



FULL/LONG TITLE OF THE TRIAL

A randomised double-blind placebo-controlled trial of Brensocatib (INS1007) in patients with severe COVID-19

SHORT TRIAL TITLE / ACRONYM

STOP-COVID19: **S**uperiority **T**rial **O**f Protease inhibition in **C**OVID-19

PROTOCOL VERSION NUMBER AND DATE

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator (CI) agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

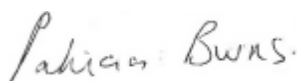
I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature:

Date: 21/01/2021



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Date: 19/01/2021



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I. LIST OF ABBREVIATIONS

| | |
|---------|--|
| AE | Adverse Event |
| ALT | Alanine aminotransferase |
| AR | Adverse Reaction |
| ARDS | Acute Respiratory Distress Syndrome |
| AST | aspartate aminotransferase |
| CI | Chief Investigator |
| CNORIS | Clinical Negligence and Other Risks Insurance Scheme |
| CoVs | Coronavirus |
| CT | Computed Tomography |
| CTA | Clinical Trial Authorisation |
| CTIMP | Clinical Trial of Investigational Medicinal Product |
| DMC | Data Monitoring Committee |
| DSUR | Development Safety Update Report |
| ECMO | Extracorporeal membrane oxygenation |
| eCRF | electronic Case Report Form |
| eGFR | estimated Glomerular Filtration Rate |
| GCP | Good Clinical Practice |
| HRA | Health Research Authority |
| ICF | Informed Consent Form |
| IMP | Investigational Medicinal Product |
| ISF | Investigator Site File (This forms part of the TMF) |
| L | litre |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| NET | Neutrophil extracellular traps |
| NEWS | National Early Warning Score |
| NGT | Nasogastric tube |
| NHS R&D | National Health Service Research & Development |
| NP | Nasopharyngeal |
| PCR | Polymerase Chain Reaction |
| PI | Principal Investigator |
| PIS | Participant Information Sheet |
| PPE | Personal Protective Equipment |

| | |
|-------|---|
| REC | Research Ethics Committee |
| RNA | Ribonucleic acid |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAR | Serious Adverse Reaction |
| SARS | Severe Acute Respiratory Syndrome |
| SpO2 | peripheral capillary oxygen saturation |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TCTU | Tayside Clinical Trials Unit |
| TMF | Trial Master File |
| TMG | Trial Management Group |
| TRuST | Tayside Randomisation System |
| TSC | Trial Steering Committee |
| WHO | World Health Organisation |

II. TRIAL SUMMARY

| | | |
|--|---|--|
| Trial Title | A randomised double-blind, placebo-controlled trial of Brensocatib (INS1007) in patients with severe COVID-19 | |
| Internal ref. no. (or short title) | STOP-COVID19: S uperiority T rial O f Protease inhibition in COVID-19 | |
| Clinical Phase | III | |
| Trial Design | Multi-centre prospective, randomized placebo-controlled trial | |
| Trial Participants | Patients presenting to hospital with PCR confirmed COVID-19 (SARS-CoV-2 infection) | |
| Planned Sample Size | 400 | |
| Treatment duration | 28 days | |
| Follow up duration | 29 days | |
| Planned Trial Period | 12 months | |
| | Objectives | Outcome Measures |
| Primary | To evaluate the efficacy of Brensocatib to improve clinical outcomes in COVID-19 up to day 29 | Clinical status on a 7-point ordinal scale |
| Investigational Medicinal Product(s) | Brensocatib (INS1007) | |
| Formulation, Dose, Route of Administration | Oral tablet, 25mg once per day | |

III. FUNDING AND SUPPORT IN KIND

| FUNDER(S) | FINANCIAL AND NON FINANCIALSUPPORT GIVEN |
|--|--|
| Insmed Incorporated, 700 US Highway 202/206, Bridgewater, NJ 08807, USA | Supply of Investigational Medicinal Product (IMP) and placebo £672,306 |

IV. ROLE OF TRIAL SPONSOR AND FUNDER

The roles and responsibilities of the Sponsor and Funder will be detailed in the Clinical Research Agreement.

V. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

The trial will be coordinated by a Trial Management Group (TMG), consisting of the grant holders, including the CI, collaborators, statistician, research assistant, trial manager and research nurse where appropriate. Details of membership of the TMG will be held in the Trial Master File (TMF). The TMG will meet regularly to ensure all practical details of the trial are progressing well and working well and everyone within the trial understands them. Minutes of the TMG meetings will be maintained in the TMF.

The functions of the Trial Steering Committee (TSC) will be undertaken by the TMG. No independent TSC will be convened for this trial.

A Data Monitoring Committee (DMC) will be established to oversee the safety of trial participants. The terms of reference of the DMC are detailed in the DMC Charter and held in the TMF. Minutes of the DMC will be maintained in the TMF.

The CI will be responsible for the conduct of the trial. Site delegate(s) will oversee the trial and will be accountable to the CI. A trial-specific Delegation Log will be prepared for the trial site, detailing the duties of each member of staff working on the trial.

The trial will be conducted in accordance with the principles of GCP.

In addition to Sponsorship approval, a favourable ethical opinion will be obtained from an appropriate NHS REC. Authorisation from the MHRA, and appropriate National Health Service Research & Development (NHS R&D) permissions will be obtained prior to commencement of the trial.

VI. PROTOCOL CONTRIBUTORS

Chief Investigator, Prof James Chalmers: Initial draft, review and final approval

Co-investigator, Prof Jacob George: Review

Senior Trial Manager, Margaret Band: Review

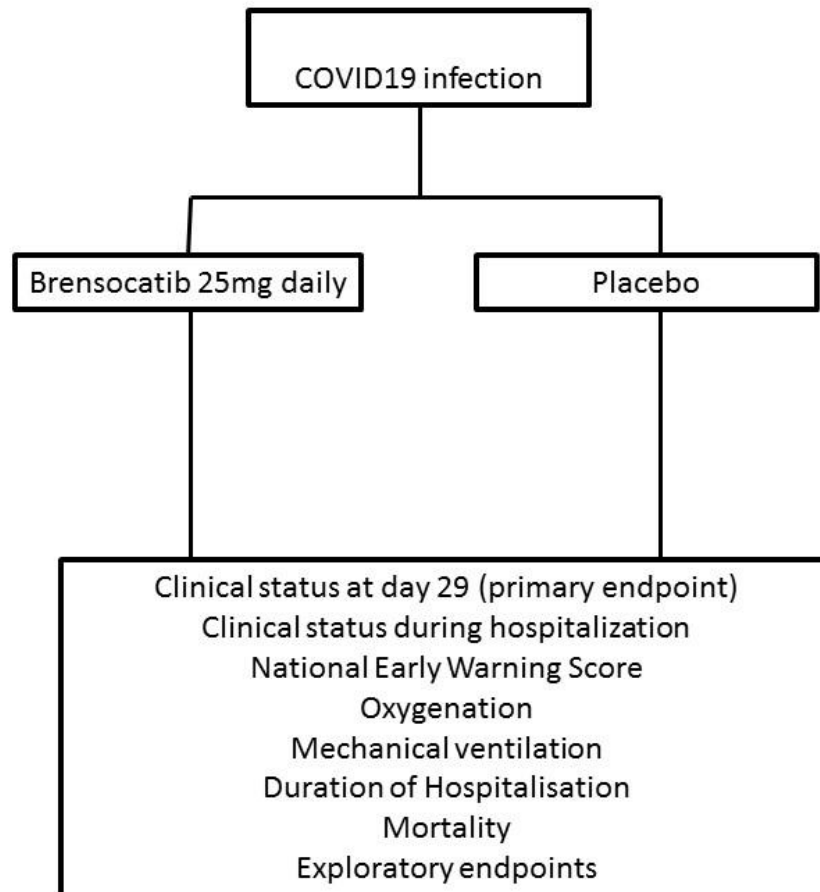
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VII. KEY WORDS: SARS-CoV-2, Coronavirus, COVID-19.

VIII. TRIAL FLOW CHART



1. BACKGROUND

COVID-19 is a respiratory disease caused by a novel coronavirus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and causes substantial morbidity and mortality.¹⁻³ This clinical trial is designed to evaluate the potential of Brensocatib as a novel host directed therapy for the treatment of adult patients hospitalised with COVID-19. We hypothesise that Brensocatib, by blocking damaging neutrophil proteases⁴, will reduce the incidence of acute lung injury and acute respiratory distress syndrome (ARDS) in patients with COVID-19, thereby resulting in improved clinical outcomes at day 15 and day 29, fewer days dependent on oxygen or mechanical ventilation, and shorter length of hospital stay.

Coronavirus (CoVs) are positive-sense single stranded enveloped Ribonucleic acid (RNA) viruses, many of which are commonly found in humans and cause mild symptoms.⁵ Over the past two decades, emerging pathogenic CoVs capable of causing life-threatening disease in humans and animals have been identified, namely severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) and Middle Eastern respiratory syndrome coronavirus (MERS- CoV).^{1,6}

In December 2019, the Wuhan Municipal Health Committee (Wuhan, China) identified an outbreak of viral pneumonia cases of unknown cause.⁵ Coronavirus RNA was quickly identified in some of these patients. This novel coronavirus has been abbreviated as SARS-COV-2 and has 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV. This novel coronavirus has been designated SARS-CoV-2, and the disease caused by this virus has been designated COVID-19. Initial infections were travel associated with individuals having contact with Wuhan or other affected areas but the disease has now spread to affect hundreds of thousands of patients worldwide with widespread community transmission across the globe.³

Outbreak forecasting and mathematical modelling suggest that these numbers will continue to rise.

Global efforts to evaluate novel antivirals and therapeutic strategies to treat COVID-19 have intensified but to date dexamethasone is the only therapy shown to reduce mortality in COVID-19 while repurposed antiviral drugs did not show clinical benefits in the World Health Organisation SOLIDARITY trial.

Mortality from COVID-19 has been estimated at between 0.5% and 3.4% of infected patients and occurs most frequently because of the development of ARDS.⁸⁻¹⁰ In contrast to some, particularly bacterial pneumonias, where patients present with acute respiratory failure and sepsis, the dynamics of COVID-19 infection demonstrate a slow deterioration in oxygenation with the development of bilateral infiltrates in a high proportion of patients, consistent with the development of ARDS.² Patients subsequently require mechanical ventilation.

Treatments that could prevent the requirement for mechanical ventilation or shorten the duration of intensive care unit stay by reducing the severity of ARDS are therefore the number 1 target for COVID-19 therapy.

Neutrophils in ARDS

Neutrophil influx into the extravascular compartments of the lungs is a defining characteristic of ARDS.¹¹ During ARDS, circulating neutrophils become primed, resulting in reduce deformability and retention within the pulmonary capillary bed.¹¹ They then migrate across the endothelium through the interstitium and epithelium into the airways themselves. As neutrophils migrate they are activated and release oxidants, proteases and neutrophil extracellular traps.¹²⁻¹⁴ All of these processes are important in killing bacterial pathogens but in ARDS these processes become prolonged and excessive leading to progressive lung damage. Neutrophil elastase and other neutrophil proteases such as proteinase-3 and

cathepsin-G cause tissue injury resulting in increased epithelial and endothelial permeability which leads to the influx of protein-rich alveolar oedema.¹¹

Mortality in ARDS correlates directly with the extent of neutrophilia in the lung.¹⁵ Both human clinical data and murine studies demonstrate a key role for neutrophils in ARDS.^{11,16–18} Neutrophil depletion in multiple models of ARDS including those induced by lipopolysaccharide, acid, ventilator lung injury, transfusion and other stimuli, reduces the severity of acute lung injury including endothelial-epithelial cell damage and capillary-alveolar permeability.^{19–22}

Neutrophil proteases and particularly neutrophil elastase are believed to be central to the neutrophil induced lung damage.¹⁷ Neutrophil elastase is a serine protease contained within primary neutrophil granules which is released in response to neutrophil activation or neutrophil extracellular trap formation.²³ It is involved in the pathogenesis of multiple inflammatory diseases and therapeutic development of neutrophil elastase inhibitors for use in ARDS has been ongoing for many years. Neutrophil elastase is markedly elevated in human ARDS samples¹⁶ and the inhibition of neutrophil elastase has been demonstrated to reduce epithelial injury in multiple animal models of lung injury across multiple stimuli including LPS, bleomycin, ventilation, sepsis and many others.^{17,24–27} Neutrophil elastase is critical to the development of neutrophil extracellular traps, which are highly damaging webs of DNA studded with proteases and other neutrophil derived toxins.^{12,28} Neutrophil extracellular traps (NET) formation and the failure to clear NETs have been strongly implicated in the development and poor outcomes from ARDS.¹⁸ Inhibition of neutrophil elastase reduces the formation of NETs.¹²

A challenge therapeutically has been how to inhibit neutrophil elastase since administration of competitive inhibitors either orally or through the inhaled route may not be sufficient to block elastase activity in the lung.^{29,30}

2. RATIONALE

Neutrophil elastase, proteinase-3 and cathepsin-G are activated during neutrophil maturation in the bone marrow through dipeptidyl peptidase 1 (DPP1; also known as cathepsin C), which removes the N-terminal dipeptide sequence of neutrophil serine proteases allowing active enzymes to be packaged into granules prior to release of neutrophils into the circulation.⁴ Brensocatib (INS1007, formerly AZD7986) is an orally delivered selective, competitive, and reversible inhibitor of DPP1. Brensocatib has been shown to inhibit neutrophil serine protease activity in blood in both animal models and healthy volunteers.⁴

We recently conducted a large phase 2 study of Brensocatib in patients with bronchiectasis designed to test if treatment with Brensocatib could reduce infective exacerbations and reduce neutrophil elastase activity in the lung in bronchiectasis patients. The study met its primary endpoint of time to first exacerbation and key secondary endpoint of the frequency of exacerbations as well as showing marked reductions in neutrophil elastase concentrations in sputum. Due to the need to replace the circulating pool of neutrophils with new neutrophils which are deficient in elastase, Brensocatib does not have its effect immediately, but rather over several days. Elastase concentrations were reduced at the first time point at day 14 in the phase 2 study, with very large reductions observed at the second time point at day 28.

A. Kaplan-Meier Plot for Time to First Exacerbation

Figure 1. Time to First Exacerbation and Number of Exacerbations (Intention-to-Treat Population).

Figure 2. Reductions in sputum neutrophil elastase

In a cohort of 191 hospitalised COVID-19 patients with a completed outcome, the median time from illness onset to discharge was 22·0 days (IQR 18·0–25·0) and the median time to death was 18·5 days (15·0–22·0). Thirty-two patients (17%) required invasive mechanical ventilation and the median time from onset to mechanical ventilation was 14·5 days.² Therefore endpoint assessments at day 15 and 29 are

proposed below. We hypothesise that the mechanism of action of Brensocatib to reduce protease activity will be more rapid in COVID-19 patients compared to bronchiectasis due to a more rapid turnover of neutrophils in acute illness. The objective is to test whether by reducing neutrophil protease activity in neutrophils we can prevent or reverse the development of ARDS and thereby improve outcomes in individuals with COVID-19 infection.

2.1. Assessment and Management of Risk

Importantly, despite the fact that bronchiectasis patients have chronic infection with bacteria such as *Pseudomonas aeruginosa*³¹, no increase in infections was seen in the phase 2 trial. It is therefore anticipated that Brensocatib is safe, even in patients with secondary bacterial infection, as Brensocatib does not impair other antimicrobial responses in contrast with other more potent immunosuppressive drugs such as steroids which are now in clinical trials for COVID-19. More than 50% of bronchiectasis exacerbations are viral³², and therefore the safety and efficacy demonstrated in the phase 2 bronchiectasis study are considered encouraging to go forward to a study in COVID-19.

A DMC will be convened to review unblinded data from the trial. The independent DMC will review adverse events, serious adverse events (SAEs) and laboratory data. The trial stopping criteria will be the discovery of an unexpected, significant, or unacceptable risk to the participants caused by treatment with the IMP as determined by the DMC.

This trial is categorised as:

Type B = Somewhat higher than the risk of standard medical care

See Appendix 1

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Hypothesis

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

3.1. Primary objective

The overall objective of the study is to evaluate the clinical efficacy of Brensocatib compared to placebo on top of standard care in adult patients hospitalised with COVID-19.

3.2. Secondary objectives

See Section 3.7

3.3. Outcome measures/endpoints

See Section 3.7

3.4. Primary endpoint/outcome

See Section 3.7

3.5. Secondary endpoints/outcomes

See Section 3.7

3.6. Exploratory endpoints/outcomes

See Section 3.7

3.7. Table of endpoints/outcomes

| Objectives | Outcome Measures | Timepoint(s) |
|--|--|---|
| Primary Objective Participant clinical status (on a 7-point ordinal scale) In accordance with WHO recommendations the primary endpoint will be determined by a pilot trial of the first 100 participants. | 7-point ordinal scale: 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. | Up to day 29 |
| Secondary Objectives | Outcome Measures | Timepoint(s) |
| Evaluate the clinical efficacy of Brensocatib relative to standard care in adult patients hospitalised with COVID-19 | Clinical Severity Time to an improvement of one category from admission using 7-point 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, 15 and 29. . Baseline to days 3, 5, 8, 11, 15 and 29. |
| | National Early Warning Score (NEWS): Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first. Change from baseline | Daily whilst hospitalised Days 8, 15, 29 |
| | Oxygenation: Oxygen free days Incidence and duration of new oxygen use during the trial | 1-29 days 0-29 days |
| | Mechanical Ventilation: Ventilator free days | 1-29 days |
| | | |

| | | |
|---|--|--|
| | Incidence and duration of new mechanical ventilation use during the trial. | 1-29 days |
| | Hospitalisation: Duration of hospitalisation (days). | Date of admission and discharge |
| | Mortality: 28-day mortality | Date of death |
| Evaluate the safety of the intervention through 28 days of follow-up as compared to the control arm | Cumulative incidence of SAEs Discontinuation or temporary suspension of treatment Changes in white cell count, haemoglobin, platelets, creatinine, total bilirubin, ALT, and AST over time (hospitalised participants only) Adverse events of special interest- hyperkeratosis, infections and dental complications | 1-29 days 1-29 days Days 0/1, 3, 5, 8, 11, 15, 29 1-29 days |
| Exploratory Objectives | Outcome Measures | Timepoint(s) |
| Evaluate the virologic efficacy of Brensocatib | Percent of participants with SARS-CoV-2 detectable in nasopharyngeal (NP) sample (in hospital, Tayside only) Quantitative SARS-CoV-2 virus in NP samples. (Tayside only) | Day 15 and day 29 Day 15 and day 29 |
| | *Neutrophil elastase and heparin binding protein measurement in blood (in hospital, Tayside only) *Neutrophil functional studies (NET formation, phagocytosis, elastase release, neutrophil proteomics- (Tayside and Sheffield only) | Days 1, 8, 15, 29 Days 1, 15, 29 |
| Quality of life | EQ-5D-5L administered via telephone (if at home) or in person if still in hospital | Day 29 |

*These analysis will be omitted in circumstances where there is no laboratory availability to process the samples in time, it is not possible to carry out analysis on stored samples.

4. TRIAL DESIGN

This is a multi-centre, randomised, double-blind, placebo-controlled, parallel group trial with two treatment arms, with 400 participants planned to be randomised

The two treatment arms are as follows:

1. Brensocatib 25mg once daily for 28 days

2. Placebo once daily for 28 days

The use of these drugs, including a placebo comparator, is considered to be ethical, as there are no antiviral therapies for COVID-19, and UK and WHO guidance recommends that novel agents should only be evaluated in the context of a randomized clinical trial. Patients in both arms will therefore receive all other therapies required to manage their condition (standard of care) with the exception of other investigational products as described in section 6.2.

Following trial completion or discontinuation, participants should be continued on standard of care.

Randomisation will be stratified by

1. Site
2. Age: <65 years/≥65 years, as age has been shown to be a key risk factor for severe disease and mortality

5. TRIAL SETTING

This is a multi-centre trial recruiting from 15 NHS Trusts/Boards within UK, if required to fulfil recruitment more NHS Trusts/Boards will be added. Participants will be recruited from those presenting with symptoms of COVID-19 in an acute setting. This may include accident and emergency departments, COVID-19 treatment units and those admitted to secondary care for other reasons with COVID-19.

6. PARTICIPANT ELIGIBILITY CRITERIA

It is likely that the assessments to confirm eligibility will be carried out by the clinical team during routine care of patients being assessed for COVID-19. Where these assessments have been carried out by the clinical team the most recent of these results will be used to prevent duplication and further exposure of the trial staff to patients with COVID-19.

6.1. Inclusion criteria

- Male or female
- ≥16 years of age
- SARS-CoV-2 infection (clinically suspected⁺ or laboratory confirmed^{*}).
- Admitted to hospital as in-patient less than 96 hours prior to randomisation[^]
- Illness of any duration, and at least one of the following:
 - Radiographic infiltrates by imaging (e.g. chest x-ray, computed tomography (CT) scan)
OR
 - Evidence of rales/crackles on physical examination
OR
 - Peripheral capillary oxygen saturation (SpO₂) ≤94% on room air prior to randomization
OR
 - Requiring supplemental oxygen.
OR
 - Lymphocyte count <1 x 10⁹ cells per litre (L)
- Participant (or legally authorized representative) provides written informed consent
- Able to take oral medication
- Participant (or legally authorised representative) understands and agrees to comply with planned trial procedures.

*Laboratory-confirmed: SARS-CoV-2 infection as determined by polymerase chain reaction (PCR), or other commercial or public health assay in any specimen < 96 hours prior to randomization.

*Clinically suspected: in general, SARS-CoV-2 infection should be suspected when a patient presents with (i) typical symptoms (e.g. influenza-like illness with fever and muscle pain, or respiratory illness with cough and shortness of breath); and (ii) compatible chest X-ray findings (consolidation or ground-glass shadowing); and (iii) alternative causes have been considered unlikely or excluded (e.g. heart failure, influenza). However, the diagnosis remains a clinical one based on the opinion of the managing doctor

^Where a patient has been admitted to hospital for a non COVID-19 reason and develops COVID-19 symptoms whilst an in-patient, randomisation may occur up to 96 hours from onset of symptoms.

6.2. Exclusion criteria

- Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 5 times the upper limit of normal, result within 72 hours of randomization (the result closest to randomization should be used if several results are available).
- History of severe liver disease
- Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30), result within 72 hours of randomization (the result closest to randomization should be used if several results are available)
- Absolute neutrophil count less than 1.0×10^9 cells per L within 72 hours of randomization (the result closest to randomization should be used if several results are available)
- Current treatments with potent Cyp3A4 inducers/inhibitors (e.g. Itraconazole, Ketoconazole, diltiazem, verapamil, phenytoin or rifampicin)
- HIV treatments - current treatment with protease/integrase inhibitors or non-nucleoside reverse transcriptase inhibitors*
- Pregnant or breast feeding.
- Anticipated transfer to another hospital which is not a trial site within 24 hours.
- Allergy to Brensocatib
- Use of any investigational drug within five times of the elimination half-life after the last trial dose or within 30 days, whichever is longer. Co-enrolment with COVID-19 trials is allowed as per co-enrolment agreements and/or individual decision by the CI.

Women of child-bearing potential must be willing to have pregnancy testing prior to trial entry.

*The Liverpool HIV checker (<https://www.hiv-druginteractions.org/checker>) should be used to check for any HIV drug interactions. Simvastatin could be used as a surrogate for Brensocatib as it metabolised similarly by CYP 3A4 pathway.

6.3. Co-enrolment

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.

7. TRIAL PROCEDURES

7.1. Recruitment

400 male and female adults ≥ 16 years of age with COVID-19 who meet all eligibility criteria will be enrolled.

Sites will be informed when the target of participants has been reached and will be instructed not to recruit any further participants. All participants already consented to take part at this point will go forward to randomisation and will be followed to the end of trial.

It is anticipated that patients with COVID-19 will present to participating hospitals, and that no other efforts to recruit potential participants are needed. Recruitment efforts may also include dissemination of information about this trial to other medical professionals.

7.1.1. Participant identification

Identification of potentially eligible participants will be by a member of the trial staff delegated this role by the PI. The trial staff will identify patients admitted to COVID-19 assessment units and elsewhere in the hospital with a possible diagnosis of COVID-19. Screening

The trial staff will access laboratory systems to screen patients with a possible diagnosis of COVID-19 for a positive SARS CoV PCR result. For patients with a positive SARS CoV PCR result the trial staff will check further inclusion criteria via medical records. Trial staff will work closely with the managing clinical teams who may also provide patient lists.

7.1.2. Ineligible participants

Anonymised information on participants who are not randomised for CONSORT reporting will include:

- the reason not eligible for trial participation, or if they are eligible but declined

Where participation in the trial has been discussed with the participant and the individual is found to be ineligible for trial participation, they will be thanked and the reasons for the ineligibility fully explained.

Participants who meet one or more of the exclusion criteria will be withdrawn from the trial. The participant may be rescreened if their medical condition changes significantly.

7.2. Payment

No payment will be provided to participants as all assessments will be either carried out whilst already in hospital or over the phone after discharge. Participants in Tayside and Sheffield will receive travel expenses for attendance at the day 29 visit.

7.3. Consent

The Principal Investigator (PI) retains overall responsibility for the conduct of research at their site. This includes the taking of informed consent of participants at their site. They will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of GCP and Declaration of Helsinki.

Patients admitted to hospital with a possible diagnosis of COVID-19 will be provided with a participant information sheet (PIS) while in hospital. As the trial treatment should commence as soon as possible

after a diagnosis of COVID-19 has been confirmed, participants may have less than 24 hours to decide whether they wish to participate.

Only trial staff experienced in consenting participants for CTIMPs will be delegated this role. The consent process will be completed face-to-face, and due to the infectious nature of COVID-19, only staff trained in the use of the appropriate personal protective equipment (PPE) will be delegated this role. Staff completing the consent process will wear the appropriate PPE and follow the hospital's infection control measures for having contact with patients with COVID-19.

Due to the highly infectious nature of COVID-19 the consenting process described below will be followed. Where a participant requests to speak with a physician from the trial team the consent process will not be completed until the participant has spoken to the physician and had all their questions answered to their satisfaction.

The original Informed Consent Form (ICF) will be signed by the participant and staff receiving the consent. The original ICF will be photographed and a copy printed for filing in the ISF. The original ICF will remain with the participant and will be given to the participant or destroyed on discharge depending on local infection control policies. If the original ICF is destroyed a copy of the ICF should be given to the participant prior to discharge, or posted to them. Alternatively, the person taking the consent will have an envelope with a pro forma for the relevant information on it. The ICF is placed in the envelope by person taking consent prior to them leaving the room whilst the research staff hold the envelope outside. The information on the envelope is completed and the envelope stored securely. After 7 days the envelope will be opened and the ICF filed. A copy of the ICF should be given to the participant prior to discharge, or posted to them.

For adults who lose capacity, their previous wishes will remain legally binding and this will remain valid unless the protocol changes significantly. If this occurs and further consent is required from a participant who has lost capacity, their legal representative will be asked for their consent, see below. In all cases the CI or delegate will consult with carers and take note of any signs of objection or distress from the participant – the participant will be withdrawn if they raise objection. Where appropriate, the participant will be withdrawn from any further research intervention and agreement will be sought from a carer to allow data collection.

Adults with incapacity

As patients requiring admission to hospital for treatment of COVID-19 are more likely to be older, there is likely to be a higher rate of co-morbid disease which may affect the patient's ability to consent, e.g. dementia. With a symptom of high temperature being a feature of COVID-19 there may also be a proportion of patients experiencing delirium which could affect their capacity to give informed consent. It is felt that it is important to include these patients in the trial to give a representative sample of patients with COVID-19, especially as older patients and those with underlying medical conditions are likely to have poorer outcomes. Where patients are thought to lack the capacity to give informed consent, this will be sought from their legal representative. The participant's treating clinician will make the decision as to whether the participant lacks capacity.

In Scotland those who can act as legal representative are:

- Personal legal representative i.e.
 - Adult's Welfare Guardian or Welfare Attorney, or if not appointed:
 - The adult's nearest relative, if neither are reasonably contactable:
- Professional legal representative, i.e. a doctor responsible for the medical treatment of the adult if they are independent of the trial, or a person nominated by the healthcare provider.

In England and Wales those who can act as a legal representative are:

- Personal legal representative, i.e. a person not connected with the conduct of the trial who is suitable to act as the legal representative by virtue of their relationship with the adult, and is available and willing to do so. If one is not available:
- Professional legal representative, i.e. a doctor responsible for the medical treatment of the adult if they are independent of the study, or a person nominated by the healthcare provider.

The PIS which the legal representative will receive will include:

- That they are being asked to give consent on behalf of the incapacitated adult,
- That they are free to decide whether they wish to make this decision or not,
- That they are being asked to consider what the adult would want, and to set aside their own personal views when making this decision,
- Sufficient information, in an understandable form, about the trial to ensure that they can make an informed decision.

The participant themselves will also receive information, according to their capacity of understanding, about the trial and its risks and benefits.

Where a participant regains their capacity to consent during the course of the trial, informed consent will be obtained. The participant will be given a PIS which explains what has happened so far and what their on-going consent is for. If a participant regains their capacity to consent after discharge from hospital but before the end of their involvement in the trial, the trial staff will discuss the trial with the participant on the phone and post a consent form for the participant to complete and return. A record of this will be detailed in the participant's medical records. If a participant regains their capacity to consent but refused to give consent to continue in the trial, they will be asked if the data collected up to that point can be used. If refused, all data for that participant will be removed from analysis. This decision will be documented in the participant's medical records.

Eligibility for participation in the trial will be confirmed by the PI or medically qualified delegate.

7.3.1. Additional consent provisions for collection and use of participant data and biological specimens in ancillary trials, if applicable

Excess biological samples that are being taken for clinical reasons (Tayside only) and research samples taken (Tayside and Sheffield only) may be stored in research in labs at the University of Dundee for future research, including commercial research, if no longer required for clinical purposes. Specimens will be used for submission to ethically approved research tissue banks for future unspecified research held within Tayside and will be registered with NHS Tayside Tissue Bank. Future use of those specimens will be governed by the NHS Tayside Tissue Bank by a COVID-19 specific committee.

Consent from participants will be gained for:

- use of their data and specimens in future research unrelated to the clinical condition under trial
- contact by trial staff for further ethically approved future research

Where a participant subsequently rescinds their consent for this data, specimens and/or future contact, all data and specimens collected for these reasons will be destroyed. Any data collected to the point of withdrawal will be retained for reasons of public interest in the area of public health (Article 9(2)(i) GDPR).

7.4. The randomisation scheme

Participants will be allocated to receive either Brensocatib (25mg once daily for 28 days) or placebo in addition to standard of care. Randomisation will be 1:1 intervention:placebo. Randomisation will be stratified by site and age: <65 years/≥65 years.

7.4.1. Method of implementing the randomisation/allocation sequence

After successful completion of screening the participant will be assessed for eligibility for randomization. This will be documented in the electronic Case Report Form (eCRF).

Participants will be randomised by the PI or delegate to one of the two treatment regimens as noted in Section 8.1.

The PI or delegate will use a centrally controlled web-based GCP compliant randomisation system, TRuST, run by the UKCRC registered Tayside Clinical Trials Unit (TCTU). TRuST is provided by the Health Informatics Centre, University of Dundee. TCTU use a validated randomisation program and will securely backup both the randomisation seed and the randomisation allocation. TRuST will provide an immediate allocation on screen and confirmation of allocation will be emailed to the site PI, person completing randomisation and clinical trials pharmacy. The trial manager, data manager and CI will receive treatment allocation emails for all participants at all sites.

Access to be able to randomise a participant will only be given after completion of appropriate training.

7.5. Blinding

Double-blind, placebo-controlled Participants will be allocated via the randomisation system to receive either active treatment or matching placebo, see section 8.1 The active treatment/placebo will be packaged and labelled so as to not identify the contents. Trial staff and participants will be blind to the allocation received. The final unblinding of the treatment allocation will occur after the creation of a final locked database.

7.6. Emergency Unblinding

TCTU will provide each PI with a login to the interactive web-based randomisation system, Tayside Randomisation System (TRuST), for 24-hour emergency unblinding at their site only. The CI will also have access to unblind participants at all sites. The date, reason and result will be documented and signed by the person carrying out the unblinding. This will be stored in a sealed envelope in the ISF. Disclosure of the unblinding result will be to individuals involved in the participant's care only. Where possible, the participant will remain in the trial and continue with the trial procedures.

In addition, a paper copy of the allocation will be stored securely in NHS Tayside Clinical Trials Pharmacy. Unblinding will only be carried out where a physician considers that it is necessary for clinical safety.

7.7. Baseline data

Baseline data will be collected as per Schedule of Procedures, Appendix 4, and as described below, section 7.8. Only information directly related to the objectives and outcome measures detailed in the protocol shall be collected.

7.8. Trial assessments

Trial assessments will be performed according to the Schedule of Procedures, Appendix 4.

After informed consent, the following assessments will be reviewed to determine eligibility requirements as specified in the inclusion and exclusion criteria:

- Focused medical history, taken from medical records, including the following information:
 - Approximate day of onset of COVID-19 symptoms
 - History of chronic medical conditions related to inclusion and exclusion criteria
 - Medication allergies
 - Review medications and therapies for this current illness
- Review recent radiographic imaging (x-ray or CT scan)
- Physical examination findings
- SpO₂ on air
- Obtain blood for screening laboratory evaluations if not done in the preceding 72 hours:
 - ALT
 - AST
 - Creatinine
 - eGFR
 - Lymphocyte count

Clinical screening laboratory evaluations will be performed locally by the site laboratory. The overall eligibility of the participant to participate in the trial will be assessed once all screening values are available. The screening process can be suspended prior to complete assessment at any time if exclusions are identified by the trial staff. Equally, if a patient qualifies for participation based on one inclusion criteria of severe, e.g requirement for supplemental oxygen, it is not necessary to perform a physical examination to confirm the presence of rales or crackles as the patient is already eligible. Trial participants who qualify will be immediately randomized.

It is likely that the above assessments to confirm eligibility will be carried out by the clinical team during routine care of patients being assessed for COVID-19. Where these assessments have been carried out by the clinical team in the preceding 72 hours, the most recent of these results will be used to prevent duplication and further exposure of the trial staff to patients with COVID-19. If any screening procedures have not been carried out in the previous 72 hours (96 hour for positive SARS-CoV-2 test) hours for these will be completed by the trial staff. Screening procedures will only be recorded/carried out after consent.

For all baseline assessments and follow-up assessments, refer to Schedule of Procedures for procedures to be done, and details below for each assessment.

Clinical Assessments

It is expected that these clinical assessments will be carried out by the clinical team during routine clinical care and documented on a NEWS chart. Where the assessments have been carried out, the results of the assessment closest to 8am on the day will be used to prevent duplication and further exposure of the trial staff to patients with COVID-19.

- Blood pressure and pulse, lying or seated
- Tympanic temperature
- SpO₂
- Record if SpO₂ has been measured on air or oxygen concentration the participant was receiving.

Ordinal Scale

The ordinal scale is an assessment of the clinical status on a given trial day. Each day, the worst score for that day will be recorded. The scale is as follows:

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.

NEWS Score

The NEWS score has demonstrated an ability to discriminate patients at risk of poor outcomes. (Smith, 2016). This score is based on 7 clinical parameters. The NEWS2 Score is being used as an efficacy measure.

This should be evaluated at the assessment recorded closest to 8am on a given trial day. These parameters can be obtained from the hospital chart.

Exploratory assessment- viral shedding

Where practical at the Tayside site only, nasal swabs will be obtained on day 15 and day 29 to evaluate viral clearance by PCR.

Exploratory assessment- neutrophil studies

At the Tayside and Sheffield sites only, additional blood will be taken for isolation of peripheral blood neutrophils, as per outcome measures section 3.7.

Exploratory assessment- quality of life

The validated EQ-5D-5L quality of life tool will be administered to patients who are able to complete the questionnaire either in person (those still in hospital) or over the telephone (those at home) to determine the impact of treatment on quality of life.

Clinical Evaluation

As these participants are in-patients receiving care for COVID-19, they will be monitored as per clinical need. Where already obtained for clinical need the following blood results will be recorded at days 1, 3, 5, 8, 11, 15, 29:

- White cell count, haemoglobin, platelets, neutrophils, eosinophils, lymphocytes
- creatinine, eGFR
- AST and ALT

Participants discharged home will not receive further safety assessments. It is not necessary to perform further blood tests on inpatients for the purposes of safety. Routine blood tests taken as part of routine clinical care will be used. If tests are not performed for clinical reasons they will be treated as missing data for analysis.

7.9. Long term follow-up assessments

Participants will receive long term clinical follow-up as deemed appropriate by local clinical teams.

7.10. Qualitative assessments

N/A

7.11. Withdrawal criteria

Participants are free to withdraw at any time and are not obliged to give a reason(s). The CI, PI or delegate will make a reasonable effort to ascertain the reason(s), both for those who express their right to withdraw and for those lost to follow-up, while fully respecting the individual's rights.

The PI may withdraw a participant at any time if it felt to be in the best interest of the participant and treatment continuation would be detrimental to the participant's wellbeing. In addition, the trial drug will be discontinued in the following circumstances:

- Persistent adverse effects which are determined to be severe, persistent, treatment-related and not responsive to treatment
- If an allergic reaction to trial drug occurs, the trial drug will be stopped and treatment will be initiated as appropriate
- Absolute neutrophil count less than 1.0×10^9 cells per L at any time.

A full explanation for discontinuation of trial drug will be provided to the participant. As the trial is being conducted on an intention to treat basis, if the participant has been randomised and given one or more dose of IMP, s/he will be asked to complete trial assessments as per the protocol, if the CI/PI considers it appropriate, to allow for an intention to treat analysis, but will be censored in the per-protocol analysis. Participants are free to refuse to do so. Withdrawn participants will not be prescribed trial drug.

Those withdrawn, including those lost to follow-up, will be identified and a descriptive analysis of them provided, including the reasons for their loss, if known, and its relationship to treatment and outcome.

7.12. Storage and analysis of clinical samples

Storage and analysis of samples will only occur at the Tayside and Sheffield sites. The anonymisation, processing and storing of these specimens will be detailed in a local Laboratory Manual.

Sheffield:

- Will collect blood samples as per Schedule of Procedures, Appendix 4.
- Neutrophil function studies will be carried out at the Sheffield site.
- Blood will be processed and stored at Sheffield for later transfer to the Tayside laboratory for further analysis. Excess may be stored in the Tayside laboratory for future research use after trial results have been obtained.

Tayside:

- Will collect blood, sputum, endo-tracheal and nasal swab samples as per Schedule of Procedures, Appendix 4.
- Will carry out analysis as per exploratory end points.
- Preparations of blood, sputum and nasal swabs may be stored for future research use after trial results have been obtained.
- Excess biological samples that are being taken for clinical reasons may be stored for future use if no longer required for clinical purposes

7.13. End of trial

The end of trial is defined as completion of day 29 assessments for last participant at all sites. The Sponsor and/or CI have the right at any time to terminate the trial for clinical or administrative reasons.

The end of the trial will be reported to the Sponsor, REC, MHRA and NHS R&D Office(s) within 90 days, or 15 days if the trial is terminated prematurely. The CI will ensure that any appropriate follow-up is arranged for all participants.

A final clinical trial report will be submitted to the MHRA via EudraCT within 1 year of the end of the trial and will also be provided to the Sponsor and REC.

8. TRIAL TREATMENTS

8.1. Name and description of investigational medicinal product (IMP)

| | Investigational Medicinal Product | Dosage, form and strength |
|-------|-----------------------------------|---------------------------|
| Arm 1 | Brensocaticib (INS1007) | 25mg once daily |
| Arm 2 | Placebo | 25mg once daily |

Treatment is administered for 28 days in total.

Tablets will be dispensed in bottles containing 35 tablets. Participants will be given the bottle allocated to them on discharge and instructed to take the tablets only for a total of 28 days. Written information, Participant Diary, will be given telling them when to stop taking their tablets. Participants will also be phoned on day 29 as per Schedule of Procedures, at this point they will be reminded that they should stop taking their tablets.

8.2. Regulatory status of the drug

No marketing authorisation

8.3. Product Characteristics

Brensocaticib is a film-coated, oral tablet available in a dose strength of 25 mg. The tablets are round, biconvex, brown film-coated tablets. The tablets are an immediate-release dosage form with rapid dissolution characteristics under in vitro test conditions. Each tablet contains active ingredient Brensocaticib 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.

Matching Placebo

The matching placebo tablet contains microcrystalline cellulose and sodium stearyl fumarate and is coated identically to Brensocaticib tablets.

8.3.1. Packaging and Labelling Information

Brensocaticib and matching placebo will be packed in individual high-density polyethylene bottles, labelled and stored as described below.

Labels will be prepared in accordance with Good Manufacturing Practice Annex 13 requirements and local regulatory guidelines. The trial drug label on the bottle specifies the appropriate storage.

8.3.2.Storage

All trial drug supplies must be stored in accordance with the label information. Until dispensed to the trial participants, the trial drugs will be stored at room temperature between 2°C and 30°C, at the sites in a securely locked, limited access storage area under appropriate storage conditions, accessible to authorized personnel only.

8.4. Accountability Procedures

All IMP will be supplied by Insmed Incorporated. Trial medication will be received by a delegated person at the trial site Clinical Trial Pharmacy, handled and stored safely and properly, and kept in a secured location as detailed in the IMP Management Plan. All trial clinical supplies will be dispensed only in accordance with the protocol.

The PI or delegated trial staff will maintain an accurate record of the receipt and dispensing of the IMP in a drug accountability log. Monitoring of drug accountability will be performed as per Sponsor Monitoring Plan. Clinical staff will be asked to return all unused medications and packaging at the end of the trial or at the time of discontinuation of treatment. When discharged participants will be given a stamped addressed envelope to return unused IMP to trial staff. On return of the medicines, the trial staff will perform a check of returns and this will be recorded on the drug accountability log. Unused treatment will be disposed of by the Clinical Trial Pharmacy as per local Standard Operating Procedure. Non returned IMPs will be recorded by clinical trials pharmacy staff as per the IMP management plan.

8.5. Preparation and labelling of Investigational Medicinal Product

Preparation and labelling of trial medication will be performed by Insmed Inc. with annex 13-compliant labels. Trial medication will be supplied to Sharp Clinical Service (UK) Ltd who will act as Importer of Record for the Sponsor. Sharp will be responsible for distribution of trial medication to trial sites.

8.6. Drug storage and supply

Will be detailed in a trial IMP Management Plan.

8.7. Dosage schedules

Route of administration: oral. Where a participant is unable to take oral medication they will be excluded from the trial. If during the treatment phase a participant becomes unable to take oral medication their treatment will be given by nasogastric tube (NGT) where the participant has this in place for clinical reasons. After crushing, the tablet should be placed in water for 5-10 mins, after pushing through NGT, flush with 10 mL of water (or saline), and clamp NGT for 30 mins.

Frequency of administration: once daily, before breakfast. On day of randomisation the first dose may be given up to 5pm, after that point the first dose should be given the following day before breakfast. The day of first dose received will be deemed to be day 1 of the trial.

Missed doses: if a dose is missed this should be given within 10 hours of the missed dose.

Maximum duration of treatment: 28 days. Where a participant misses a dose due to being unable to take oral medication, or for any other reason, the treatment duration will not be extended.

8.8. Dosage modifications

No changes to dosage or regimen will be made during the course of the trial

8.9. Known drug reactions and interaction with other therapies

Results of prior studies indicate that there was little or no effect of a strong CYP3A4/5 inhibitor (itraconazole) on the exposures of Brensocatib. However, co-administration of inhibitors of more than 1 INS1007 elimination pathway (e.g. CYP3A4/5 with CYP2C8 and/or CYP2D6 inhibitors) should be cautioned as there is no information on the combined interaction potential. For this reason we have excluded patients taking strong CYP3A4/5 inhibitors with the exception of clarithromycin or other macrolide antibiotics. Macrolides were permitted in the phase 2 “Willow” trial of Brensocatib (INS1007)

8.10. Concomitant medication

Details of concomitant medications will be recorded on the trial eCRF on a concomitant medications form.

8.11. Trial restrictions

Participants should take their usual medication as well as any other medications prescribed for treatment of COVID-19 as directed by their clinical team. No concomitant medications will be stopped for trial enrolment purposes.

Participants should not be prescribed Itraconazole, Ketoconazole, diltiazem, verapamil, phenytoin, rifampicinprotease/integrase inhibitors or non-nucleoside reverse transcriptase inhibitors whilst taking trial medication. The Liverpool HIV checker (<https://www.hiv-druginteractions.org/checker>) can be used to check for interactions. Simvastatin should be used as a surrogate for Brensocatib as it metabolised similarly by CYP 3A4. It will be a clinical decision by the PI as to whether trial drug or restricted drug is stopped.

Females of childbearing potential and males must be willing to use a highly effective method of contraception (hormonal or barrier method of birth control; abstinence). Contraception should be continued until at least 30 days after final dose of IMP taken. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
 - oral
 - intravaginal
 - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
 - oral
 - injectable
 - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

8.12. Assessment of compliance with treatment

Trial drug compliance will be assessed by trial staff in hospitalised participants by checking drug returns and medication record sheet. The PI or delegate will collect unused medication and packaging from the clinical team. Where participants are discharged from hospital during the treatment phase, returns will not be requested, trial staff will ask participants at the day 29 phone call how many tablets are remaining and this will be recorded on the accountability log. Trial drug compliance will be assessed from the information provided by the participant and the above medication checks

8.13. Name and description of each Non-Investigational Medicinal Product

N/A

9. PHARMACOVIGILANCE

9.1. Definitions

| Term | Definition |
|---|--|
| Adverse Event (AE) | Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. |
| Adverse Reaction (AR) | <p>An untoward and unintended response in a participant to an IMP which is related to any dose administered to that participant.</p> <p>The phrase "response to an IMP" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.</p> <p>All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as ARs. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative etiology that would explain the event.</p> |
| Serious Adverse Event (SAE) | <p>A SAE is any untoward medical occurrence that:</p> <ul style="list-style-type: none">• results in death• is life-threatening• requires inpatient hospitalisation or prolongation of existing hospitalisation• results in persistent or significant disability/incapacity• consists of a congenital anomaly or birth defect <p>Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.</p> <p>NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.</p> |
| Serious Adverse Reaction (SAR) | An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided. |
| Suspected Unexpected Serious Adverse Reaction (SUSAR) | A SAR, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information. |

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

9.2. Operational definitions for (S)AEs

Deterioration of the existing condition, COVID-19, with the exception of death, or known side-effects recorded as primary or secondary endpoints are not reported as (S)AEs or (S)ARs but are recorded separately. All events resulting in deaths will be reported as SAEs.

The following events will be deemed as expected in participants with COVID-19 and will not be recorded as AEs:

- cough
- pyrexia
- headache
- tiredness
- diarrhoea
- aches and pains
- nasal congestion
- runny nose
- sore throat
- Anosmia
- Loss of taste
- deterioration in renal and or liver function and changes in full blood count parameters; these will be recorded as endpoints for the evaluation of safety of the IMP

Anticipated AEs for the trial drug are listed in the Reference Safety Information these would not be considered to be SUSARs unless the severity of the event was considered to be unexpected.

All SAEs and SARs will be reported to sponsor, see section 9.3, with the exception of hospitalisation as this is recorded as an end point.

9.3. Recording and reporting of SAEs, SARs AND SUSARs

AEs will be recorded on the AE Log in the eCRF and will be assessed for severity and causality by the CI or PI. AEs occurring from the time a participant consents to join the trial until the participant's day 29 will be recorded. An AE may be classified as a SAE or AR. An initial assessment of expectedness/listedness for SAEs will be conducted by the PI based on the Reference Safety Information (RSI).

Participants discharged from hospital before the end of trial will be given a diary to record adverse events, this will be used as an aide memoire for them to report AEs at the telephone follow-up call. This diary will not be returned to the trial staff.

The PI will make a clinical judgment as to whether or not an AE is of sufficient severity to require the participant's discontinuation of treatment. A participant may also voluntarily discontinue treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant should be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

AEs and SAEs will be followed up until recovered/recovered with sequelae/death or for 30 days after participant's day 29 whichever happens first. SUSARS will be followed until resolution.

The CI, PI or delegate will check the medical records for the occurrence of AEs and hospitalisations at every data collection point/telephone call during the trial. Serious AEs (SAEs) will be submitted on an SAE form to the Sponsor Pharmacovigilance Section Tay.pharmacovigilance@nhs.scot within 24 hours

of becoming aware of the SAE. All SAEs need to be assessed and signed off by the PI or a delegated doctor within the 24hr reporting window. Site PIs will also notify the CI when submitting an SAE.

The evaluation of expectedness will be made based on the knowledge of the reaction and the relevant safety information (RSI) in the Brensocatib Investigators Brochure (IB) (see section 9.4). The Sponsor will make the definitive assessment on expectedness for the purposes of SUSAR reporting.

The Sponsor is responsible for reporting SUSARs to the UK competent authority, the MHRA, and the Research Ethics Committee (REC). Fatal or life threatening SUSARs will be reported within 7 days and non-fatal and non-life threatening SUSARs within 15 days.

9.4. Reference Safety Information

RSI is described in Section 6.6 of the IB. The RSI is used to assess the expectedness of events and will be checked by the CI for changes on the anniversary of the issue date of the CTA. Any change to the RSI for the IMP will be reviewed and if it changes significantly this may result in a substantial amendment to submit the updated IB.

9.5. Responsibilities

Principal Investigator (PI):

- Checking medical records for AEs and ARs.
- Using medical judgement in assigning seriousness, causality and whether the event/reaction was anticipated using the approved Reference Safety Information.
- Confirmation of eligibility criteria

Chief Investigator (CI) / delegate:

- Clinical oversight of the safety of participants participating in the trial, including an ongoing review of the risk / benefit.
- Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated (in line with the Reference Safety Information) where it has not been possible to obtain local medical assessment.
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol.
- Assigning Medical Dictionary for Regulatory Activities (MedDRA) to all SAEs and SARs.
- Preparing the clinical sections and final sign-off of the Development Safety Update Report (DSUR).
- Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database.
- Reporting safety information to the independent oversight committees identified for the trial (DMC).
- Notifying PIs of SUSARs that occur within the trial.
- Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.

Sponsor:

- Immediate review of all SUSARs.
- Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.

- Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

Data Monitoring Committee:

In accordance with the Trial Terms of Reference for the DMC, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis. The DMC will also advise on continuation/discontinuation of the trial at these reviews.

9.6. Notification of deaths

All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, the IMP, or an unrelated event. Reporting of deaths will follow the SAE reporting process and will be reported within 24 hours of the PI or delegate becoming aware of the death.

9.7. Pregnancy reporting

All pregnancies within the trial (either the trial participant or the participant's partner, with participants consent) will be reported to the CI and the Sponsor using the relevant TASC Pregnancy Notification Form within 24 hours of notification. The TASC Pregnancy Notification Form will be submitted to the Sponsor Pharmacovigilance Section Tay.pharmacovigilance@nhs.scot. The pregnancy will be followed up until the end of the pregnancy. If the trial participant is a male, informed consent for follow-up will be sought from his female partner.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE

9.8. Overdose

An overdose will be defined as taking more than 50mg of trial medication in a 24-hour period.

Whilst in hospital, the trial medication will be held and given to participants as per drug record by the clinical team. On discharge from hospital, participants will take home enough medication to complete 28 days of treatment.

An overdose itself is not an AE. However, if the overdose results in clinical signs and symptoms, it requires expedited reporting as if it is an SAE. In the case of an overdose, the PI or delegate should use clinical judgment in treating the overdose, and inform the Sponsor immediately.

9.9. Reporting urgent safety measures

The CI, PI or delegate will take appropriate immediate urgent safety measures in order to protect the participants against any immediate hazard to their health or safety. If any urgent safety measures are taken, the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

9.10. The type and duration of the follow-up of participants after adverse reactions (AR).

Participants with unresolved ARs at end of trial will be followed up until 30 days after participant's day 29. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be followed up until resolution. Any

SUSAR will be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.

9.11. Development safety update reports

The DSUR will be prepared jointly by the Sponsor Pharmacovigilance Section and CI and submitted by the Sponsor to the MHRA on the anniversary of the date of Clinical Trial Authorisation (CTA).

The DSUR and reports of SUSARs in the UK, with an HRA CTIMP Safety Report Form, will be sent to REC by the Sponsor Pharmacovigilance Section. Any other safety reports, for example, reports of a DMC, will be sent by the CI to REC, with a Safety Report Form, and to the Sponsor.

10. STATISTICS AND DATA ANALYSIS

10.1. Sample size calculation

In accordance with the WHO multicentre adaptive trial design recommendations, this trial is intended to allow for adaptation of blinded confirmation or modification of the primary endpoint³³. A brief summary is provided here. Details will be described in the interim evaluation analysis plan.

Blinded endpoint confirmation or modification

The current plan is to evaluate the primary endpoint up to day 29. Because there is uncertainty about the clinical course and potential different trajectories according to baseline disease severity, the day of the primary endpoint may be modified based on a blinded evaluation of various time points (e.g., days 7-29). [Posch, 2012] This will occur by a blinded evaluation by the statistician and trial steering committee without knowledge of treatment assignment.

The primary outcome uses an ordinal severity scale with 7 categories. The null hypothesis being tested is whether the odds of improvement on the ordinal scale is the same for the placebo and experimental treatment arms (i.e., whether the common odds ratio differs from 1).

The proportions of participants in the different categories of the ordinal scale at day 29 in the placebo and treatment arm assuming an odds ratio (OR) of 2 are given below. The odds ratio represents the odds of improvement in the ordinal scale for treatment relative to placebo control [Whitehead, 1993]

Table 4 displays four scenarios considered for outcomes under placebo for sample size determination. There is significant uncertainty with these assumptions given the limited data available.

Table 5 shows a range of sample sizes for odds ratios ranging from 1.5 to 2.5 for 85% power. For 90% power, increase the sample size by 17%. Table 6 displays the probabilities of being in different categories of the ordinal scale under an odds ratio of 2.

Table 4: Four scenarios considered for outcomes under placebo for sample size determination

| | Anticipated |
|---|-------------|
| Severity Outcome | outcome (%) |
| Death | 2 |
| Hospitalised, on mechanical ventilation or ECMO | 1 |

| | |
|--|----|
| Hospitalised, on non- invasive ventilation or high flow oxygen Devices | 2 |
| Hospitalised, requiring supplemental oxygen | 7 |
| Hospitalised, not requiring supplemental Oxygen | 8 |
| Not hospitalised, limitation on activities | 38 |
| Not hospitalised, no limitations on activities | 42 |

Table 5. Sample size calculations for scenarios in Table 4 for a two-arm trial assuming 85% power and various true odds ratios.

| True odds ratio | Total sample size |
|-----------------|-------------------|
| 1.5 | 774 |
| 1.75 | 412 |
| 2.0 | 272 |
| 2.25 | 201 |
| 2.5 | 159 |

Table 6. Treatment ordinal outcome proportions under odds ratio of 2 for scenario in Table 4 at day 15.

| Anticipated | | |
|--|-----------|-------------|
| Severity Outcome | Control % | Treatment % |
| Death | 2 | 1 |
| Hospitalised, on mechanical ventilation or ECMO | 1 | 0.5 |
| Hospitalised, on non- invasive ventilation or high flow oxygen devices | 2 | 1 |
| Hospitalised, requiring supplemental oxygen | 7 | 3.8 |
| Hospitalised, not requiring supplemental oxygen | 8 | 4.7 |
| Not hospitalised, limitation on activities | 38 | 29.7 |
| Not hospitalised, no limitations on activities | 42 | 59.2 |

Note that columns may not sum to exactly 100 due to rounding errors.

Prior to the commencement of the trial, we took the anticipated WHO scenario and the odds ratio of 2 which required enrolment of 272 participants. Allowing for a potential loss to follow-up of 9% (27 participants) this meant we will required 300 participants (150 per arm) to achieve 85% power at 5% significance. This was subsequently reviewed as part of a pre-specified blinded sample size re-evaluation by an independent statistician. The results of this re-evaluation, using data for the primary endpoint available in December 2020 found that 300 patients enrolled would provide approximately 88% power to detect an odds ratio of 2.0. This, along with the results of other COVID-19 trials were reviewed by the Trial Steering Committee (TSC) and DMC who noted that other COVID-19 therapeutics had achieved odds ratios lower than 2.0 in the majority of cases. Based on this, the TSC and DMC recommended targeting an odds ratio of 1.75. At least 80% power for an odds ratio of 1.75 requires enrolment of a minimum of 360 patients with 400 patients provided approximately 85% power. A final sample size of 400 subjects was therefore recommended by the TSC and subsequently approved by the DMC in December 2020. Planned recruitment rate

Recruitment is expected to be completed by the end of January 2021.

10.2. Statistical analysis plan

The primary analysis will be based on an intention-to-treat population, including participants randomized. Similarly, safety analyses will be based a modified intent-to-treat population consisting of all participants who were randomized.

This is a controlled randomized trial testing a superiority hypothesis with a two-sided type I error rate of 0.05. Secondary hypotheses have been ordered according to relative importance. These will be described according to the appropriate summary statistics (e.g., proportions for categorical data, means with 95% confidence intervals for continuous data, median for time-to-event data).

A statistical analysis plan (SAP) will be prepared for analysis of primary and secondary outcomes and will include a plan for handling missing data.

10.2.1. Summary of baseline data and flow of participants

Detailed in SAP

10.2.2. Primary outcome analysis

Detailed in SAP

10.2.3. Secondary outcome analysis

Detailed in SAP

10.3. Subgroup analyses

Detailed in SAP

10.4. Adjusted analysis

Detailed in SAP

10.5. Interim analysis and criteria for the premature termination of the trial

For reasonable cause, the PI may terminate a participant's participation in the trial prematurely. The Sponsor may decide to terminate the trial prematurely. If this occurs, written notification of the trial

termination is required to be sent to all the sites. Some conditions that may warrant trial termination include the following:

- Discovery of an unexpected, significant, or unacceptable risk to the participants in the trial,
- Decision on the part of the funder to suspend or discontinue development of the investigational product,
- Decision by a regulatory authority or the Sponsor to stop the trial at any time, were applicable.

If the trial is prematurely terminated, all participants who received a dose of any of the trial drugs and have not completed their trial period will be discontinued from the trial drug immediately; all the safety procedures required to be performed will be conducted. All discontinued participants will be followed up by a phone call 30 days after discontinuation for collection of AEs. The Sponsor will notify the appropriate Regulatory bodies in the respective countries regarding the reason for terminating the trial.

The DMC will evaluate the results of the trial in an unblinded fashion for safety. Participant population

The participant populations whose data will be participated to the trial analysis – both for the primary analysis and any applicable secondary analyses will be all-treated population, i.e. any participant randomised into the trial that received at least one dose of trial drug. Procedure(s) to account for missing or spurious data will be detailed in the SAP.

The primary analysis will be based on the intention-to-treat principle. The extent of missing data will be examined and the reason for drop-out ascertained. Multiple imputation may be used to impute missing values if necessary and where assumptions for missing at random data are met. Where imputation is used, a sensitivity analysis will be conducted considering only cases without missing data. Complete case analysis where missing participants are excluded will be carried out as a secondary analysis.

10.6. Economic evaluation

No economic evaluation is planned.

11. DATA MANAGEMENT

11.1. Data collection tools and source document identification

Medical records will be used as source data. The EQ-5D (interviewer administration) will be completed by the research staff and act as source data, the completed form will be filed in the medical notes. All trial data relevant to a participant's general medical history will be recorded in the medical record. The medical record will be flagged to state that the patient is participating in the STOP-COVID19 trial.

The PI or delegate will maintain source documents for each participant in the trial, consisting of hospital medical records containing demographic and medical information, laboratory data, electrocardiograms, trial questionnaires and the results of any other tests or assessments.

An eCRF, using CASTOR Electronic Data Capture system, will be provided by TCTU. The trial system will be based on the protocol for the trial. Development and validation of the trial database and quality control will be done according to TCTU procedures.

The eCRF will not collect more information than is required to meet the aims of the trial and to ensure the eligibility and safety of the participant.

The PI may delegate eCRF completion but is responsible for completeness, plausibility and consistency of the eCRF. Delegated trial staff will enter the data required by the protocol into the eCRFs following training in the definitions and methods used in completing the eCRF. Any queries will be resolved by the

CI or delegated member of the trial team. On completion of data collection the PI must certify that the data entered into the eCRFs are complete and accurate. PI sign off of the eCRF will be embedded in the eCRF with the PI using their own login.

Data verification and cleaning and extraction of data will be performed as per TCTU local procedures and detailed in the Data Management Plan.

Data preservation and sharing will be in accordance with established procedures at the University of Dundee. General laboratory data methods and results will be documented in laboratory notebooks and then analysed and written up for publication for dissemination to the scientific community (Tayside only). All electronic data will be stored on secure University of Dundee or cloud-based servers which have restricted access and have disaster recovery systems in place.

11.2. Access to Data

The CI, PIs and all institutions involved in the trial will permit trial related-monitoring, audits, REC review, and regulatory inspection. In the event of an audit, the CI will allow the Sponsor, representatives of the Sponsor or regulatory authorities direct access to all trial records and source documentation.

11.3. Archiving

Archiving of trial documents will be as detailed in the archiving plan, in compliance with Sponsor SOPs. All trial documentation, electronic and paper, will be kept for 25 years. Medical records will be maintained in compliance with local NHS policy on retention of medical records. The Sponsor will be responsible for archiving the Trial Master and Sponsor File, sites will be responsible for archiving local trial records including the Investigator Site File (ISF) and Pharmacy Site File.

12. MONITORING, AUDIT & INSPECTION

12.1. Monitoring

A trial risk assessment will be carried out by the Sponsor prior to Sponsorship approval being granted. The Sponsor has determined the appropriate extent and nature of monitoring for the trial and will appoint appropriately qualified and trained monitors independent to the trial team. A Monitoring Plan will be developed by the sponsor based on the trial risk assessment which may include on site monitoring. The Monitoring Plan will be reviewed regularly using a risk-based approach and up-dated as required. The Monitoring Plan will detail the procedures and anticipated frequency of monitoring, processes reviewed. It is anticipated that due to the COVID-19 pandemic that monitoring will be completed remotely. Sites must have access to source data for purposes of remote monitoring and assist the Sponsor in monitoring of the trial. In recognition that source data may come from different sources at each site, sites shall ensure that a source data identification list is supplied to the Monitoring Team in advance of any monitoring review and ensure they have this data is available on the agreed date and time to facilitate the review

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Research Ethics Committee review & reports

Before the start of the trial, approval will be sought from Scotland A REC (approved to review trials requiring ethical approval under the Adults with Incapacity (Scotland) Act 2000) for the trial protocol, ICF and other relevant documents, e.g. GP information letters

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial.

All correspondence with the REC will be retained in the TMF.

An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. It is the CI's responsibility to produce the annual reports as required.

The CI will notify the REC of the end of the trial. If the trial is ended prematurely, the CI will notify the REC, including the reasons for the premature termination. Within one year after the end of the trial, the CI will submit a final report with the results, including any publications/abstracts, to the REC.

A copy of all REC reports will be submitted to the Sponsor.

13.2. Peer review

This trial has been funded by Insmed Incorporated who have reviewed the grant application and the protocol has been reviewed and approved by the Sponsor Committee responsible for this.

Resulting publications will be reviewed by the referees of the journal to which the paper will be submitted.

13.3. Public and Patient Involvement

Due to limited time in the development of the protocol, minimal public and patient involvement has been planned in the set-up phase. Lay person review of the PIS, ICF and diary has been completed by the Edinburgh Clinical Research Facility – Covid-19 Patient Public Involvement Advisory Group. Feedback from the group has been adopted throughout these documents. We will involve the European Lung Foundation, a European patient group, in dissemination of research results.

13.4. Regulatory Compliance

The trial will not commence until a CTA is obtained from the Medicines and Healthcare products Regulatory Agency (MHRA) and Favourable REC opinion. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments

Before any site can enrol participants into the trial, the CI, PI or delegate will ensure that appropriate approvals from participating organisations are in place.

For any amendment to the trial, the CI, PI or delegate, in agreement with the sponsor, will submit information to the appropriate body in order for them to issue approval for the amendment. The CI, PI or delegate will work with sites (NHS R&D departments at sites as well as the trial delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the trial as amended.

13.5. Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used, e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol. The CI will not implement deviations to the protocol except where necessary to eliminate an immediate hazard to trial participants.

Accidental protocol breaches can happen at any time. They will be adequately documented on the relevant forms and reported to the CI and Sponsor using the TASC Breach Reporting and CAPA Form. In

the event that there is a breach of the protocol, the nature of and reasons for the breach will be recorded in the TMF and documented in the trial TASC Breach Report Log. Breaches from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

13.6. Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree –

- a) the safety or physical or mental integrity of the participants of the trial; or
- b) the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor of a clinical trial will notify the licensing authority in writing of any serious breach of

- a) the conditions and principles of GCP in connection with that trial; or
- b) the protocol relating to that trial, as amended from time to time.

If a serious breach of the protocol or GCP is suspected, this will be reported to the Sponsor immediately using the TASC Breach Reporting & CAPA Form and will be recorded in the eCRF and documented in the trial TASC Breach Report Log.

If a breach necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and categorisation and then to the appropriate REC, MHRA and NHS R&D for review and approvals as appropriate.

13.7. Data protection and participant confidentiality

The CI and trial staff will comply with the requirements of the General Data Protection Regulation (EU) 2016/679 (GDPR) and the UK Data Protection Act 2018 or any subsequent amendment or replacement thereof with regard to the collection, storage, processing and disclosure of personal data and will uphold the principles of GDPR in Article 5.

The CI and trial staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or local equivalent.

All trial records and data will be managed in a manner designed to maintain participant confidentiality. All records, electronic or paper, will be kept in a secure storage area with access limited to appropriate trial staff only. Computers used to collate data will have limited access measures via user names and passwords. Age, gender and ethnicity will be the only personal identifiable details held on CASTOR Electronic Data Capture system.

Personal data or data concerning health will not be released without the existence of a legal basis for processing under Articles 6 and 9 of GDPR, such as official authority 6(1)e or substantial public interest 9(2)g. The CI and trial staff will not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the Sponsor will be required for the disclosure of any said confidential information to other parties.

Access to collated participant data will be restricted to the CI and appropriate delegated trial staff.

Where data requires to be transferred, an appropriate Data Transfer Agreement will be put in place.

Published results will not contain any personal data that could allow identification of individual participants.

13.8. Financial and other competing interests

The CI has received fees for consulting from the trial funder, Insmed Inc. and holds research grants from Insmed. Any conflict of interest declared by site staff shall be notified to the Sponsor and retained in the TMF.

13.9. Indemnity

The University of Dundee and Tayside Health Board are Co-Sponsoring the trial.

Insurance. – The University of Dundee will obtain and hold Clinical Trials Insurance cover for legal liabilities arising from the trial.

Tayside Health Board will maintain its membership of the Clinical Negligence and Other Risks Insurance Scheme (CNORIS) which covers the legal liability of Tayside in relation to the trial.

Where the trial involves University of Dundee staff undertaking clinical research on NHS participants, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

Indemnity. The Co-Sponsors do not provide trial participants with indemnity in relation to participation in the Trial but have insurance for legal liability as described above.

Where other Scottish Health Boards are participating as trial sites, those other Scottish Health Boards will maintain membership of CNORIS to cover their liability in relation to their conduct of the trial.

Where other UK NHS organisations are participating as trial sites, those other UK NHS organisations will maintain membership of a scheme similar to CNORIS.

13.10. Amendments

Amendments to protocol will be conducted in compliance with Sponsor SOPs. The decision to amend the protocol will lie with the CI after consultation with the TMG, trial statistician and funder. The CI will seek Sponsor approval for any amendments to the Protocol or other approved trial documents. The Sponsor will decide whether an amendment is substantial or non-substantial. The CI will be responsible for submitting the amendment to the appropriate regulatory authorities and communicating amendments to sites. Amendments to the protocol or other trial documents will not be implemented without approval from the Sponsor and subsequent approval from the appropriate REC and/or MHRA, as appropriate, and NHS R&D Office(s). The amendment history will be detailed in an Amendment Log.

13.11. Post-trial care

As the trial treatment is for a 28 day treatment period only, and if used in clinical care would be a one-off treatment for COVID-19, no advantage is expected from continuing the trial treatment after the initial 28 days. Trial treatment will not be made available to participants at the end of the trial.

13.12. Access to the final trial dataset

The CI and Trial Statistician will have access to the final trial dataset. Access to the final trial dataset to others will be approved by the CI.

14. DISSEMINATION POLICY

14.1. Dissemination policy

Details of the trial and clinical trial final report will be published on the EudraCT database, the latter no later than 12 months after the end of trial, and will be available to the public via the EU Clinical Trial Register. The report will be made available to the Funder. The report can be used for publication and presentation at scientific meetings. Trial investigators have the right to publish orally or in writing the results of the trial. The criteria for authorship will follow the criteria of the International Committee of Medical Journal Editors.

Publications will be reviewed according to the agreed contractual terms but will not restrict the general rights outlined above for the Investigators to publish the results of the trial.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion). A newsletter giving a summary of the results of the trial will be made available to participants.

14.2. Authorship eligibility guidelines and any intended use of professional writers

The data arising from this trial resides with the trial team and ownership with the University of Dundee. The criteria for authorship will follow the criteria of the International Committee of Medical Journal Editors. On completion of the trial, the trial data will be analysed and tabulated, and a clinical trial final report will be prepared. The CI will be responsible for authorship of the final report.

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16. APPENDICIES

16.1. Appendix 1-Risk

| | | | | |
|---|--------------------|------------------------------------|-------------------------|--|
| <p>Risks associated with trial interventions</p> <p><input type="checkbox"/> A ≡ Comparable to the risk of standard medical care</p> <p><input type="checkbox"/> B ≡ Somewhat higher than the risk of standard medical care</p> <p><input checked="" type="checkbox"/> C ≡ Markedly higher than the risk of standard medical care</p> | | | | |
| <p>Justification: This is an investigational therapy but has been shown to be safe and well tolerated over a 6 month period in over 200 patients with bronchiectasis. The treatment is therefore expected to represent a low risk of adverse effects for 28 days treatment.</p> <p>Undesirable effects are detailed in section 6.3 of the IB</p> | | | | |
| What are the key risks related to therapeutic interventions you plan to monitor in this trial? | | How will these risks be minimised? | | |
| IMP/Intervention | Body system/Hazard | Activity | Frequency | Comments |
| Increase in severity of infections | Lung | Close monitoring | as clinically indicated | Not expected in view of phase 2 data |
| Hyperkeratosis | Skin | Patients told to report | Daily while in hospital | Rare over 6 months in phase 2 |
| Dental complications | Teeth | Patients told to report | Daily while in hospital | Not expected with short treatment duration |
| Neutropenia | Blood | Regular blood tests | as clinically indicated | Not observed in phase 2 study. |
| <p>Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. DMC, independent data review, etc.)</p> <p>Participant safety will be reviewed periodically by the DMC.</p> <p>An information sheet will be provided for clinical staff caring for the participant detailing dosing instructions and possible adverse effects.</p> | | | | |
| <p>Outline any processes (e.g. IMP labelling +/- accountability +/- trial-specific temperature monitoring) that have been simplified based on the risk adapted approach.</p> <p>Nil</p> | | | | |

16.2. Appendix 2 - Trial management / responsibilities

Responsibilities will be detailed the co-sponsorship and model trial agreements.

16.2.1. Participant registration/randomisation procedure

TCTU TRuST web-based randomisation system will be used: <https://hicservices.dundee.ac.uk/TRuST/>

Sites will be provided with a randomisation guide detailing the web-based randomisation system process. Prior to recruitment individuals delegated this task and on completion of training will be given a username and password.

16.2.2. Data management

Data management will be overseen by TCTU Data Management Team (DMT).

Local sites will be expected to enter data directly on to the eCRF Worksheets will be provided to facilitate this process but their use is not mandatory. Worksheets, where used, will not record source data and will not be used for monitoring purposes.

All data from participants should be entered on the eCRF within 7 days of the last data collection point for that participant.

Data queries will be generated by the DMT and emailed to sites, return of queries should be within 2 weeks.

16.2.3. Preparation and submission of amendments

TCTU Trial Management Team will be responsible for working with the CI to submit any amendments.

16.2.4. Preparation and submission of Annual Safety Report/Annual

TCTU Trial Management Team will be responsible for liaising with the CI to submit REC annual reports.

The Sponsor Pharmacovigilance Team will be responsible for liaising with the CI to submit Annual Safety Reports.

16.2.5. Data protection/confidentiality

The CI and trial staff will comply with the requirements of the EU General Data Protection Regulation and the Data Protection Act 2018 or any subsequent amendment or replacement thereof with regard to the collection, storage, processing and disclosure of personal data and will uphold the Principles of GDPR in Article 5.

The CI and trial staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or local equivalent.

16.2.6. Trial documentation and archiving

Archiving trial site data will be the responsibility of individual sites. Payment for archiving will be provided as per site agreement.

16.3. Appendix 3 – Authorisation of participating sites

16.3.1. Required documentation

The following data should be made available to TCTU Trial Management Team prior to site initiation:

- PI CV, signed and dated
- PI GCP certificate
- Protocol signature page, signed and dated by PI
- Copy of signed Participating Site Agreement
- Copy of R&D confirmation of capacity and capability

The following data should be made available and held within the ISF/PSF prior to site initiation:

- CV, signed and dated for all trial staff listed on Delegation Log
- GCP certificate for all trial staff listed on Delegation Log

16.3.2. Procedure for initiating/opening a new site

Site Initiation will be carried out remotely due to COVID-19 pandemic.

Site Initiation will be performed by Sponsor monitors and TCTU Trial Management Team.

TCTU Trial Management Team will initiate release of trial drug to the site after R&D confirmation of capacity and capability.

16.3.3. Principal Investigator responsibilities

The PI's legal responsibilities will be listed in the Participating Site Agreement a summary is given below:

- Attendance at the initiation teleconference,
- Training of new members of trial staff in the protocol and its procedures,
- Ensuring that the ISF is accurately maintained,
- Dissemination of important safety or trial related information to all stakeholders within their site
- Safety reporting within the required timelines
- Ensuring data entry to eCRF and responses to data clarification queries are completed within the required timelines.
- Certify data entered on eCRF is correct and complete.
- Ensuring any trial staff coming into contact with participants have the appropriate Personal Protective Equipment and training in its use.
- Archiving of site trial data.

16.4. Appendix 4 – Schedule of Procedures

| | Screening ^d | Randomization ^d | | | Follow-up Assessments | Follow-up assessments | Follow-up Assessments | Unscheduled Assessments |
|--|------------------------|--|------------------------------|---|---|---|---|-----------------------------------|
| Timeline | Day 0 or 1 | Day 1 Up to 24 hours after screening | Daily whilst hospitalised | Days 3, 5 & 11 ^c (telephone call if at home) | Day 8 ^c (telephone call if at home) | Day 15 ^c (telephone call if at home) | Day 29 ^c (telephone call if at home ^b) | As Required in the event of AE |
| Informed Consent | X | | | | | | | |
| Inclusion/Exclusion Criteria Check | X | X | | | | | | |
| Medical History | X | | | | | | | |
| Record Concomitant Medications | X | X | | | X | X | X | X |
| Check Vital Signs* [^] | X | X | | | X [∞] | X [∞] | X [∞] | X |
| ECG* | X | | | | | | | |
| Full blood count* ⁺ | X | | | X [∞] | X [∞] | X [∞] | X [∞] | |
| Urea and electrolytes* ⁺ | X | | | X [∞] | X [∞] | X [∞] | X [∞] | |
| Liver function tests* ⁺ | X | | | X [∞] | X [∞] | X [∞] | X [∞] | |
| SARS CoV-2 PCR* | X | | | | | | | |
| Record SARS CoV-2 PCR results, only if done for clinical reasons | | | | X | X | X | X | |
| Nasal swab for SARS CoV-2 PCR* (Tayside only) | | | | | | X [∞] | X | |
| Research Blood Sample * (Tayside and Sheffield only) | | X | | | X [∞] | X [∞] | X | X |
| Sputum sample for storage if available* ⁺ (Tayside only) | | X | | | X [∞] | X [∞] | X | |
| Endotracheal aspirate sample for storage if available* ^{++a} (Tayside only) | | | | | X [∞] | X [∞] | X [∞] | |
| Clinical status on 7 point scale | X | X | X | X | X | X | X | X |
| NEWS recording* | X | X | X | X [∞] | X [∞] | X [∞] | X [∞] | |

| | Screening ^d | Randomization ^d | | | Follow-up Assessments | Follow-up assessments | Follow-up Assessments | Unscheduled Assessments |
|---|------------------------|---|---------------------------|--|---|--|--|--------------------------------|
| Timeline | Day 0 or 1 | Day 1 Up to 24 hours after screening | Daily whilst hospitalised | Days 3, 5 & 11 ^c (telephone call if at home) | Day 8 ^c (telephone call if at home) | Day 15 ^c (telephone call if at home) | Day 29 ^c (telephone call if at home ^b) | As Required in the event of AE |
| EQ-5D questionnaire | | | | | | | X | |
| Record supplemental oxygen* | X | X | | | X [∞] | X [∞] | X [∞] | X |
| Record CT scan results, only if done for clinical reasons | X | X | X | X [∞] | X [∞] | X [∞] | X [∞] | X [∞] |
| Pregnancy Testing (urine or blood) If Applicable | X | | | | | | | |
| Record Adverse Events | | X | X | X | X | X | X | X |
| Randomisation | | X | | | | | | |
| Dispense Trial Drugs | | X | | | | | | |
| Drug Return And Compliance Check | | | | | | | X | |

^a Vital Signs: Blood Pressure, pulse, temperature, oxygen saturation

*indicates procedures that will be performed by the clinical team as part of routine care but results will be recorded and included in the eCRF. If not performed by the clinical team, but clinically indicated, the research team may assist in this being performed but all processes will avoid duplication and exposure to potentially infected participants.

[†]Excess biological samples that are being taken for clinical reasons may be stored for future use if no longer required for clinical purposes (Tayside only).

^a For those participants who are intubated.

[∞]These assessments will not be completed if the participant has been discharged from hospital.

^b For the Tayside and Sheffield site only, the day 29 assessments will be carried out face-to-face either at a NHS facility or at the participant's home. Home visits will only be carried out if no one in the household has symptoms of COVID-19.

^cResearch blood samples (Tayside and Sheffield only) and, once discharged, assessments may be completed within +/- 1 day

^dScreening and randomisation may occur on the same day if all eligibility criteria are met. Day of first dose of IMP will be considered as day 1 for the calculation of follow up assessments.

16.5. Appendix 5 – Safety Reporting Flow Chart

| Activity | Responsibility | Timing | Comments |
|---|------------------|--|--|
| Review medical records for evidence of AEs whilst in hospital or ask participant if discharged. | Trial staff | Days 3, 5, 8, 11, 15, 29 | Recorded on eCRF system. Where Trial Staff are not available on these specific days this should be completed asap. |
| Review of recorded AEs for causality and seriousness | PI (or delegate) | Within 24 hour of recording | Recorded on eCRF and/or medical records. |
| Reporting SAEs - All SAEs need to be assessed and signed off by the PI or delegated doctor. | PI (or delegate) | Within 24 hours of becoming aware of SAE | SAE form: https://www.ahspartnership.org.uk/tasc/for-researchers/sops/safety-and-pharmacovigilance Reported to: Tay.pharmacovigilance@nhs.scot j.chalmers@dundee.ac.uk |
| Reviewing of SAEs | Sponsor | Within 24 hours of receiving SAE form | |
| Reporting of SUSARs to MHRA | Sponsor | Within 7 days if life threatening or fatal. Within 15 days for others | |

16.6. Appendix 6 – Amendment History

| Amendment No. | Protocol version no. | Date issued | Author(s) of changes | Details of changes made |
|----------------------------|----------------------|-------------|----------------------|---|
| N/A prior to full approval | 2 | 04-05-20 | M Band/J Chalmers | Requested by MHRA: Inclusion criteria to include hospitalised participants. Contraception to be used for 30 days after last dose of IMP. |
| AM02 | 3 | 20-05-20 | M Band/J Chalmers | Removal of the requirement for Caldicott Guardian approval for research staff to identify potential participants. Conforms to advice from Confidentiality Advisory Group and Public Benefit and Privacy Panel. Additional guidance on handling Informed Consent Form with COVID-19 patients. Minor clarifications to protocol. |
| AM04 | 4 | 30-06-20 | M Band/J Chalmers | Inclusion criteria to include clinically suspected COVID-19. Exclusion criteria to exclude currently taking phenytoin or rifampicin Clarification of co-enrolment. Clarification of handling ICF Addition of visit instead of phone call for participants at day 29 (Tayside only). Itraconazole, Ketoconazole, diltiazem, verapamil, phenytoin or rifampicin added as trial restrictions Minor clarifications to protocol. |
| AM07 | 5 | 03-07-20 | M Band/J Chalmers | Update of consent process to reflect process requested by and confirmed with REC for AM05 approval Addition of Sheffield to take research bloods Clarification that day 1 of trial will be day of first dose of IMP |
| AM09 | 6 | 19-08-20 | M Band/J Chalmers | Update eligibility with criteria for hospitalisation timelines Update eligibility with excluded medications Update on trial restrictions – excluded medications |

| | | | | |
|------|---|----------|-------------------|---|
| | | | | Removal of long-term follow-up Clarification on IMP accountability procedures for discharged participants, Clarification on safety reporting flow chart Addition of recording SARS CoV-2 PCR results when done for clinical reasons |
| AM12 | 7 | 10-10-20 | M Band/J Chalmers | 3.7 Exploratory blood analysis omitted if no lab capacity 16.4 Clarification that research samples taken on Day 29 for Tayside & Sheffield |
| AM13 | 8 | 12-12-20 | M Band/J Chalmers | I Addition of Key Contacts 1 Update to background with current scientific knowledge 6.2 Exclusion criteria changed to: Current treatments with potent Cyp3A4 inducers/inhibitors (e.g Itraconazole, Ketoconazole, diltiazem, verapamil, phenytoin or rifampicin) 7.1 & 10.2 Recruitment to continue beyond 300, final recruitment target will be confirmed after the evaluation of the power calculation 9.3 & 16.5 Clarification of SAE reporting process 10.1 Update to blinded endpoint confirmation process. |
| AM14 | 9 | | M Band/J Chalmers | Update to sample size and justification of change |