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

Statistical Analysis Plan

TRIAL FULL TITLE	**A randomised double-blind placebo-controlled trial of Brensocatib (INS1007) in patients with severe COVID-19**
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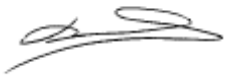
James Chalmers		05/04/2021
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1 Table of Contents

1 Table of Contents 3
2 Abbreviations and Definitions 6
3 Introduction 6
3.1 Preface 6
3.2 Purpose of the analyses 6
4 Study Objectives and Endpoints 7
4.1 Study Objectives 7
4.2 Endpoints 7
4.3 Derived variables 8
5 Study Methods 9
5.1 General Study Design and Plan 9
5.2 Inclusion-Exclusion Criteria and General Study Population 10
5.2.1 Inclusion criteria 10
5.2.2 Exclusion criteria 11
5.2.3 Co-enrolment 11
5.3 Randomisation and Blinding 12
5.4 Study Variables 13
6 Sample Size 17
7 General Considerations 20
7.1 Timing of Analyses 20
7.2 Analysis Populations 20
7.2.1 Full Analysis Population 20
7.2.2 Per Protocol Population 20
7.2.3 Preliminary analysis population 20
7.2.4 Safety Population 20
7.3 Covariates and Subgroups 20
7.4 Missing Data 21

7.5 Interim Analyses and Data Monitoring 21
7.5.1 Planned Schedule of Interim Analyses 21
7.5.2 Scope of Adaptations 21
7.5.3 Stopping Rules 21
7.5.4 Adjustment of Confidence Intervals and p-values 22
7.5.5 Documentation of Interim Reports 22
7.6 Preliminary analysis 23
7.7 Multi-centre Studies 23
7.8 Multiple Testing 23
8 Summary of Study Data 24
8.1 Subject Disposition 24
8.2 Protocol Deviations 24
8.3 Demographic and Baseline Variables 24
8.3.1 Other Baseline Characteristics 25
8.4 Treatment Compliance 25
8.5 Loss to follow-up 25
9 Efficacy Analyses 26
9.1 Primary Efficacy Analysis 26
9.2 Secondary Efficacy Analyses 26
9.2.1 Time to clinical improvement (1 category) 26
9.2.2 Clinical status at Day 3, 5, 8, 11, 15, 29 26
9.2.3 Change in 7-point scale 26
9.2.4 Time to discharge or to a NEWS of ≤2 26
9.2.5 Change in NEWS from baseline to days 8, 15 and 29 27
9.2.6 No of days free from oxygen 27
9.2.7 Duration of new oxygen used 27
9.2.8 Number of patients receiving new mechanical ventilation 27
9.2.9 No of days free from ventilation 27

9.2.10 Duration of new ventilation used 27
9.2.11 Duration of hospital stay – days 27
9.2.12 28-day mortality 27
9.3 Exploratory Efficacy Analyses 28
10 Safety Analyses 28
10.1 Extent of Exposure 28
10.2 Adverse Events 29
10.3 Deaths, Serious Adverse Events and other Significant Adverse Events 29
10.4 Pregnancies 29
10.5 Clinical Laboratory Evaluations 29
10.6 Other Safety Measures 29
11 Other Analyses 29
11.1 Quality of Life (EQ-5D-5L) 30
12 Reporting Conventions 30
13 Technical Details 30
14 Summary of Changes to the Protocol 30
15 References 30
16 Listing of Tables, Listings and Figures 31

2 Abbreviations and Definitions

AE	Adverse Event
CRF	Case Report Form
IMP	Investigational Medical Product
SAP	Statistical Analysis Plan

3 Introduction

3.1 Preface

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. 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 proteases, 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.

3.2 Purpose of the analyses

These analyses will assess the efficacy and safety of Brensocatib in comparison with placebo and will be included in the clinical study report.

4 Study Objectives and Endpoints

4.1 Study Objectives

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.

4.2 Endpoints

Primary outcome

The primary outcome is participant clinical status (on a 7-point ordinal scale) at day 29.

Secondary outcome

Clinical severity:

1. Time to an improvement of one category from admission to day 29 using 7-point ordinal scale
2. Clinical status on 7-point ordinal at days 3, 5, 8, 11, 15 and 29
3. Change on 7-point ordinal from baseline to day 15
4. Proportion of participants showing improvement on 7-point ordinal scale at day 15
5. Mean change in the 7-point ordinal scale from baseline (day 1) to days 3, 5, 8, 11, 15 and 29.

National Early Warning Score (NEWS):

1. Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.
2. Change from baseline to days 3, 5, 8, 11, 15 and 29

Oxygenation:

1. Oxygen free days
2. Incidence and duration of new oxygen use during the trial

Mechanical ventilation:

1. Ventilation free days
2. Incidence and duration of new mechanical ventilation use during the trial

Hospitalisation:

Duration of hospitalisation (days)

Mortality:

29 day mortality

Safety of the intervention:

1. Cumulative incidence of serious adverse events (SAEs) from day 1 to 29.
2. Discontinuation or temporary suspension of treatment from days 1 to 28.

Quality of life

1. EQ-5D-5L at day 29

4.3 Derived variables

The primary endpoint is an assessment of the clinical status on a given trial day using a 7-point ordinal scale. Each day, the worse score for 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.

The NEWS score is based on 7 clinical parameters:

1. Respiration rate (per minute)
2. SpO_2 Scale 1(%)
3. Air or Oxygen
4. Systolic blood pressure (mmHg)
5. Pulse (per minute)
6. Consciousness
7. Temperature (^oC)

5 Study Methods

5.1 General Study Design and Plan

(ICH E3;9)

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:

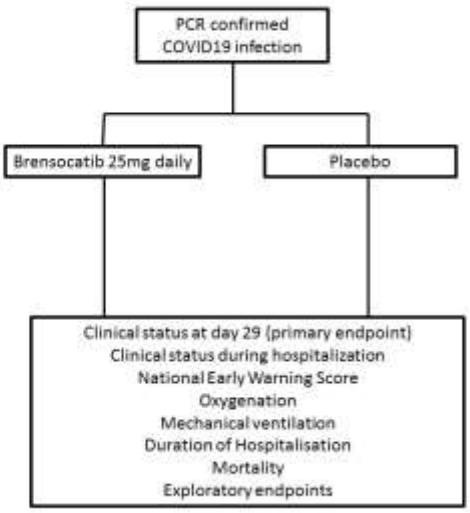
1. Brensocatib 25mg once daily for 28 days
2. Placebo once daily for 28 days

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

The proposed primary outcome assessed on a 7-point ordinal scale at day 28.



5.2 Inclusion-Exclusion Criteria and General Study Population

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.

5.2.1 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 10^9 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.

5.2.2 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 x 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.

5.2.3 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.

Enrolment in observational trials will not be an exclusion to participation.

Co-enrolment in another CTIMP is not acceptable

5.3 Randomisation and Blinding

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: $<$65 years/$\geq$65 years. Randomisation will be done centrally using a web-based validated randomisation program provided by Tayside Clinical Trials Unit. The trial is doubled-blind, participants and trial staff are blind to allocation, unblinding will take place after database lockdown. Emergency unblinding procedures are described in section 7.6 of the protocol.

5.4 Study Variables

Table 1: Study variables

	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	

	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
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∞	
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∞

	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
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	

^ 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.

[c]Research blood samples (Tayside and Sheffield only) and, once discharged, assessments may be completed within +/- 1 day

[d]Screening 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.

6 Sample Size

(ICH E3; 9.7.2. ICH E9; 3.5)

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 endpoint.[1]

Blinded endpoint confirmation or modification

The trial was originally designed with the option of modifying the primary endpoint. However, decision was made to retain the original primary outcome.

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 28 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.[2]

Table 2 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 3 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 4 displays an anticipated scenario for the primary outcome of the ordinal scale under an odds ratio of 2.

Table 2: anticipated scenario for the primary outcome

	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 3. Sample size calculations for scenarios in Table 2 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 4. 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 (Appendix 1).

7 General Considerations

7.1 Timing of Analyses

The final analysis will be conducted following last patient last visit assuming that at least 400 patients have been enrolled.

7.2 Analysis Populations

(ICH E3; 9.7.1, 11.4.2.5. ICH E9; 5.2)

7.2.1 Full Analysis Population

The primary analysis will be based on the intention-to-treat principle, which will include all participants who are randomised and received at least one dose of randomised therapy.

7.2.2 Per Protocol Population

Per-protocol (PP) analyses restricted to participants who completed the trial or died without a major protocol violation/deviation.

7.2.3 Preliminary analysis population

Includes all subjects in the full analysis population with complete endpoint data available as of 5/4/2021 for preliminary analysis on an unlocked database.

7.2.4 Safety Population

Safety analyses will be based a modified intent-to-treat population consisting of all participants who were randomised and received at least one dose of randomised therapy.

7.3 Covariates and Subgroups

(ICH E3; 9.7.1, 11.4.2.1. ICH E9; 5.7)

7.3.1 Covariates

The primary analysis will be adjusted for the stratification variables (site and age). Baseline ordinal scale will be included if considered necessary.

7.3.2 Subgroups

The primary endpoint will be analysed for the following participant subgroups:

1. Age (years): (a) <65 years and (b) ≥ 65

2. Sex at birth: (a) Male and (b) Female
3. Symptom duration (days): (a) <10 and (b) ≥10
4. Baseline 7-point ordinal scale: (a) 3, (b) 4 and (c) 5
5. Co-enrolment into RECOVERY: (a) Yes and (b) No
6. Co-treatment with dexamethasone: (a) Yes and (b) No (if a meaningful number if patients did not receive dexamethasone)

7.4 Missing Data

(ICH E3; 9.7.1, 11.4.2.2. ICH E9;5.3. EMA Guideline on Missing Data in Confirmatory Clinical Trials)

All reasonable efforts will be taken to minimise loss to follow-up, which is expected to be minimal as data collection for primary and secondary outcomes using trial-specific eCRFs is combined with linkage to routine clinical data on study outcomes. The number and percentage of participants with follow-up information at day 29 after the randomisation will be reported. For all participants who were discharged and alive but have missing clinical status, a clinical status scale of 2 (Not hospitalised, limitation on activities) will be applied.

7.5 Interim Analyses and Data Monitoring

(ICH E3; 9.7.1, 11.4.2.3. ICH E9; 4.1, FDA Feb 2010 "Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics")

7.5.1 Planned Schedule of Interim Analyses

No planned interim analysis but DMC has the rights to request for one.

7.5.2 Scope of Adaptations

No planned interim analysis.

7.5.3 Stopping Rules

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. The DMC will also determine the adequacy of the assumptions in table 4 with regard to the proportion of patients experiencing the endpoints in the ordinary scale at day 29 on blinded data after at least 100 participants have been recruited. Following this interim evaluation the DMC may make the following recommendations to the TMG:

1- To continue the trial without modifications

2- To continue the trial with a modification of the sample size

3- To continue the trial with a change in the primary endpoint

4- To terminate the trial due to a low likelihood of achieving statistically significant results (futility)

7.5.4 Adjustment of Confidence Intervals and p-values

No planned interim analysis and adjustment of confidence intervals and p-values.

7.5.5 Documentation of Interim Reports

Snapshots of the data available at each interim report to the DMC and/or TSC will be preserved. All documentation of analysis plans, programming code and reporting provided at each interim will be preserved.

7.6 Preliminary analysis

An analysis for preliminary efficacy and safety will be performed on an unlocked database using the full analysis population. The preliminary analysis will focus on the primary endpoints and a limited number of key secondary endpoints plus safety. The endpoints to be evaluated in the preliminary analysis are as follows:

Primary endpoint: Clinical Status on the WHO ordinal scale at day 29

Key secondary endpoints: Time to improvement on the ordinal scale, proportion of patients requiring mechanical ventilation, mortality, duration of hospitalization

Safety: Proportion of patients with one or more adverse events, proportion of patients with serious adverse events

Virologic efficacy of Brensocatib: Neutrophil elastase measurement in blood by treatment arm.

7.7 Multi-centre Studies

(ICH E3;9.7.1, 11.4.2.4. ICH E9; 3.2)

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.

Centre will be treated as random effect in the mixed ordinal logistic regression model and analysis of secondary outcomes.

7.8 Multiple Testing

(ICH E3; 9.7.1, 11.4.2.5. ICH E9; 2.2.5)

Due allowance for multiple testing will be made in the interpretation of the results: the larger the number of events on which a comparison is based and the more extreme the P-value after any allowance has been made for the nature of the particular comparison (i.e. primary or secondary; pre-specified or exploratory), the more reliable the comparison and, hence, the more definite any finding will be considered. 95% confidence intervals will be presented for the main comparisons.

8 Summary of Study Data

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum or median for non-normally distributed data with their interquartile range. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. All summary tables will be structured with a column for each treatment in the order (Control, Experimental) and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

8.1 Subject Disposition

The summary statistics will be produced in accordance with section 8.

8.2 Protocol Deviations

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.

8.3 Demographic and Baseline Variables

Subject demographic data and baseline characteristics ((eg, sex, race/ethnicity, age and co-morbidities)) will be summarized by treatment group and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data and by the number and percentage of participants for categorical data.

Age group (< 65 and ≥ 65) will be summarized by treatment group and overall.

8.3.1 Other Baseline Characteristics

The following baseline disease characteristics will be summarized by treatment group and overall using descriptive statistics:

- Clinical status (7-point ordinal scale)
- Severity of illness
- Participants with confirmed SARS-CoV-2 PCR test and those treated as clinically suspected who never had a positive swab

8.4 Treatment Compliance

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. For patients that attended for day 29 visits, medications will be returned and unused medication counted and documented.

8.5 Loss to follow-up

All reasonable efforts will be taken to minimise loss to follow-up, which is expected to be minimal as data collection for primary and secondary outcomes using trial-specific eCRFs is combined with linkage to routine clinical data on study outcomes. The number and percentage of participants with follow-up information at day 29 after the randomisation will be reported.

9 Efficacy Analyses

9.1 Primary Efficacy Analysis

The primary endpoint will be analysed using a mixed ordinal logistic regression, assuming proportional odds ratios adjusted for age and sites as a random effect. The odds ratio, 95% confidence interval and p-value for comparing treatments will be provided. The assumption of odds proportionality will be assessed using Brant Test[3] of Parallel Regression Assumption. If the test indicate that proportional odds assumption is violated, the model will be run as a generalised ordered logistic model.

9.2 Secondary Efficacy Analyses

9.2.1 Time to clinical improvement (1 category)

The endpoint will be analysed with a time-to-event framework. Cox models will be used, and the survivor function will be estimated. The hazard ratio and 95% confidence interval will be provided. Participants without the endpoint being analysed will be censored on the day of the last non-missing ordinal scale assessment. The model will adjust for age and sites. Kaplan-Meier estimates for the time to event will also be plotted.

9.2.2 Clinical status at Day 3, 5, 8, 11, 15, 29

The number and percentage of participants in each clinical status category for day 3, 5, 8, 11, 15 and 29 will be summarized by treatment group. In addition, stacked bar charts by study day will be produced by treatment group using the definition specified in Section 4.3.

9.2.3 Change in 7-point scale

Change in ordinal scale at specific time points will be summarized by proportions (e.g., proportion who have a 1-, 2-, 3-, or 4-point improvement or 1-, 2-, 3-, 4-point worsening). Mean changes from baseline to days 3, 5, 8, 11, 15 and 29 will be reported.

9.2.4 Time to discharge or to a NEWS of ≤2

The endpoint will be analysed with a time-to-event framework. Cox models will be used, and the survivor function will be estimated. The hazard ratio and 95% confidence interval will be provided. Participants without the endpoint being analysed will be censored on the day of the last non-missing ordinal scale assessment. The

model will adjust for age and sites. Kaplan-Meier estimates for the time to event will also be plotted.

9.2.5 Change in NEWS from baseline to days 8, 15 and 29

Change in NEWS at specific time points will be summarized by proportions (e.g., proportion who have a 1-, 2-, 3-, or 4-point improvement or 1-, 2-, 3-, 4-point worsening). Mean changes from baseline to days 8, 15 and 29 will be reported.

9.2.6 No of days free from oxygen

Number of days free from oxygen support will be compared between the treatment arms using the negative binomial regression with time in ICU as the offset. Number of days will be calculated as the number of days free from oxygen support reported on the 7-point ordinal scale eCRF.

9.2.7 Duration of new oxygen used

Duration of new oxygen used will be calculated and will be compared between the treatment arms using the negative binomial regression with time in ICU as the offset.

9.2.8 Number of patients receiving new mechanical ventilation

The number and percentage of participants who received new mechanical ventilation will be presented. Comparison between the treatment arms will be performed using a Fisher's Exact test.

9.2.9 No of days free from ventilation

Number of days free from ventilation will be compared between the treatment arms using negative binomial regression with time in ICU as the offset.

9.2.10 Duration of new ventilation used

Duration of new ventilation used will be calculated and will be compared between the treatment arms using negative binomial regression with time in ICU as the offset.

9.2.11 Duration of hospital stay – days

Duration of hospitalization will be calculated only for participants who are discharged alive on or prior to Day 29 and will be compared between the treatment arms using negative binomial regression.

9.2.12 28-day mortality

All-cause mortality will be estimated using the Kaplan-Meier product limit method with all available data. The treatment arms will be compared using the log-rank test, and hazard ratios and 95% confidence intervals will be provided. Participants who did not die will be censored on the last study day.

9.3 Exploratory Efficacy Analyses

The virologic efficacy of Brensocatib will be evaluated.

1. The percentage of participants with SARS-CoV-2 detectable in nasopharyngeal (NP) sample (in hospital, Tayside only)
2. Quantitative SARS-CoV-2 virus in NP samples (Tayside only)
3. *Neutrophil elastase and heparin binding protein measurement in blood (in hospital, Tayside only)
4. *Neutrophil functional studies (NET formation, phagocytosis, elastase release, neutrophil proteomics- (Tayside and Sheffield only)

*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.

10 Safety Analyses

Safety endpoints include 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. Adverse events of special interest; hyperkeratosis (skin), infection, and dental complications will be reported. These events will be analysed univariately. The proportion of participants who had adverse events will compared between both the groups using Poisson regression. Adverse events leading to premature discontinuation from the study intervention and serious AEs will be presented either in a table or a listing.

10.1 Extent of Exposure

The summary statistics will be produced in accordance with section 8.

10.2 Adverse Events

For the calculation of incidence of adverse events (i.e., on a per subject basis), each subject will only be counted once and any repetitions of adverse events within a subject will be ignored; the denominator will be the number of subjects in the Treated population. All adverse events reported will be included in the summaries and analyses. Adverse events incidences will be reported by System Organ Class and Preferred Term.

10.3 Deaths, Serious Adverse Events and other Significant Adverse Events

Listings of death and other serious adverse events will be presented.

10.4 Pregnancies

For any subjects in the Treated population who become pregnant during the study, every attempt will be made to follow these subjects to completion of pregnancy to document the outcome, including information regarding any complications with pregnancy and/or delivery.

10.5 Clinical Laboratory Evaluations

Clinical safety laboratory adverse events are collected Day 0/1, 3, 5, 8, 11 and Day 15 and 29 if able to return to clinic or still hospitalized. Parameters evaluated include white blood cell count, platelet, haemoglobin concentration, creatinine, total bilirubin, ALT and AST. Laboratory safety parameters will be graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017). The distribution of Grade 3 and 4 chemistry and haematology laboratory results by time point and treatment group will be presented.

Descriptive statistics including mean, median, standard deviation, maximum, and minimum values and change from baseline by time point, for all and each chemistry and haematology laboratory parameter will be summarized by treatment arm.

10.6 Other Safety Measures

Not applicable

11 Other Analyses

11.1 Quality of Life (EQ-5D-5L)

This will be compared at Day 29. Standard measure specific algorithms will be used to derive scores from and handle missing data in the QoL questionnaires. A mixed model will be used in the analysis.

12 Reporting Conventions

P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places; p-values less than 0.0005 will be reported as "0.999". The mean, standard deviation, and other statistics will be reported to1 decimal place greater than the original data. The minimum and maximum will use the same number of decimal places as the original data. Proportions will be presented as 2 decimal places; values greater than zero but < 0.5% will be presented as "99. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures

13 Technical Details

STATA version 16 will be used to analyse all the data and to generate all tables, figures and listings.

14 Summary of Changes to the Protocol

There are no changes to report.

15 References

1. World Health Organisation, Master Protocol: A Multi-centre, Adaptive, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Patients. 2020

2. Whitehead, J. (1993), Sample size calculations for ordered categorical data. Statist. Med., 12: 2257-2271.

3. Brant R. Assessing proportionality in the proportional odds model for ordinal logistic regression. Biometrics. 1990 Dec;46(4):1171-8. PMID: 2085632.

16 Listing of Tables, Listings and Figures

Table 1: Stratification variables

Variable	Brensocatib N =	Placebo N =
Age – n (%)		
<65		
>=65		
Sites – n (%)		

Table 2: Demographic

Variable	Brensocatib N =	Placebo N =
Age (mean SD)		
Gender – n (%)		
Male		
Female		
Ethnicity – n (%)		
English/ Welsh/ Scottish/ Northern Irish/ British		
Irish		
Gypsy or Irish Traveller		
Any other White background		
White and Black Caribbean		
White and Black African		
White and Asian		
Any other Mixed/ Multiple ethnic background		
Indian		
Pakistani		
Bangladeshi		
Chinese		
Any other Asian background		
African		
Caribbean		
Any other Black/ African/ Caribbean background		
Arab		

Any other ethnic group
Unknown

Living status – n (%)

Own home (on own or with others)

Sheltered housing

Care home (nursing or residential)

Prison

Other

Comorbidities

a. Chronic Neutropenia
b. Chronic cardiac disease, including congenital heart disease
c. Hypertension
d. COPD
e. Chronic pulmonary disease (not COPD or asthma)
f. Asthma (physician diagnosed)
g. Chronic kidney disease (eGFR less than 44 ml/min, on dialysis or previous transplant)
h. Moderate or severe liver disease
i. Mild liver disease
j. Chronic neurological disorder
k. Malignant neoplasm
l. Chronic hematologic disease
m. AIDS / HIV
n. Obesity
o. Diabetes with complications
p. Diabetes without complications
q. Rheumatologic disorder
r. Dementia
s. Malnutrition

Table 3: Severity of the patient population

	Brensocatib	Placebo

	N =	N =
Radiographic infiltrates by imaging (e.g. chest x-ray, computed tomography (CT) scan)		
Evidence of rales/crackles on physical examination		
Peripheral capillary oxygen saturation (SpO2) less than or equal to 94% on room air prior to randomization		
Requiring supplemental oxygen		
Lymphocyte count less than 1 x 10^9 cells per litre (L)		

Table 4: SARS-COV—2 PCR test

	Brensocatib N =	Placebo N =
Confirmed positive SARS CoV-2 PCR test		
Clinically suspected without a positive swab		

Table 5: Clinical status at randomisation

	Brensocatib N =	Placebo N =
7-point ordinal scale		
Not hospitalised, no limitations on activities		
Not hospitalised, limitation on activities;		
Hospitalised, not requiring supplemental oxygen;		
Hospitalised, requiring supplemental oxygen;		
Hospitalised, on non-invasive ventilation or high flow oxygen devices;		
Hospitalised, on invasive mechanical ventilation or ECMO (Extracorporeal membrane oxygenation)		
Death.		
NEWS Score, mean (SD)		

Table 6: Primary outcome: Clinical status at day 29 according to treatment Group.

	Brensocatib N =	Placebo N =	Effect estimate (95% CI)
Clinical status at day 29 on the 7-point ordinal scale — no. of patients (%)			
Not hospitalised, no limitations on activities			
Not hospitalised, limitation on activities			
Hospitalised, not requiring supplemental oxygen			
Hospitalised, requiring supplemental oxygen			
Hospitalised, on non-invasive ventilation or high flow oxygen devices			
Hospitalised, on invasive mechanical ventilation or ECMO (Extracorporeal membrane oxygenation)			
Death			

Table 7: Secondary outcomes – Clinical Severity According to Treatment Group.

	Brensocatib N =	Placebo N =	Effect estimate (95% CI)
Time to clinical improvement (1 category)			
Clinical status at Day 3 on the 7-point ordinal scale — no. of patients (%)			
Not hospitalised, no limitations on activities			
Not hospitalised, limitation on activities			
Hospitalised, not requiring supplemental oxygen			
Hospitalised, requiring supplemental oxygen			
Hospitalised, on non-invasive ventilation or high flow oxygen devices			
Hospitalised, on invasive mechanical ventilation or ECMO (Extracorporeal membrane oxygenation)			
Death			
Clinical status at Day 5 on the 7-point ordinal scale — no. of patients (%)			
Not hospitalised, no limitations on activities			
Not hospitalised, limitation on activities			
Hospitalised, not requiring supplemental oxygen			
Hospitalised, requiring supplemental oxygen			
Hospitalised, on non-invasive ventilation or high flow oxygen devices			
Hospitalised, on invasive mechanical ventilation or ECMO (Extracorporeal membrane oxygenation)			
Death			

Clinical status at Day 8 on the 7-point ordinal scale — no. of patients (%)	
Not hospitalised, no limitations on activities	
Not hospitalised, limitation on activities	
Hospitalised, not requiring supplemental oxygen	
Hospitalised, requiring supplemental oxygen	
Hospitalised, on non-invasive ventilation or high flow oxygen devices	
Hospitalised, on invasive mechanical ventilation or ECMO (Extracorporeal membrane oxygenation)	
Death	
Clinical status at Day 11 on the 7-point ordinal scale — no. of patients (%)	
Not hospitalised, no limitations on activities	
Not hospitalised, limitation on activities	
Hospitalised, not requiring supplemental oxygen	
Hospitalised, requiring supplemental oxygen	
Hospitalised, on non-invasive ventilation or high flow oxygen devices	
Hospitalised, on invasive mechanical ventilation or ECMO (Extracorporeal membrane oxygenation)	
Death	
Clinical status at Day 15 on the 7-point ordinal scale — no. of patients (%)	
Not hospitalised, no limitations on activities	

Not hospitalised, limitation on activities	
Hospitalised, not requiring supplemental oxygen	
Hospitalised, requiring supplemental oxygen	
Hospitalised, on non-invasive ventilation or high flow oxygen devices	
Hospitalised, on invasive mechanical ventilation or ECMO (Extracorporeal membrane oxygenation)	
Death	
Clinical status at Day 29 on the 7-point ordinal scale — no. of patients (%)	
Not hospitalised, no limitations on activities	
Not hospitalised, limitation on activities	
Hospitalised, not requiring supplemental oxygen	
Hospitalised, requiring supplemental oxygen	
Hospitalised, on non-invasive ventilation or high flow oxygen devices	
Hospitalised, on invasive mechanical ventilation or ECMO (Extracorporeal membrane oxygenation)	
Death	
Change in 7-point ordinal scale	
Day 3	
Day 5	
Day 8	
Day 11	
Day 15	
Day 29	

Table 8: Secondary outcome: National Early Warning Score (NEWS)

	Brensocatib N =	Placebo N =	Effect estimate (95% CI)
Time to discharge or to a NEWS of <= 2			
Change in NEWS from baseline			
Day 8			
Day 15			
Day 29			

Table 9: Secondary outcome: Oxygenation, mechanical ventilation, hospitalisation, and mortality

	Brensocatib N =	Placebo N =	Effect estimate (95% CI)
Oxygenation			
No of days free from oxygen			
Duration of new oxygen use			
Mechanical ventilation			
Number of patients receiving new mechanical ventilation			
No of days free from ventilation			
Duration of new ventilation used			
Duration of hospital stay - days			
28-day mortality			

Table 10: Safety analyses

	Brensocatib N =	Placebo N =	Effect estimate (95% CI)
% of patients with at least 1 AE			
Incidence of SAEs			
Discontinuation or temporary suspension of treatment			
Changes in white cell count			
Changes in haemoglobin			
Changes in platelets			
Changes in creatinine			
Changes in total bilirubin			
Changes in ALT			
Changes in AST			
Adverse events, n (%):			
Hyperkeratosis (Skin)			
Infections			
Dental complications			

Table 11: Adverse Events

Adverse Event – n (%)	Brensocatib N =	Placebo N =
Death		
Life-threatening		
Required hospitalisation		
Resulted in persistent or significant disability		
Medically significant		
Total		

Table 12: Summary of all adverse events – System Organ Class Level

	Brensocatib N =	Placebo N =	Total N=
Number of participants			
Number of participants with adverse events			
Number of participants without adverse events			
Number of adverse events			
Cardiac disorders			
Eye disorders			
Gastrointestinal disorders			
General disorders and administration site conditions			
Infections and infestations			
Injury, poisoning and procedural complications			
Investigations			

Metabolism and nutrition disorders
Musculoskeletal and connective tissue disorders
Nervous system disorders
No Code
Psychiatric disorders
Renal and urinary disorders
Respiratory, thoracic and mediastinal disorders
Skin and subcutaneous tissue disorders
Vascular disorders

Table 13: Summary of all adverse events – Preferred Term Level

	Brensocatib N =	Placebo N =	Total N=
Number of participants			
Number of participants with adverse events			
Number of participants without adverse events			
Number of adverse events			
Abdominal discomfort			
Abdominal pain			
Acute kidney injury			
Arthralgia			
Back pain			
Blood glucose increased			
Bradycardia			
Cerebrovascular accident			

Chest discomfort
Chest pain
Clostridium difficile infection
Constipation
Cough
Delirium
Diarrhoea
Dizziness
Drug eruption
Dry mouth
Dry skin
Dysarthria
Dyspepsia
Dyspnoea
Dysuria
Electrocardiogram abnormal
Epistaxis
Extravasation
Eye pruritus
Fall
Flatulence
Gastritis erosive
Gastrooesophageal reflux disease
Gingival bleeding
Gingival pain
Glossodynia
Hallucination, visual
Headache
Hiccups
Hyperglycaemia
Hyperhidrosis
Hypoaesthesia oral
Hypokalaemia
Insomnia
Lip pain

Liver function test abnormal
Lower respiratory tract infection
Malaise
Memory impairment
Mouth ulceration
Musculoskeletal pain
Nausea
Night sweats
Nightmare
No Code
Oral candidiasis
Oral mucosal blistering
Oral mucosal eruption
Pain
Pain in extremity
Palpitations
Paraesthesia oral
Peripheral swelling
Pharyngitis
Pneumonia
Pneumothorax
Pollakiuria
Pruritus
Pulmonary embolism
Pulmonary hypertension
Pyrexia
Rash
Rash macular
Rash papular
Rash pruritic
Rash pustular
Sinus bradycardia
Steroid diabetes
Subcutaneous emphysema
Suicidal ideation

Swelling face
Syncope
Thrombosis
Tongue discolouration
Toothache
Transaminases increased
Urinary tract infection
Urosepsis
Vision blurred
Vomiting

Table 14: Summary of all adverse events – descriptors

	Brensocatib N =	Placebo N =	Total N=
Severity			
No Information			
Mild			
Moderate			
Severe			
Total			
Relationship to Trial Drug			
No Information			
None			
Possible			
Probable			
Total			
Action taken			

	No Information
	None
	Hospitalisation
	IMP temporarily stopped
	IMP permanently stopped
	Con meds commenced
	Other (specify)
	Hospitalisation, Con meds commenced
	IMP temporarily stopped; IMP permanently stopped
	IMP permanently stopped; Con meds to commenced
	Total
Outcome	
	No information
	Recovered
	Recovering
	Not recovered
	Unknown
	Fatal
	Total

Table 15. Additional treatments

Additional treatments	Brensocatib N =	Placebo N =
Co-enrolment in RECOVERY		
Co-enrolment in REMAP-CAP		
Co-medications:		
Antibiotics		
Azithromycin		
Corticosteroids		
Convalescent plasma		
Hydroxychloroquine		
Lopinavir-Ritonavir		
Remdesivir		
Tocilizumab		