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

Background and Overview

STOP-COVID19

Superiority Trial Of Protease inhibition in COVID-19

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Management: Tayside Clinical Trials Unit, University of Dundee

Sponsor: University of Dundee & NHS Tayside

Background to the Trial 1

- COVID-19 is a respiratory disease caused by novel coronavirus SARS-CoV-2, first identified in Wuhan, China in December 2019
- Mortality is estimated at 0.5-3.4% of infected patients, mostly due to development of acute respiratory distress syndrome (ARDS)
- ARDS is characterised by the infiltration of neutrophils into the airways
- Once activated the neutrophils release oxidants and proteases, designed to kill bacterial pathogens present in the airways
- This process becomes prolonged and excessive in ARDS leading to progressive lung damage
- In particular, neutrophil elastase, released from neutrophils, is thought to be central to this lung damage
- Efforts to develop inhibitors of neutrophil serine proteases such as neutrophil elastase for treating ARDS have been ongoing for many years

Background to the Trial 2

- Neutrophil serine proteases are normally activated in bone marrow by dipeptidyl peptidase 1 (DPP1) during the process of neutrophil maturation
- **Brensocatib**, a drug developed by Insmed Inc., USA, inhibits DPP1 - preventing the activation of neutrophil elastases and resulting in the release of neutrophils containing inactive neutrophil serine proteases
- The effect of Brensocatib develops over several days as circulating neutrophils are replaced by new neutrophils containing inactive neutrophil elastase
- Brensocatib is taken orally
- STOP-COVID19 participants will take a course of 1 tablet (25mg) Brensocatib per day for 28 days

Hypothesis

- The trial will test the following hypothesis:

Treatment with Brensocatib in addition to standard care will be superior to standard care alone in **achieving improved clinical status** in patients initially hospitalized with COVID-19.

Primary Objective

- To evaluate the **efficacy** of Brensocatib to **improve clinical outcomes** in COVID-19 by **day 29**

Outcome measure: Clinical support status 7-point ordinal scale measured on Day 29.

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 (Extracorporeal membrane oxygenation)
7	Death

Secondary Objectives 1: Clinical Efficacy

- Evaluate the **clinical efficacy** of Brensocatib relative to standard care in adult patients hospitalized with COVID-19

Secondary Objective	Outcome Measure	Timepoints
Clinical Severity	• Time to an improvement of one category from admission using 7-point clinical support status ordinal scale • Participant clinical status on 7-point ordinal scale • Mean change in the 7-point ordinal scale	Daily whilst hospitalised Days 3,5,8,11&29 Days 1,3,5,8,11&29
NEWS2	• Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first. • Change from baseline	Daily (hospitalized) Days 8,15,29
Oxygenation	• Oxygen free days • Incidence and duration of new oxygen use during trial	Days 1-29 Days 0-29
Mechanical Ventilation	• Ventilator free days • Incidence and duration of new mechanical ventilation use during the trial.	Days 1-29 Days 1-29
Hospitalisation	• Duration of hospitalisation (days).	Admission-Discharge
Mortality	• 28-day mortality	Date of death

Secondary Objectives 2: Safety

- Evaluate the **safety** of the intervention through 28 days of follow-up as compared to the control arm

Outcome Measures	Timepoints
Cumulative incidence of **Serious Adverse events (SAEs)**	Days 1-29
Discontinuation or temporary **suspension of treatment**	Days 1-29
Changes in **white cell count, haemoglobin, platelets, creatinine, total bilirubin, ALT & AST** over time (hospitalised participants only)	Days 1, 3, 5, 8, 11, 15 & 29
Adverse Events of special interest: hyperkeratosis, infections and dental complications	Days 1-29

Exploratory Objectives

- Quality of life

Outcome Measure	Timepoint
EQ-5D-5L administered in person if in hospital or if discharged via telephone	Day 29

- Evaluate the virologic efficacy of Brensocatib
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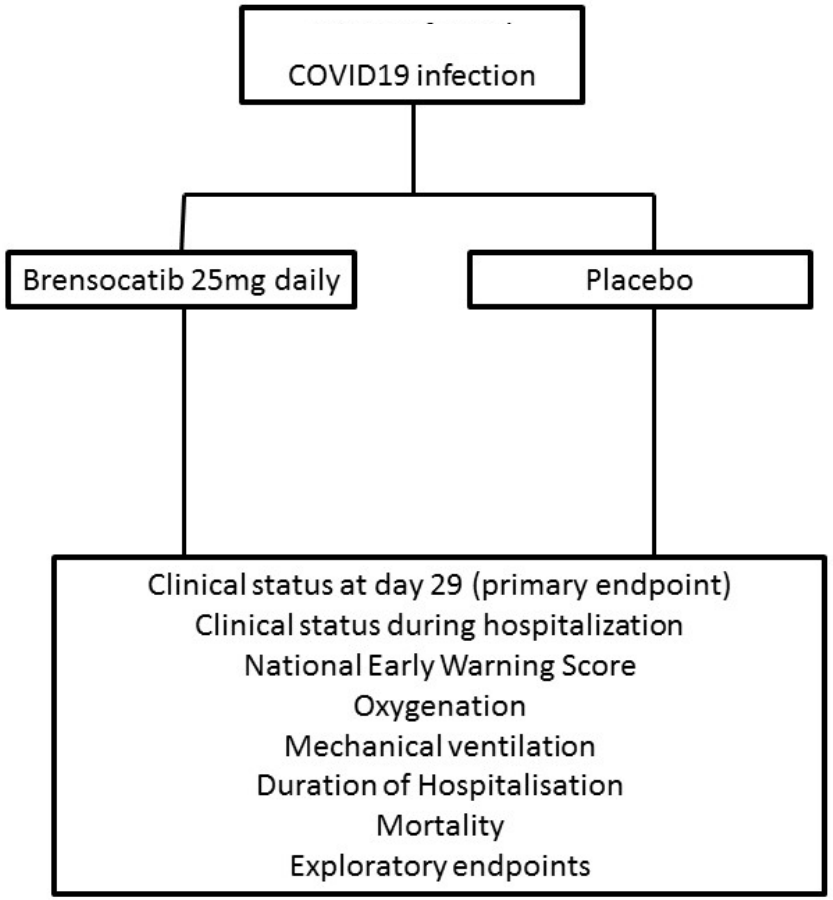
Outcome Measure	Timepoints
Percent of participants with SARS-CoV-2 detectable in Nasopharangeal sample	Days 15 & 29
Quantitative SARS-CoV-2 virus in Nasopharangeal samples.	Day 15 & 29
Neutrophil elastase and heparin binding protein measurement in blood	Days 1, 8, 15 & 29
Neutrophil functional studies: NET formation, phagocytosis, elastase release, neutrophil proteomics	Days 1, 15 & 29

Trial Design



- Target: 300 participants
- Enrolled from participating hospitals
- Randomized to receive Brensocatib or placebo

Standard Care

Participants in both arms will receive:

- All other therapies required to manage their condition (standard of care)
- No concomitant medications will be stopped for trial enrolment purposes.

Trial restrictions:

- Participants should not be prescribed Itraconazole, Ketoconazole, diltiazem, verapamil, phenytoin or rifampicin whilst taking trial medication.
- It will be a clinical decision by the PI as to whether trial drug or restricted drug is stopped.

Co-enrolment (1) - RECOVERY

RECOVERY and STOP-COVID have agreed that:

- Patients admitted to a hospital participating in both studies can be initially screened for participation in STOP-COVID19.
- If a patient is randomised to STOP-COVID19 they may then be co-enrolled into RECOVERY, all randomisation options in RECOVERY are available.
- RECOVERY and STOP-COVID19 will work closely together to share information on participating sites, interventions, and co-enrolments.

Co-enrolment (2)

- Co-enrolment into COVID-19 CTIMPs will be described in individual agreements between STOP-COVID19 and other trials. These agreements will be made available to recruiting sites.
- Where agreements are not in place for specific trials the site should contact the CI and co-enrolment will be decided on an individual participant basis. This decision will be documented in the participant's medical record.
- Co-enrolment into COVID-19 non-CTIMP intervention trials will be allowed.
- Co-enrolment to other non-COVID-19 Clinical Trials of Investigational Medicinal Product (CTIMPs) will not be allowed.
- Enrolment in observational trials or studies will be allowed.

Inclusion criteria

- Male or female
- ≥16 years
- SARS-CoV-2infection (clinically suspected+ or laboratory confirmed*).Admitted to hospital as in-patient
- Illness of any duration, and **at least one of the following**:
    - Radiographic infiltrates (e.g. chest x-ray, CT scan)
    - Rales/crackles on physical examination
    - SpO2 ≤94% on room air pre-randomisation
    - Requiring supplemental oxygen
    - Lymphocyte count <1 x 10^9 cells per L.
- Able to take oral medication
- Understands & agrees to comply with planned trial procedures
- Participant (or legal representative) provides written informed consent.

Exclusion criteria

- ALT and/or AST greater than five times the upper limit of normal
- Stage 4 severe CKD (eGFR < 30) or requiring dialysis
- Absolute neutrophil count less than 1.0 x 10^9 cells per L

Results within 72 hrs of randomisation (most recent result)

- History of severe liver disease
- Current itraconazole, ketoconazole, diltiazem, verapamil, phenytoin or rifampicin
- Pregnant or breast feeding
- Anticipated transfer to non-trial site hospital within 24hrs
- Allergy to Brensocatib
- Use of any IMP within 30 days or 5 x half-life post- last trial dose, whichever is longer. Co-enrolment with COVID-19 trials is allowed as per co-enrolment agreements and/or individual decision by the CI.