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

Participant Pathway

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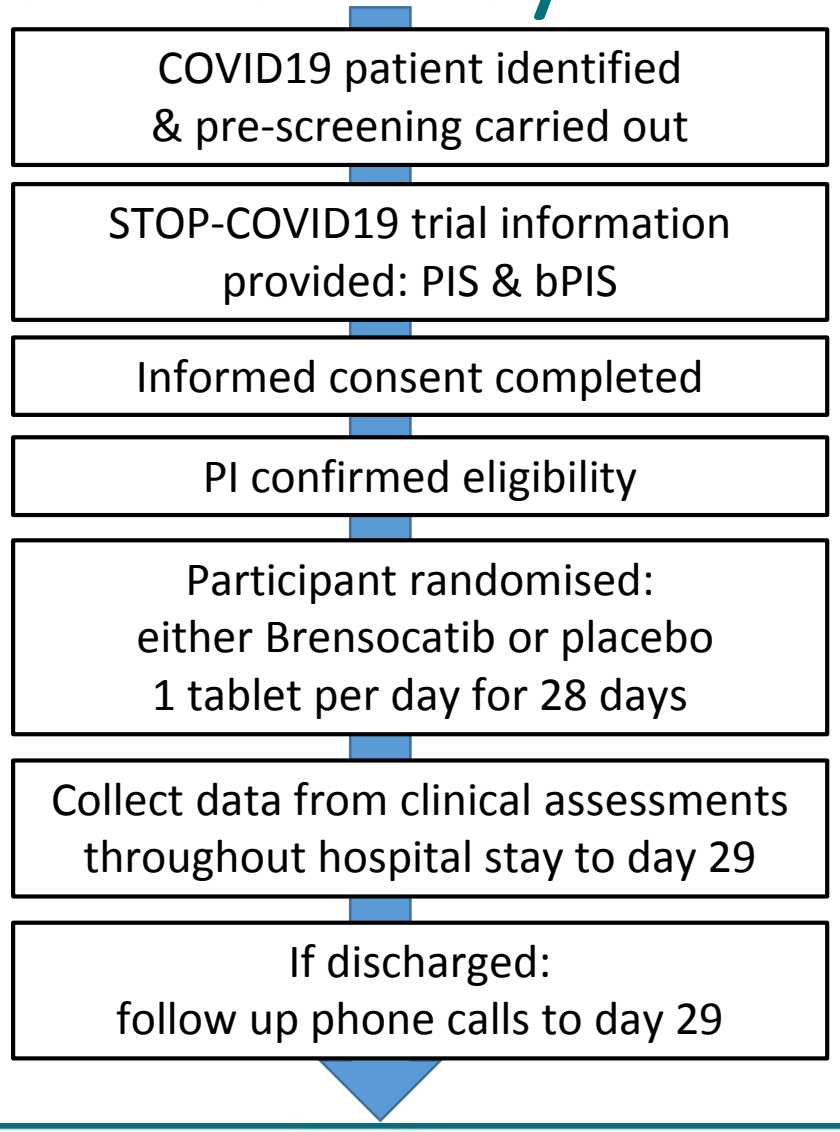

Pre-screen & Participant Identification

- Lab results to identify patients with confirmed SARS-CoV-2 within 96 hours

Or

- Clinically suspected COVID-19
- Patient lists from clinical team
- Check inclusion/exclusion via electronic or paper medical records:
  - Other labs - most recent result: within 72 hours
  - Eligibility slide set/film details Inclusion & Exclusion criteria
  - Delegated & named member of the trial team

Assessing Eligibility

- Pre-screening eligibility assessments:
  - Routine clinical care
  - Retrospective clinical assessment / medical record review
  - Most recent result - within 72 hours
  - No result available
    - ➢ Consent then trial staff request / carry out assessment.
- Any exclusion identified > stop screening
    - ➢ Screening log
- Co-enrolment STOP-COVID19 & RECOVERY
  - observational studies
- Confirm eligibility when all screening results are available
  - Meet all IC & no EC
  - PI/Medic confirm eligibility pre-randomisation
    - ➢ Medical Record PI confirmation

Informed consent

- Informed Consent slide set/film details:
  - Consent process
  - Infection control procedures
  - Adults who lack capacity
- Trained & Delegated trial staff
  - Appropriate location
- Face to face informed consent
  - PPE
  - Provide STOP-COVID19 participant/representative PIS & Brief PIS
- Due to the urgency of beginning treatment, patients may have <24 hours to decide
- Optional consent: future research using data and stored samples.

Recruitment Documentation

- Screening spreadsheet
- 3 PIS: Participant, Relative & Recovered Capacity
- 2 brief PIS: Participant & Relative
- 3 ICF: Participant, Relative & Recovered Capacity
- Medical record
- Enrolment & Randomisation Log
- Optional worksheets
- eCRF

Screening & Randomisation Options

Following Informed Consent:

- Combine screening and randomisation:
  - all screening results are available
  - AND PI (or medically qualified delegate) is available to confirm/sign-off eligibility
  - AND delegated trial staff are available to perform Randomisation
  - Dosing before 5pm.

OR

- Separate screening and randomisation:
  - No availability of trial team to perform Randomisation
  - No availability of screening sample results
  - No availability of PI, or medically qualified delegate, for eligibility sign-off
  - Clinical Trial Pharmacy closed / dosing before 5pm not achievable.

Screening / Randomisation

- Eligibility slide set/film provides detailed information
- Likely that assessments to determine eligibility will be carried out by the clinical team/routine care.
- Investigations/assessments carried out within previous 72 hours – use the most recent result; 96 hours for SARSCoV2
- Where not available research team request/collect samples
- Local lab analysis and ranges
- Where any result/finding is outwith inclusion/exclusion criteria the participant is not eligible and will not be randomised.

Screening Assessment

- Assessments to determine eligibility:

➢ Positive SARS-CoV-2 test result (within 96 hours) or clinically suspected

➢ Blood results (request if not in the last 72 hours):

- Urea & electrolytes, **creatinine and eGFR**, glucose, **ALT and/or AST**
- Full blood count - white cells, haemoglobin, platelets, **neutrophils**, eosinophils, **lymphocytes**

➢ Pregnancy test for women of child bearing potential (blood or urine)

➢ Females of child bearing potential & male partners are required to use highly effective contraception for 30 days after final IMP dose

Screening Assessment

- Focused Medical History, taken from medical notes:
  - Approximate day of onset of COVID-19 symptoms
  - History of chronic medical conditions related to IC/EC
  - Medication allergies re Brensocatib
  - Concomitant medications & therapies for current illness.
- Demographic and Clinical Information:
  - Age, Sex at birth, Ethnicity
  - Vital signs – BP, Pulse, SpO2, Tympanic Temperature
  - Supplemental O2
  - Clinical Support Status: 7-point scale (worst score so far that day)
  - NEWS2 (most recent)
  - Review recent radiographic imaging (x-ray or CT scan – infiltrates)
  - Physical examination findings related to IC/EC (rales & crackles)
  - ECG (tick box).

Randomisation Assessment

- Where screening/baseline assessments are separated use the most recent results for the following Clinical Information:
  - Vital signs: BP, Pulse, O2 saturation, Tympanic temperature
  - Supplemental O2
  - Clinical Support Status: 7-point scale (worst score for that day so far)
  - NEWS2
  - CT result
  - Con med changes
  - AEs.

Eligibility Confirmation

- Eligibility will be confirmed once all screening results are available.
- Patients are ineligible and will not be randomised if:
  - Any result/finding is out-with inclusion/exclusion criteria
  - They are likely to be transferred within 24 hours to another hospital which is not a trial site
  - They have used an investigational drug within a period equal to 5 times the elimination half life of the drug, or 30 days whichever is longer. Co-enrolment is allowed for COVID-19 trials as per agreements
- Record screening assessment in medical record and enter into STOP-COVID19 database/eCRF.

Randomisation

- Randomisation slide set/film details:
  - randomisation process

➢Participants will be randomised immediately following PI determination of eligibility

➢TRuST online randomisation system will be used

  - The trial is double blinded

➢Document in medical record

➢Inform GP: GP Letter.

Intervention

- Participants will receive one tablet per day (25 mg Brensocatib or placebo) in addition to standard of care treatment
- 28 day course of treatment
- IMP and placebo are provided by Insmed
- Tablets will be packaged in bottles, each containing 35 tablets.
- If a participant is discharged within 28 days they will be given the tablets to take at home; instruction to take to day 28.

IMP issue & Prescribing

- Clinical Trials Pharmacy
  - Research team member
  - IMP available for dosing
  - Clinical team responsible for storage and administration
- Storage @ 2-30°C
- Prescription chart completion by clinician
  - 28 days
- Administration recorded by clinical staff

Dosing

- The day of first dose will be classified as **Day 1**
- Once daily, before breakfast
- Administer with water
- Day 0 dosing before 5pm
- If NG tube: crush, dissolve in water, use syringe to push through tubs, flush with 10mL water, clamp for 30 mins then release.
- Missed dose:
  - give within 10 hours, record as late dosing
  - if over 10 hours wait for next dosing, record as missed.

Reasons for Discontinuation

Discontinue IMP for:

- Persistent SARs
- Allergy to IMP
- Neutropenia
- Commencement of following drugs: Itraconazole, Ketoconazole, diltiazem, verapamil, phenytoin or rifampicin - clinical decision by PI as to whether trial drug or restricted drug is stopped
- Pregnancy

Daily Assessments (1)

➢AEs

- Expected events that will **not be recorded** as AEs, are:

  Cough; pyrexia; headache; tiredness; diarrhoea; aches and pains; nasal congestion; runny nose; sore throat; anosmia (absent or decreased sense of smell); loss of taste; deterioration in renal and or liver function and changes in full blood count parameters .

- Pharmacovigilance and SAE reporting slide sets provide detailed information.

➢Concomitant medications

- Excluded: Itraconazole, Ketoconazole, Diltiazem, Verapamil, phenytoin, rifampicin

➢CT scan results (if done)

➢If **discharged**, collect AEs and con meds on **Days 3, 5, 8, 11, 15 and 29.**

Daily Assessments (2)

- **Clinical Support Status 7-point score;** worst score that day record retrospectively.

1. Not hospitalised, no limitations on activities
2. Not hospitalised, limitation on activities
3. Hospitalised, not requiring supplemental oxygen
4. Hospitalised, requiring supplemental oxygen
5. Hospitalised, on non-invasive ventilation or high flow oxygen devices
6. Hospitalised, on invasive mechanical ventilation or ECMO
7. Death.

- If **discharged**, telephone call assessment on **Days 3, 5, 8, 11, 15 and 29**.

Daily Assessments (3)

➢NEWS2 score

- Evaluated from assessments; closest to 8am
- Record total score, maximum 20

Physiological parameter	Score						
	3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9-11	12-20		21-24	≥25
SpO_2 Scale 1 (%)	≤91	92-93	94-95	≥96			
Air or Oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91-100	101-110	111-219			≥220
Pulse (per minute)	≤40		41-50	51-90	91-110	111-130	≥131
Conciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1-36.0	36.1-38.0	38.1-39.0	≥39.1	

Follow-up Assessments

- **Days 8, 15 and 29** during hospitalisation
  - Vital signs: BP, Pulse, O2 saturation, Tympanic temperature
  - Supplemental O2
- **Day 29** in hospital or telephone if discharged
  - EQ5D Interview version (if able)
  - IMP compliance check:
    - Hospital only IMP return

Follow-up Samples

- **Days 3, 5, 8, 11, 15 & 29** - use result closest to 8am

➢Urea and electrolytes

➢Renal function: creatinine & eGFR

➢Liver function tests: ALT & AST

➢Full blood count

- If not done for clinical reasons they will not be done specifically for the trial & for discharged participants:
  - treat as missing data.

Tayside & Sheffield Only Sub-Study

- Tayside/Sheffield Participant Information Sheets & Consent Forms
- Sample and data storage
- Laboratory Manual