IMP Management Plan

Clinical Trial: **Value of inhaled treatment with Aztreonam lysine in bronchiectasis - VITAL- BE**

IRAS number: 252929

Chief Investigator: Prof James Chalmers

Sponsor: University of Dundee/NHS Tayside

This document describes the process for IMP management at site. The IMP in this trial is Cayston (Aztreonam lysine) 75mg for nebulisation and matching placebo.

Abbreviations / terms used

TM	Trial Manager
CTP	Clinical Trial Pharmacy
IMP	Investigational Medicinal Product
ISF	Investigator Site File
PSF	Pharmacy Site File
SOP	Standard Operating Procedure
TASC	Tayside Medical Science Centre
TRuST	Tayside Randomisation System

Appendices

1. Regulation of CTIMPs

Statutory requirements for the conduct of all interventional trials involving medicines are imposed by the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 which implement the requirements of EU directives 2001/20/EC and 2005/28/EC.

2. IMP

Each participant will be randomised to receive either Cayston or placebo 75mg three times per day. The Cayston/placebo is a powder and will be supplied in vials containing 75mg. The Cayston/placebo vials will be supplied to the participant along with saline ampoules (1ml 0.17% w/v sodium chloride) to be used for reconstitution by the participant prior to nebulisation. A nebuliser handset will be supplied to the participant with each 28 day treatment supply, can be dispensed by either the Pharmacist or Research team depending on local preference.

Participant treatment with IMP will be in 28 day cycles with participants taking the allocated dose for 28 days then no IMP for 28 days, repeated for the12 months of the trial, 6 cycles in total.

The Cayston/placebo vials, saline ampoules and nebuliser handsets will be provided free of charge to the CTP. The nebuliser machines to be used will be supplied free of charge to the research team and each participant will be given a nebuliser machine by the research team. The research team will be responsible for participant training in the reconstitution of the nebuliser solution and use of nebuliser handset and nebuliser machine.

3. Receipt

The stock control of the Investigational Medicinal Product (IMP) will be managed by the Tayside Randomisation System (TRuST) (see VitalBE TRuST Pharmacy Users Guide in PSF).

The Clinical Trial Pharmacy (CTP) at each site will receive shipments from Sharp Clinical Services via controlled refrigerated shipments. Each shipment will be accompanied by a QP Release Certificate, temperature tracker and an Acknowledgement of Receipt. The Acknowledgement of Receipt will be emailed back to Sharp Clinical Services and copied to the Trial Manager (TM) to confirm delivery. A copy of the QP Release Certificate and Acknowledgement of Receipt should be filed in the PSF.

The vials of IMP and saline ampoules will be packed separately:
Cayston/placebo will be packed in a box containing 28 vials and will have a pack ID on the box. Saline will be packed in a box containing 29 ampoules (1 spare in case of spillage). The same saline ampoules will be used for reconstitution of the active and placebo IMP.
On receipt, each IMP pack number must be entered in TRuST to log IMP stock. This will update the drug accountability on TRuST. If entry is not done on receipt a reminder email will be sent to the CTP after 7 days.
All boxes of vials will be referred to as packs on TRuST.

4. Initial Supply

Sites will receive:

- 12 packs of Cayston/placebo 75mg (28 vials)
- 12 packs of saline (29 ampoules)
- 5 nebuliser handsets – these may be held by research team if required

5. Re-supply

The TM will manage stock contacting Sharp Clinical Services to send further shipments depending on recruitment rates. Stock levels will be maintained to ensure CTP have sufficient stock to allow 2 participants to be randomised and sufficient stock to resupply participants already recruited.

Pharmacy should contact the TM if stock levels are causing concern. If the CTP anticipate an issue regarding the delivery of IMP supply the TM should be contacted.

6. Storage

Cayston/placebo 75mg vials

Must be stored securely in a refrigerator (between 2ºC and 8ºC)

A daily temperature log will be required (paper/electronic) and should be available for review as requested for auditing purposes, a file note should be filed in the PSF as to where this is held.

Any exposure to temperatures between 8.1ºC and 25ºC or between -20ºC and 1.9ºC, for less than 24 hours, will be reported to the Clinical Trial Manager (TM) a copy of the Temperature Log should be forwarded to the TM (see contact details below). There is no requirement to quarantine IMP in this instance.

The IMP will be quarantined by CTP and reported to the TM, by email, if the IMP is exposed to temperatures:

- below -20 ºC,
- or above 25ºC,

When reporting to the TM, temperature logs from the 4 weeks prior to the excursion should be provided. IMP supplies should be quarantined locally until a response from the Sponsor has been received. Reports of temperature excursions reported to the TM will be discussed with Sharp Clinical Services and/or Gilead and the Sponsor to identify what action is necessary. The TM will inform the site of any action necessary. See TRuST Pharmacy Users Guide, for details of recording quarantined IMP on TRuST.

Participants will be advised that the IMP vials may be kept out of the fridge, at room temperature, for up to 28 days. As the maximum time the IMP vials can be out of the fridge is 28 days the IMP vials MUST be stored in the fridge when in CTP.

Saline ampoules

Must be stored securely at room temperature (lower limit 2 ºC, upper limit 40 ºC).

A daily temperature log will be required (paper/electronic) and should be available for review as requested for auditing purposes, a file note should be filed in the PSF as to where this is held.

The saline will be quarantined by CTP and reported to the TM, by email, if the IMP is exposed to temperatures:

- below 2 °C,
- or above 40°C,

When reporting to the TM, temperature logs from the 4 weeks prior to the excursion should be provided. Saline supplies should be quarantined locally until a response from the Sponsor has been received. Reports of temperature excursions reported to the TM will be discussed with Sharp Clinical Services and/or Gilead and the Sponsor to identify what action is necessary. The TM will inform the site of any action necessary.

Participants will be advised that the saline ampoules may be kept at room temperature.

7. Accountability

IMP accountability records will be maintained by TRuST. A drug accountability log (See Appendix 2) can be generated from TRuST if required locally. The use of a paper accountability log is optional and at the discretion of each site. Where IMP at site is due to expire TRuST will alert the CTP pharmacist and request its disposal and will alert Sharp Clinical Services to send out replacement supplies.

a) IMP Release

IMP will be released for each participant as defined by visit schedule, (see Appendix 3) on receipt of a VitalBE Clinical Trial Request Form generated by TRuST (see Appendix 4). The VitalBE Clinical Trial Request Form must be signed by both the PI or their delegate and a Researcher both of whom should be named on the delegation log. The PI or delegate may sign the request form up to 7 days prior to the day of the participant visit, except on randomisation visit. The Researcher must sign the request form on the day of the participant visit to confirm that there has been no significant change since the investigator/delegate signature which makes it inappropriate for the participant to continue in the trial.

The VitalBE Clinical Trial Release form will indicate that the IMP should be taken 3 times per day and three pack IDs to be dispensed to the participant for each 28 day cycle.

Any known allergies to any of the IMP ingredients will be documented as exclusion therefore the participant will not be randomised.

Participant Name, date of dispensing and number of doses per day will be added by CTP staff to each pack at time of release.

The packs dispensed will be logged via TRuST by entering the pack ID. A VitalBE Clinical Trial Release Form (see Appendix 5) will be generated by TRuST. The pharmacist or delegate should print, sign and date the release form. The TRuST

system will not allow a release form to be printed where the entered pack IDs do not match the pack IDs on the request form. Visual confirmation of the correct pack ID number on each box should be checked against the release form. Please see VitalBE TRuST Pharmacy User Guide.

The VitalBE Clinical Trial Request and Release Forms should be filed in the PSF.

NB. The participant name plus hospital number/CHI (if required by local policy) will be hand written on the VitalBE Clinical Trial Request Forms by requester to ensure no personal details are evident on TRuST.

A nebuliser handset should be dispensed along with each 28 day treatment supply. If the handset is dispensed by the research nurse/team instead of pharmacy team, this will be hand-written by the Pharmacy staff on the VitalBE Clinical Trial Release Form.

b) Visit schedule

See appendix 3.

c) Participant storage of IMP vials and extra collections

Where a participant anticipates a problem storing the IMP vials in their fridge they will be advised that the IMP vials may be stored at room temperature for up to 28 days. Where the dispensing schedule means that the IMP vials will not be used within 28 days and the participant is not able to store them in a fridge, packs will be held in CTP for collection by/courier to the participant prior to commencing their next treatment cycle. This should be documented locally.

d) Delivery of IMP to participant

At visits 3 and 4 IMP should be either collected by the participant or couriered to the participant following local SOP ensuring delivery prior to the start of the participant's next treatment cycle. Temperature monitoring during delivery is not required, however, delivery to a participant must be same day delivery and the time from removal from CTP fridge to delivery to participant must be minimized.

e) IMP Vial Returns

IMP vial returns from participants will be collected by the research team at each visit and returned to pharmacy. Each vial will be supplied with tamper evident closure; if unbroken this should be counted as unused. Where the tamper evident seal is broken the CTP staff should visually check if the vial has been used, if the vial appears to be unused this should be counted as such. CTP staff should count the total number of unused vials and enter this in TRuST.

Returned saline ampoules will not be recorded.

f) Loss of IMP

If a participant loses any of their IMP then the Research Nurse will request replacement pack for the lost IMP using TRuST, this will generate a VitalBE Clinical Trial Request Form and update the Drug Accountability Log. The VitalBE Clinical Trial Request Form can be printed from TRuST, signed and given to pharmacy for IMP release as normal.

g) Error in request/release forms

If an error occurs in completing the VitalBE Clinical Trial Request or Release Form prior to the release of the IMP a file note should be completed and a copy of

erroneous document(s) filed in the PSF. The correct request or release form should be printed from TRuST or if TRuST does not allow this, a blank copy of the form (held in the ISF and PSF) should be made and completed by hand. The TM should be made aware of any errors to enable an auditable correction on TRuST. Where an error is noticed after dispensing the appropriate action to recall the IMP should be made. The Principal Investigator and TM should be informed, and a Protocol Breach Report completed (held in PSF/ISF) as per trial procedures (see Appendix 6).

8. Disposal

After recording participant returns, any IMP vials and saline ampoules will be disposed of at site following local disposal/destruction policy; this may be carried out as unused IMP is returned and logged on TRuST and does not require additional permission from the Sponsor. This should be entered on TRuST and a Clinical Trial Disposal Form (see Appendix 7) detailing what IMP vials have been disposed of will be generated by TRuST. This should be printed, signed and filed in the PSF. The number of saline ampoules will not be printed on the disposal form and should be written by hand.

Participants should dispose of handsets at home however, if participants return used handsets they should be disposed of, in clinical waste, by research team. They should not be returned to pharmacy and no record of handset return is required in the PSF.

TRuST will alert the sites by email of any IMP which has reached the expiry date and requires disposal.

A copy of the local disposal/destruction policy (or file note to location) should be filed in the PSF.

9. Emergency Unblinding

Emergency unblinding will be carried out by the PI or delegate.

Any clinician requiring the emergency unblinding of a participant should, where possible, discuss this with the Principal Investigator, however, this should not stall or delay in any way the unblinding of trial participant treatment in emergency situations. If unblinding is required the clinician should contact the local PI or delegate. A TRuST access code will be provided to the local PI which will permit individual participant unblinding in the event of a medical emergency. An unblinding form (see Appendix 8) should be printed and signed by person performing the unblinding. It is the responsibility of the local PI to ensure that adequate training and instructions are given for anyone delegated this role to enable them to access and perform the emergency unblinding procedure. For additional details of the emergency unblinding procedure see Appendix 9.

10. Storage Outside of Pharmacy

IMP should not be removed from pharmacy until the day it is to be given to the participant. Delivery of IMP, by a member of the research team, to a participant to be seen that day is not considered to be a “site to site transfer”. The time from removal from CTP fridge to delivery to participant should be minimized.

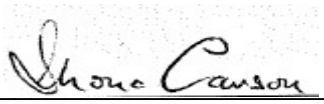
Where agreed with the Clinical Trial Manager, the IMP may be stored in another pharmacy within the NHS Trust.

11. Emergency Recall

If required, an emergency recall will be initiated by Sponsor, Sharp Clinical Services or Gilead. Site pharmacies, research teams, Principal Investigators and the Chief Investigator will be alerted by email with details of what action is required, for example disposal, quarantine or return of IMP. Information on what action is required for those participants in possession of the recalled IMP will also be provided. The TM will contact each of the sites to ensure the requested actions have been carried out.

12. Quarantine of IMP

If requested to by the Sponsor or if the storage conditions are out with the parameters described above (section 6), the IMP must be removed from the stock shelf and placed in a separate area. The IMP must be clearly marked as in quarantine and not to be dispensed. This should be entered on TRuST (see VitalBE TRuST Pharmacy User Guide). The IMP must remain in quarantine until the Sponsor has notified whether the IMP can be returned to the stock shelf and dispensed as usual or whether the IMP must be disposed of. When quarantine IMP is either returned to the stock shelf or disposed of this should be entered on TRuST.

Signed  Date 27/02/23

Shona Carson

Clinical Trials Pharmacist, Clinical Trial Pharmacy, Ninewells Hospital, Dundee

Contact details:

Clinical Trial Manager	respiratorytrials@dundee.ac.uk	01382 383265
Chief Investigator	j.chalmers@dundee.ac.uk	01382 386131
Lead Clinical Trial Pharmacist (Tayside)	shonacarson@nhs.scot	01382 632969

Appendices

9. Box and Vial Sample Labels
10. Drug Accountability Form
11. IMP Dispensing Schedule
12. Clinical Trial Request Form
13. Clinical Trial Release Form
14. Clinical Trial Disposal Form
15. Emergency Unblinding Form
16. Emergency Unblinding Procedure

APPENDIX 1

Box and Vial Sample Labels

Outer package of Cayston/Placebo vials	For Oral Inhalation only For use only with the Altera Nebuliser System Store refrigerated, 2°C to 8°C May be stored at room temperature (up to 25°C) for up to 28 days. Do not use product that has been stored at room temperature for more than 28 days. Contains: 28 single-use vials of Cayston or placebo 75mg EudraCT Number 2018-001590-24 Take …….. doses per day via inhalation as per the package leaflet. Pack number…… Participant name…… ID…… Expiry date…… Batch number…… Chief Investigator: Prof James Chalmers, Ninewells Hospital, Dundee DD1 9SY. Tel: 01382 383642 Keep out of the sight and reach of children For clinical trial use only
Outer package of saline ampoules	For Oral Inhalation only For use only with the Altera Nebuliser System Store at room temperature (up to 40°C) Contains: 29 diluent ampoules of sodium chloride (0.17% w/v sodium chloride) (1 extra ampoule provided in case of spillages) EudraCT Number 2018-001590-24 For use with Cayston as per the package leaflet.

	Participant name…… ID…… Expiry date…… Batch number…… Chief Investigator: Prof James Chalmers, Ninewells Hospital, Dundee DD1 9SY. Tel: 01382 383642 Keep out of the sight and reach of children For clinical trial use only
Vial labels	75mg Cayston/Placebo Reconstitute before use For oral inhalation only Expiry date…… Batch number…… EudraCT Number 2018-001590-24 Single use vial

APPENDIX 2

Drug Accountability Form per Participant

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IMP ACCOUNTABILITY FORM FOR PHARMACY - CAYSTON THREE TIMES PER DAY / PLACEBO THREE TIMES PER DAY

EudraCT	**2018-001590-24**	CTA Number	**21726/0289/001-0001**	IRAS	**252929**	Local CTP ID	
Chief Investigator	**Prof James Chalmers**	Tel No	**01382 386 131**	Principal Investigator		Tel No	

Participant ID:

PACKS					RECEIVED		RELEASED		RETURNED			DISPOSED OF	
PACK ID	Expiry	Batch no	Quantity (vials)	Dose	Date	User Login	Date	User Login	Date	User Login	Quantity	Date	User Login

Signed for Pharmacy Date:

APPENDIX 3

IMP Dispensing Schedule

IMP DISPENSING SCHEDULE						
	Screening Visit 1	**Baseline Visit 2**	**4 weeks Visit 3 telephone visit**	**12 weeks Visit 4 telephone visit**	**24 weeks Visit 5**	**48 weeks Visit 6**
Cayston/ placebo 75mg three times per day	Nil	3 packs of 28 vials IMP & 3 packs of 29 ampoules saline & 1 nebuliser handset*	3 packs of 28 vials IMP & 3 packs of 29 ampoules saline & 1 nebuliser handset*	3 packs of 28 vials IMP & 3 packs of 29 ampoules saline & 1 nebuliser handset*	9 packs of 28 vials IMP & 9 packs of 29 ampoules saline & 3 nebuliser handsets*	Returns only

Where the dispensing schedule means that the IMP vials will not be used within 28 days and the participant is not able to store them in a fridge, packs will be held in CTP for collection by the participant prior to commencing their next treatment cycle. IMP for visits 3 and 4 should be either collected by participant or couriered to the participant following to local SOP.

* Nebuliser handsets may be dispensed by either the Pharmacy or Research team depending on preference

APPENDIX 4 Clinical Trial Request Form

Value of inhaled treatment with Aztreonam lysine in bronchiectasis- VITAL- BE
CLINICAL TRIAL REQUEST FORM FOR PHARMACY

EudraCT	**2018-001590-24**	Sponsor	**University of Dundee and NHS Tayside**
CTA	**21726/0289/001-0001**	Protocol No.	**2016RC27**
IRAS	**252929**	Local CTP ID	

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

Participant ID:			
Participant Name:			
Date of Birth:		Hospital Number/CHI:	
Visit Number:		Visit Date:	

Please Supply	
Saline ampoules (29 ampoules per pack) - 1ml, 0.17% w/v sodium chloride	
Nebuliser handsets	**1**

Please Supply	**Cayston three times per day/ Placebo three times per day**					
Dose						
Pack ID						

Investigator's or delegate's Signature: May be signed up to 7 days prior to patient visit (except randomisation visit).		Date:
Research Nurse's Signature: To confirm that there has been no significant change since the investigator/delegate signature above which makes it inappropriate for the patient to continue in the study. If so please give details (To be signed on day of patient visit.)		Date:

FOR TRuST Validation:			
Barcodes			

APPENDIX 5 Clinical Trial Release Form

Value of inhaled treatment with Aztreonam lysine in bronchiectasis- VITAL- BE

CLINICAL TRIAL RELEASE FORM

EudraCT	**2018-001590-24**	Sponsor	**University of Dundee and NHS Tayside**
CTA	**21726/0289/001-0001**	Protocol No.	**2016RC27**
IRAS	**252929**	Local CTP ID	

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

Participant ID:

Please Supply	
Saline ampoules (29 ampoules per pack) - 1ml, 0.17% w/v sodium chloride	
Expiry	
Nebuliser handsets *	**1**

Please Supply	**Cayston three times per day/ Placebo three times per day**					
Dose						
Expiry						
Quantity	**28 vials**					
Pack ID						

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

FOR TRuST Validation:			
Barcodes			

VitalBE IMP Release Form V130-07-19 Download Date:

APPENDIX 6

TASC SOPs

TASC SOP 59: Reporting Breaches in Clinical Research

http://www.ahspartnership.org.uk/tasc/for-researchers/sops/research-governance

APPENDIX 7

Clinical Trial Disposal Form

Value of inhaled treatment with Aztreonam lysine in bronchiectasis- VITAL- BE

CLINICAL TRIAL DISPOSAL FORM

EudraCT	**2018-001590-24**	Sponsor	**University of Dundee and NHS Tayside**
CTA	**21726/0289/001-0001**	Protocol No.	**2016RC27**
IRAS	**252929**	Local CTP ID	

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

FOR PHARMACY USE:	
Pack ID:	**Quantity (vials)**

Disposed as CTP Policy by	
Date of Disposal	

VitalBE Disposal Form V1.0 30-07-2019 Download Date:

APPENDIX 8

Emergency Unblinding Form

Value of inhaled treatment with Aztreonam lysine in bronchiectasis- VITAL- BE

EMERGENCY UNBLINDING FORM

Unblinding should only occur when patient safety is compromised. Ensure there is a genuine need to perform unblinding

Sponsor	**University of Dundee and NHS Tayside**		
Protocol No.	**2016RC27**	EudraCT	**2018-001590-24**
Chief Investigator	**Prof James Chalmers**	IRAS	**252929**

Person Performing the Unblinding:	
Person Requesting the Unblinding:	
Role:	
Contact Number:	
Email:	
Reason for Unblinding Request:	
Date of Request:	

Study Participant ID:			Site:		
Pack ID:					
Date of birth:		Initials:		Gender:	

Unblinding Result

Aztreonam Lysine (Cayston) for inhalation 75mg three times per day/Matched placebo three times per day	

TRuST Unblinding Performed by:

Name:		Designation:	
Signature:		Date:	

Download Date: 01/02/2023 16:37:01

APPENDIX 9 Emergency Unblinding Procedure

Emergency Unblinding Procedure

- The PI will have responsibility for carrying out the unblinding procedure. This role may be delegated to appropriate staff to allow for 24 hour access to unblinding.

- The trial code should only be broken for valid medical or safety reasons e.g. in the case of a severe adverse event where it is necessary for the PI or treating health care professional to know which treatment the participant is receiving before the participant can be treated.

- Subject always to clinical need, where possible members of the research team should remain blinded.

13. TRuST Unblinding Login Details

Username: ……..

Password:……

The password will be emailed to the PI and this should be changed on first login with the new password written here.

- If the TRuST system is down the PI or delegate should contact the VitalBE Trial Manager or Chief Investigator during normal working hours or the NHS Tayside On-call Pharmacist for out of hours unblinding.

14. Local Contact Details

	Name	Contact details
Principal Investigator		
Delegate		
Out of hours		

- Contact details for PI, delegate and out of hours must ALL be completed.

15. Other contact Details

- **Clinical Trial Manager** available during normal working hours:
  Fiona McLaren-Neil

  01382 383830

  respiratorytrials@dundee.ac.uk

- **Chief Investigator** available during normal working hours if required:
  Prof James Chalmers
  0774 012 4122
  j.chalmers@dundee.ac.uk

- **NHS Tayside On-Call Pharmacist** out with normal working hours via Ninewells Hospital switchboard 01382 660111 ask for on call Pharmacist

16. Emergency unblinding procedure

- The PI will have responsibility for carrying out the unblinding procedure. This role may be delegated to appropriate staff to allow for 24 hour access to unblinding.

- A label will be put on the inside cover of the participants, medical notes on randomisation detailing the name of the trial, participant trial number, trial medication, PI details and contact for emergency unblinding. An alert sticker will be put on the outside of the participants' medical notes to alert readers that participants are in a clinical trial. Where electronic records only are kept local practice for alerting healthcare professionals to the fact that the participant is in a clinical trial will be followed, details of this practice should be filed in the ISF.

- The treating healthcare professional will contact the PI or delegate to request unblinding.

- The PI will be provided with login details (see above) for TRuST (Tayside Randomisation System) which will give access for unblinding.

- The PI or delegate will log on to TRuST and complete the unblinding procedure, see TRuST Users Guide. It is the responsibility of the PI to ensure that adequate training and instructions are given to delegates to access and perform the emergency unblinding procedure.

- The name of trial subject number or initials and date of birth or pack ID (available on IMP bottle) will be required.

- Where the participant's trial subject number is not known it may be possible to unblind using site, participant's initials and date of birth or pack ID number

- An Emergency Unblinding Form should be completed by the PI/delegate performing the unblinding. This is generated from TRuST and can then be printed and signed. Where it is not possible to print and sign an unblinding form immediately the PI or delegate should log on to TRuST and print and sign the form within 24 hours. The unblinding form should be sealed in an envelope and filed in the ISF.

- On receipt of the treatment allocation details the treating health care professional will deal with the participant's medical emergency as appropriate.

- The web-based system will email the PI, the CI, the Sponsor and the Clinical Trial Manager that unblinding has taken place but not of the treatment allocation details.

- The participant should remain in the trial where possible.