- Any questions contact GREAT-2 Clinical Trial Manager

Gillian Martin Great-2-TM@dundee.ac.uk 01382 381955

TRuST other functions

See GREAT-2 Training Presentation 3 Randomisation

- Recording IMP as discontinued
- Recording IMP as lost
- Allocating replacement packs
- Viewing randomisation details
- Viewing drug accountability

See GREAT-2 presentation 15 Pharmacy IMP Accountability

- Recording packs as damaged
- Recording packs as expired
- Quarantine packs

Emergency Unblinding

Unblinding

- Emergency unblinding will be carried out by the PI or delegate.
- TRuST access will be provided to the local PI for individual participant unblinding in the event of a medical emergency.
- Local Clinical Trial Pharmacy will hold unblinded Clinical Trial Request Forms, unblinding must be carried out in TRuST. TRuST informs Sponsor, CI and TM
- Disclosure of the unblinding result should be to individuals involved in the participant's care only.
- PI and those delegated this task must complete 3 dummy unblinding. This must be recorded in Training Log in ISF
- See the GREAT-2 Unblinding presentation for details of how to perform unblinding in TRuST

IMP/Placebo Preparation

Non-IMP Materials Required

Pharmacy/clinical site should procure:

- Water for injection
- Antihistamine
- Polypropylene syringes to be used for dose preparation.
- Low protein binding 0.2 µm or 0.22 µm filter
- Plastic IV bag coloured sleeves

Tayside Clinical Trials Unit will provide:

- 0.9% Saline 250 ml for infusion, these are PVC, other saline bags should **not** be used

IMP/Placebo preparation

- IMP & Placebo vials are to be stored at 2 – 8°C in clinical trial pharmacy
- Each vial contains:
  - Gremubamab 200mg lyophilised powder

  or
  - Placebo 4ml liquid
- Prior to infusion, Gremubamab 1500 mg and Gremubamab 500 mg will be reconstituted with sterile water for injection.
- Placebo does not require reconstitution
- Both Gremubamab will be diluted to a volume of 250ml 0.9% saline
- Preparation should always use aseptic technique.
- Gremubamab/placebo should not be removed from 2 - 8ºC storage until all other procedures required prior to participant dosing have been completed.

Clinical Trial Request Form – Clinical Trial Pharmacy Actions

- When an Unblinded Clinical Trial Request Form for Pharmacy is received, or after pharmacy have performed the randomisation, the clinical trial pharmacist must check the treatment allocation, check that the number of packs allocated is correct and ensure that the request form is signed before pack IDs can be released.

- The Clinical Trial Request Form must be filed in the pharmacy site file

Reconstitution of Gremubamab

- IMP preparation can be performed by a pharmacist or a study team member trained in drug preparation – individuals performing this role must be recorded on the delegation log

1) Clean the rubber stopper of the investigational product vial with 70% ethanol or equivalent and allow to air dry.

2) Tilt the vial containing Gremubamab and slowly add 4 mL of sterile water for injection such that the liquid stream is directed along the wall of the vial and not directly upon the lyophilized cake.

3) The solution must be swirled intermittently until all solids have been dissolved. DO NOT SHAKE OR VIGOROUSLY AGITATE THE VIAL. At the end of reconstitution, invert the vial to dissolve any product that might be on the cap.

4) Visually inspect to ensure that the entire content of the lyophilized product is reconstituted. The reconstituted solution should appear clear to opalescent and colourless to slightly yellow. A thin layer of bubbles on the surface of the liquid is normal.

5) If any proteinaceous strands are seen stop infusion preparation and inform the TM.

Infusion Bag Preparation

1) The IMP/placebo vial rubber stopper should be cleaned with 70% ethanol or equivalent and allowed to air dry. To avoid foaming, the vial should not be shaken.

2) Polyvinyl chloride (PVC) IV bags only and polypropylene syringes should be used for dose preparation as no incompatibilities have been observed between Gremubamab and these materials. Do not exceed the manufacturer specified maximum allowable needle sticks into the bag.

3) A volume of 0.9% (w/v) saline equivalent to the required investigational product dose volume (Table below) must be withdrawn from a pre-filled PVC infusion bag, supplied by Trial Management Team

4) The required volume of reconstituted Gremubamab or placebo (Table below) must be withdrawn from the vials using a 19-, 20-, or 21-gauge × 1.5 inch needle and added directly to the saline infusion bag.

5) Mix the bag by gently inverting to ensure homogeneity of the dose in the bag; do not shake the contents.

Infusion Bag Preparation continued

6) Label the infusion bag with the supplied Infusion bag Label. The following should be added to the infusion bag label

- Date and time of initial reconstitution – time of needle puncture of the first vial of Gremubamab or placebo
- Participant name
- Participant trial ID number

7) Gremubamab is sensitive to light. Therefore, plastic IV bag coloured sleeves of appropriate sizes should be used to ensure product quality is not compromised.

Volume of Gremubamab/Placebo to add to each dose

	Dose per vial	Final dose required	Number of vials required	Volume of sterile water to add to each vial	Volume of saline to remove from IV bag	Number of vials added to IV bag	Total Filled Bag Volume (mL)
Gremubamab 500 mg	200 mg	500 mg	3	4 ml	10 ml	2.5 vials = 10 ml	250 ml
Gremubamab 1500 mg	200 mg	1500 mg	8	4 ml	30 ml	7.5 vials = 30 ml	250 ml
Placebo	N/A	N/A	8	N/A placebo comes as 4 ml vial	30 ml	7.5 vials = 30 ml	250 ml

- Each dose preparation will have a remaining 2 ml that is not used (from the remaining unused ½ vial)
- Unused Gremubamab/ placebo should be disposed of and recorded by pharmacy as per local policy

Expiry of prepared dose

- Total in-use storage time from needle puncture of the first vial of Gremubamab or placebo for investigational product preparation to start of administration should not exceed 4 hours at room temperature or 24 hours at 2^{o}C to 8^{o}C.
- If storage time exceeds these limits, a new dose must be prepared from new vials and the TM must be notified immediately.
- Any unused portion must be disposed of as per local policy.

Breach Reporting

What is a breach?

- Any departure from:
  - Approved Protocol
  - Conditions of approvals
  - Principles of GCP
  - Written procedures (SOPs)
  - Regulatory requirements
  - Insurance cover
  - Contractual obligations
  - Confidentiality and GDPR
- Our Sponsor does not recognise deviations – all deviations should be classified as breaches and reported.

Breach reporting

- Breach reporting is the responsibility of the site team
- Breach reporting is made directly to the Sponsor
- Online breach reporting form must be downloaded from TASC website to ensure you are using correct version. The form can be found under TASC SOP59:

https://www.dundee.ac.uk/tasc/policies-sops-templates/study-progress

- Email copy of breach report form to tascpotentialbreach@dundee.ac.uk & copy in GREAT-2-TM@dundee.ac.uk
- Every breach must be documented on the Breach Log in the site file or pharmacy file

Corrective And Preventive Action (CAPA)

Corrective

- What did you do to fix it?

Preventive

- Preventive action is to stop the problem from happening again or to stop other sites doing the same
- What can you do to stop it happening again?

Are breaches always serious?

No.

- The majority are technical breaches that do not result in harm to the trial participants or significantly affect the scientific value of the reported results
- But…several non-serious breaches can become one Serious Breach as collectively they do have a detrimental impact
- Therefore ALL must be reported to Sponsor & to great-2-tm@dundee.ac.uk and documented on the Breach Log
- If you are unsure, report anyway

Documents required for site activation:

- Delegation Log
- Training Logs
- IMP received at site
- Lab packs received at site
- Access to TRuST for delegated team members for randomisation
- Access to TRuST for IMP release (pharmacy)
- PI trained & have access to unblinding on TRuST
- At least one team member trained and have access to Castor
- At least PI trained & have login details for the PV database