IMP Management Plan

Clinical Trial: **Superiority Trial Of Protease inhibition in COVID-19**

IRAS number: 281986

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 Brensocatib (INS1007) /placebo tablets 25mg.

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

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 Brensocatib or placebo 25mg once per day. The Brensocatib 25mg tablet is a film-coated, oral tablet available in a dose strength of 25mg. The tablets are round, biconvex, brown film-coated tablets. Each tablet contains active ingredient Brensocatib and the following inactive US Pharmacopeia/National Formulary or European Pharmacopoeia compendia ingredients: microcrystalline cellulose, dibasic calcium phosphate dihydrate, sodium starch glycolate, silicon dioxide, and glyceryl behenate. The tablet is film coated with hypromellose, polyethyleneglycol, titanium dioxide, iron oxide red, iron oxide yellow, and iron oxide black. The matching placebo tablet contains microcrystalline cellulose and sodium stearyl fumarate and is coated identically to Brensocatib tablets.

Participant treatment with IMP will be for 28 days. Where a participant is discharged from hospital, the remaining IMP will be issued to be taken at home. If a dose is missed, a replacement dose should be given within 10 hours of the missed dose. Should a dose be missed or unable to be taken for any reason, the treatment duration will not be extended.

The IMP should be given before breakfast at approximately the same time each day. On day of randomisation the first dose of IMP may be given up to 5pm, with the following dose before breakfast the next day. If a participant is randomised later in the day and IMP is not given prior to 5 pm the first dose should be given before breakfast the next day.

3. Receipt

The stock control of the Investigational Medicinal Product (IMP) will be managed by the Trial Manager.

The Clinical Trial Pharmacy (CTP) at each site will receive shipments from Sharp Clinical Services via controlled shipments. Each shipment will be accompanied by a QP Release Certificate and an Acknowledgement of Receipt. The Acknowledgement of Receipt will be emailed back to Sharp Clinical Services (see contacts below) 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.

Brensocatib /placebo will be packed in high-density polyethylene bottles containing 35 tablets and will have a pack ID on the bottle.

4. Initial Supply

Sites will receive:

- 10 bottles of Brensocatib /placebo 25mg (35 tablets) (site 01 Tayside to receive 20 bottles)

5. Re-supply

The TM will manage stock contacting Sharp Clinical Services to send further shipments depending on recruitment rates.

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

Brensocatib/placebo 25mg tablets

Must be stored securely between 2ºC and 30ºC.

A daily temperature log will be required (paper/electronic) for storage in CTP 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 IMP will be quarantined by CTP and reported to the TM, by email, if the IMP is exposed to temperatures:

- below 2ºC,
- or above 30ºC,

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 Insmed and the Sponsor to identify what action is necessary. The TM will inform the site of any action necessary.

7. Accountability

IMP accountability records will be maintained by each site. A drug accountability log is provided (See Appendix 1) Where IMP at site is due to expire the CTP pharmacist should alert the TM who will arrange with Sharp Clinical Services to send out replacement supplies.

a) IMP Release

IMP will be released for each participant in bottles of 35 to allow administration once per day for 28 days. Should a participant be discharged from hospital they will be provided with the remainder of the IMP to complete 28 days.

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

At Sites where all IMP will be kept in Pharmacy

Participant name, participant number, site name and date of dispensing will be added by CTP staff to each bottle at time of release.

At point of randomisation Tayside Randomisation System (TRuST) will generate a pack ID. The CTP will be notified of this allocation by email. A signed STOP-COVID19 Trial Request form (Appendix 2) along with a printed copy of the treatment allocation email will be taken to CTP which will confirm the treatment allocation. Following dispensing of the allocated bottle, the STOP-COVID19 Clinical Trial Request Forms should be filed in the PSF.

At sites where IMP may be stored outwith pharmacy, to enable Out-of-Hours access to IMP

CTP will approve a secure storage area that can be accessed by the Investigator or Research Nurse. IMP will be transferred to this storage area and an Accountability Log will be stored alongside. The Investigator or Research Nurse will select the correct bottle of IMP following randomisation

Participant name, participant number, site name and date of dispensing will be added by Investigator or Research Nurse to each bottle at time of release. The Accountability Log will be updated. The STOP-COVID19 Clinical Trial Request Form should be signed and then countersigned by a second person confirming that the correct bottle has been selected and details added to label are correct

Details of this process may be tailored to each participating site and will be approved by the Clinical Trial Pharmacy at site.

b) Loss of IMP

If a participant is discharged with tablets to take home and subsequently loses their IMP this will not be replaced. The Research Nurse should record the IMP as lost in the eCRF.

c) Error in request

If an error occurs in completing the STOP-COVID19 Clinical Trial Request prior to the release of the IMP a file note should be completed and a copy of erroneous document(s) filed in the PSF. A correct Request Form should be provided by the Research Nurse. 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 3).

d) Returns

Any IMP returned to CTP should be counted and logged on the accountability log (taking account of any current quarantine and infection control practices).

Where participants are discharged from hospital prior to completing the 28 day course of tablets the participant will be phoned on day 29 to ask them to stop taking the tablets and to ask how many are left. The Research Nurse will document the amount of tablets remaining on day 29 in the eCRF. Participants will be asked to return the bottle with IMP to the site in a stamped addressed envelope which will be provided to the participant. Participants will also receive written instructions on this.

8. Disposal

Any IMP returned to Clinical Trial Pharmacy should be disposed of at site following local disposal/destruction policy. Disposals should be recorded on the Clinical Trial Disposal Form (Appendix 4) This may be carried out as unused IMP is returned and does not require additional permission from the Sponsor.

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 5) 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 6.

10. Storage Outside of Pharmacy

When in use the bottle of tablets may be stored in the ward drug trolley or in a POD locker. A temperature log for storage outside pharmacy once the IMP has been allocated to a participant is not required. It must only be used for the participant detailed on the label and should go with the participant if they are transferred to a different ward and/or home with them on discharge.

Where agreed with the TM, 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 or Sharp Clinical Services. 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. 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.

Signed Shona Carson Date 06 JUL 2020

Shona Carson

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

Contact details:

Clinical Trial Manager	stop-covid19@dundee.ac.uk	01382 383097
Chief Investigator	j.chalmers@dundee.ac.uk	01382 386131
Lead Clinical Trial Pharmacist (Tayside)	shonacarson@nhs.net	01382 632969
Sharp Clinical Services	SCSUK-ShipmentRequests@sharpclinical.com	

Appendices

1. Drug Accountability Form
2. Clinical Trial Request Form
3. Clinical Trial Disposal Form
4. TASC SOPs
5. Emergency Unblinding Form
6. Emergency Unblinding Procedure
7. Sample Labels

APPENDIX 1

Drug Accountability Form

STOP-COVID19

STOP-COVID19: **S**uperiority **T**rial **O**f **P**rotease inhibition in **COVID-19**

IMP ACCOUNTABILITY FORM FOR PHARMACY

EudraCT	2020-001643-13	**IRAS**	281986	Local CTP ID	
Chief Investigator	Prof James Chalmers	**Principal Investigator**		Tel No	

PACKS			**RECEIVED**		**RELEASED**			**RETURNED**			**DISPOSED OF**	
Pack ID	Batch no	Expiry	Date	Signature	Date	Participant ID	Signature	Date	Quantity	Signature	Date	signature

Signed for Pharmacy Date:

APPENDIX 2 Clinical Trial Request Form

STOP-COVID19

STOP-COVID19: Superiority Trial Of Protease inhibition in COVID-19
CLINICAL TRIAL REQUEST FORM FOR PHARMACY

EudraCT	**2020-001643-13**	Sponsor	**University of Dundee and NHS Tayside**
IRAS	**281986**	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:	
Date:	

Please Supply	**Brensocatib (INS1007) / Placebo** **1 bottle of 35 tablets**
Dose	**25mg – one tablet once per day**
Pack ID	

Investigator's or delegate's Signature:		Date:	

APPENDIX 3

TASC SOPs

TASC SOP 59: Reporting Breaches in Clinical Research

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

APPENDIX 4

Clinical Trial Disposal Form

STOP-COVID19: Superiority Trial Of Protease inhibition in COVID-19

CLINICAL TRIAL DISPOSAL FORM

EudraCT	**2020-001643-13**	Sponsor	**University of Dundee and NHS Tayside**
IRAS	**281986**	Local CTP ID	

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

FOR PHARMACY USE:	
Pack ID:	**Quantity**

Disposed as CTP Policy by	
Date of Disposal	

APPENDIX 5

Emergency Unblinding Form

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.	**01.01.20**	EudraCT	**2020-001643-13**
Chief Investigator	**Prof James Chalmers**	IRAS	**281986**

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

Brensocatib 25mg one daily/Placebo 25mg once daily	

TRuST Unblinding Performed by:

Name:		Designation:	
Signature:		Date:	

Download Date:

APPENDIX 6 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.

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 STOP-COVID19 Trial Manager or Chief Investigator during normal working hours or the NHS Tayside On-call Pharmacist for out of hours unblinding.

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.

Other contact Details

- **Clinical Trial Manager** available during normal working hours:
- **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

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.

APPENDIX 7

Sample Labels