STATISTICAL ANALYSIS PLAN

BGBC020

A Multicentre, Phase 2, Randomised Study to Assess the Efficacy and Safety of Bemcentinib for the Treatment of COVID-19 in Hospitalised Patients

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 17NOV2020) for BGBC020

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorising that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorised Version
0.1	26Oct2020	PPD	Not Applicable – Prepared based on Protocol Amendment 2.0
0.2	11Nov2020	PPD	• Accept Sponsor's updates • Remove Adverse Events of Special Interest
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1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of efficacy, safety, pharmacokinetic (PK) and pharmacodynamic (PD) data for BGBC020, "A Multicentre, Phase 2, Randomised Study to Assess the Efficacy and Safety of Bemcentinib for the Treatment of COVID-19 in Hospitalised Patients". It describes the data to be summarised and analysed, including specifics of the statistical analyses to be performed.

This SAP is based on the protocol amendment 2.0, dated 08 October 2020.

2. STUDY OBJECTIVES AND END POINTS

2.1. PRIMARY OBJECTIVES AND END POINTS

Objectives	Endpoints
To evaluate the efficacy of bemcentinib as add-on therapies to standard of care (SoC) in patients hospitalised with coronavirus disease 2019 (COVID-19).	Time to sustained clinical improvement of at least 2 points (from randomisation) on a 9-point category ordinal scale, live discharge from the hospital, or considered fit for discharge (a score of 0, 1, or 2 on the ordinal scale), whichever comes first, by Day 29 (this will also define the "responder" for the response rate analyses).

2.2. KEY SECONDARY OBJECTIVES AND END POINTS

Objectives	Endpoints
To evaluate the ability to prevent deterioration according to the ordinal scale by 1, 2, or 3 points	The proportion of patients not deteriorating according to the ordinal scale by 1, 2, or 3 points on Days 2, 8, 15, and 29
To evaluate the number of oxygen-free days	Duration (days) of oxygen use and oxygen-free days
To evaluate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load	Qualitative and/or quantitative polymerase chain reaction (PCR) determination of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in oropharyngeal/nasal swab while hospitalised on Days 1, 3, 5, 8, 11, 15, and 29

2.3. OTHER SECONDARY OBJECTIVES AND END POINTS

Objectives	Endpoints
To evaluate ventilator-free days and incidence and duration of any form of new ventilation use	Duration (days) of ventilation and ventilation-free days Incidence of any form of new ventilation use and duration (days) of new ventilation use
To evaluate duration of organ support (eg, including respiratory, renal, and cardiac support)	Duration (days) of organ support
To evaluate response rate (see primary endpoint for definition of responder)	Response rate (number and %) by treatment arm at Days 2, 8, 15, and 29
To evaluate time to discharge	Time to live discharge from the hospital
To evaluate overall mortality	• Mortality at Days 15, 29, and 60 • Time from treatment start date to death
Change in the ratio of the oxygen saturation to fraction of inspired oxygen concentration (SpO_2/FiO_2)	SpO_2/FiO_2, measured daily from randomisation to Day 15, hospital discharge, or death
To evaluate the safety of bemcentinib as add-on therapy to SoC in patients with COVID-19	• Physical examination. • Clinical laboratory examinations. • Vital signs (blood pressure/heartrate/temperature/ respiratory rate). • Adverse events
To evaluate intensive care unit (ICU) and hospitalisation length	Duration (days) of ICU and hospitalisation
To evaluate National Early Warning Score 2 (NEWS2)	• NEWS2 assessed daily while hospitalised and on Days 15 and 29. • Time to a NEWS2 of ≤2, maintained for at least 24 hours
To evaluate improvement taking into account worsening and death	Ranked trajectory over 29 days, with trajectory ranked in the following order of the ordinal scale: • [ascending order] The worst score • [ascending order] The last recorded score • [ascending order] The number of days at worst score • [ascending order] The best score that occurs after the worst score (this will equal the worst score if the worst score is the last score) • [descending order] The number of days the patient is at 4), counting only days after the last occurrence of the worst score (the number of days for this item will be 0 if the worst score is the last score)

2.4. EXPLORATORY OBJECTIVES AND END POINTS

Objectives	Endpoints
To evaluate PK of bemcentinib	PK concentration and parameters
To evaluate SARS-CoV-2 viral load	Qualitative and/or quantitative PCR determination of SARS-CoV-2 in blood (on Day 1) and saliva (while hospitalised) on Days 1, 3, 5, 8, 11, 15, and 29 (may become a secondary endpoint once the assays are available)
To collect samples for serology research, viral genomics, serum antibody production, and COVID-19 diagnostics	Analysis of samples collected at baseline prior to treatment and at specific time points

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

BGBC020 is a study designed to rapidly seek and determine the nature of signals of efficacy and safety of bemcentinib in the treatment of hospitalised patients with SARS-CoV2. The study design is analogous to the first stage of the ACCORD-2 platform protocol, a multicentre national UK government sponsored protocol in the United Kingdom in which bemcentinib is being evaluated. BGBC020 (this protocol) is therefore analogous to ACCORD-2, a seamless, Phase 2, adaptive, randomised platform study, designed to rapidly test candidate agents in the treatment of COVID-19 disease.

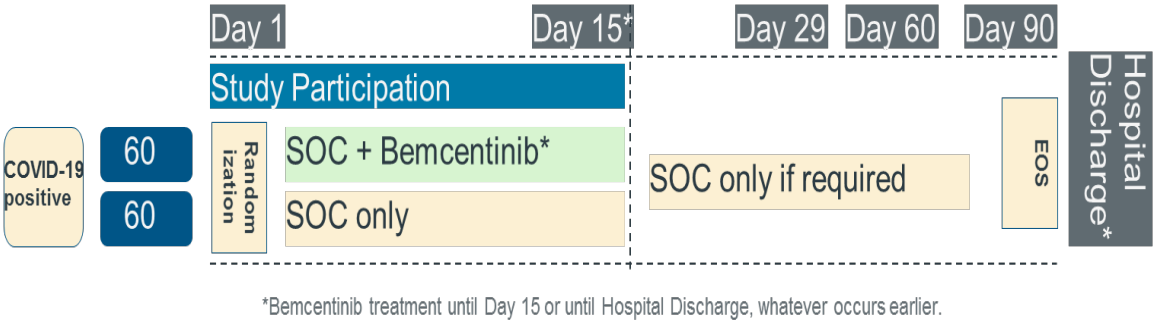
BGBC020 (referred to henceforth as "the current study") will include hospitalised adult patients (≥18 years) who have infection with SARS CoV-2, the virus that causes COVID-19, as confirmed by laboratory tests and/or validated point of care tests. For inclusion, patients will need to have clinical status of Grade 3 (hospitalised - mild disease, no oxygen therapy) to Grade 5 (hospitalised – severe disease, non-invasive ventilation or high-flow oxygen), as defined by a 9-point ordinal scale, which was detailed in the World Health Organization R&D Blueprint "Novel Coronavirus - COVID-19 Therapeutic Trial Synopsis" (February 2020). Medical history will record the estimated date and time of first symptoms.

This study will aim to evaluate the safety and efficacy of bemcentinib for treatment of COVID 19 disease.

First dose of bemcentinib must take place within 72 hours of Investigator receipt of laboratory or validated point of care test confirmation of SARS-CoV-2 infection. If a patient has a confirmed result prior to hospital admission which is more than 72 hours old, first dose of bemcentinib should take place within a calendar day of admission to hospital, where in the opinion of the Investigator, the reason for admission is relevant to ongoing COVID-19 infection. Any exceptions to this must be authorised by the Medical monitor and/or Sponsor medical team.

Patients will be randomised to the treatment arm to receive bemcentinib (as an add-on to standard of care [SoC]) or to control arm where only SoC will be administered.

Patients will be screened on Day -1 or Day 1 and will remain in the hospital from Day 1 until fit for discharge. Dosing with bemcentinib (as an add-on to SoC) will commence on Day 1 until Day 15 or discharge. The last day of assessments while hospitalised will be on Day 29. An outpatient visit will be conducted on Day 60 (±4 days), with an end of study visit conducted on Day 90 (±6 days).



Protocol Appendix 8 for details of study procedures during special circumstances.

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 1.3 of the BGBC020 protocol amendment 2.0.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

Additional details for statistical analyses are provided in this SAP.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Safety analysis by the Independent Data Monitoring Committee (IDMC)
- Final analysis

4.1. REVIEW COMMITTEES

4.1.1. STEERING COMMITTEE (SCIENTIFIC REVIEW COMMITTEE)

A Steering Committee has been assembled for the executive oversight and supervision of this study. The Steering Committee will serve this role through regular scheduled meetings or teleconferences and, if necessary, additional ad hoc meetings.

The Steering Committee will be expected to provide guidance, advice, and recommendations to the BGBC020 study on relevant clinical issues related to the strategy, implementation, and conduct of the study. This may include, but not necessarily be limited to:

- Advice on the strategy and design of the protocol and any subsequent amendments or revisions.
- Advice on issues of study enrolment including patient accrual, number and location of investigator sites,

recruitment goals, and patient eligibility/ineligibility issues.

- Advice on issues relating to the clinical conduct of the protocol including protocol violations/deviations and investigative site or Ethics Committee/Institutional Review Board concerns/issues, and regulatory engagement.
- Advice on safety issues.

4.1.2. INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

An independent IDMC will be established for this study to assess safety on an ongoing basis throughout the study. The committee will be established for the purpose of objectively monitoring the safety data and will not include any assessment of efficacy data. The IDMC members will perform ongoing safety surveillance and provide recommendations to the Sponsor Steering Committee regarding study conduct.

The IDMC will consist of at least 4 independent experts appointed by the study Sponsor based on their expertise. IDMC members will not be Investigators in the study, nor will they have any conflict of interest with the Sponsor or its designees.

Further details (eg, frequency of data reviews and study committee composition and membership) will be provided in the IDMC charter. The charters will define the criteria, frequency of reviews, data, and source documentation required to adjudicate all events.

4.2. IDMC DATA REVIEW

IDMC will review safety information of the participating patients when 40, 80 and 120 patients have completed Day 15 or discharged before Day 15. The outputs for review will include:

- Tables showing by treatment arm summaries of:
  - Treatment Emergent Adverse Events (TEAEs) by System Organ Class (SOC) and Preferred Term (PT)
  - Serious AEs (SAEs) by SOC and PT
  - Serious Adverse Reactions (SARs) by SOC and PT. SARs are defined as any AEs related to study treatment, non-study treatment, or study procedure
  - Grade 3 or higher cardiac events (include ventricular arrhythmias and Torsade de pointes) by PT
  - QT, QTc, QTcF, and QTcB shift from Baseline to the highest post-Baseline value: ≤470 msec, >470-<501 msec and ≥501 msec
  - QT, QTc, QTcF, and QTcB change from Baseline to the highest post-Baseline value: >30 msec increase from Baseline and >60 msec increase from Baseline
  - Shift from Baseline in overall ECG interpretation to the worst post-Baseline interpretation: normal, abnormal not clinically significant, abnormal clinically significant
  - Change from Baseline in NEWS2 score
- By patient listings of:
  - SAEs

- SARs
- Treatment-emergent adverse events (TEAEs) leading to discontinuation of study treatment
- Deaths
- Cardiac events (include ventricular arrhythmias and Torsade de pointes) of Grade 3 or worse
- Patients with QTcF ≥501 msec leading to discontinuation of study treatment
- ECG results of patients with abnormal ECG interpretation
- Grade 3or higher laboratory assessments [selected parameters: haemoglobin, white blood cell count (total), neutrophils, lymphocytes, platelets; sodium, creatinine, potassium, aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyltransferase (GGT), total bilirubin (TBL), glucose, creatinine kinase, activated partial thromboplastin time (aPTT)]

Further outputs may be requested by the IDMC prior to the first meeting.

4.3. FINAL ANALYSIS

The final analysis will be performed when at all randomised patients have completed or discontinued by the End of Study Visit.

All final, planned analyses identified in this SAP will be performed by IQVIA Biotech Biostatistics or IQVIA PK Biostatistician (PK TFLs) following Sponsor Authorisation of this SAP and Database Lock (DBL).

5. ANALYSIS SETS

5.1. INTENTION TO TREAT ANALYSIS SET

The intention to treat (ITT) analysis set includes all patients who are randomised and match the inclusion/exclusion criteria of the protocol.

For analyses and displays based on the ITT analysis set, patients will be classified according to randomised treatment.

5.2. SAFETY ANALYSIS SET

The safety analysis set (SS) will contain all patients who are randomised and receive at least one dose of study intervention (bemcentinib or SoC).

For analyses and displays based on the safety analysis set, patients will be classified according to the actual treatment received, i.e. in the event of a patient randomised to SoC receiving bemcentinib, the patient will be classified under bemcentinib plus SoC arm.

5.3. PHARMACOKINETIC ANALYSIS SET

The PK analysis set (PKS) will contain all patients who are randomised and take at least 1 dose of bemcentinib and have quantifiable bemcentinib concentrations post-dose without protocol deviations or events affecting the pharmacokinetic results.

Protocol deviations or events which may have the potential to affect PK results are described in Section 18.1; refer to Section 5.5 for a description of the review process for assessing the deviations or events.

5.4. PHARMACODYNAMIC ANALYSIS SET

The pharmacodynamic analysis set (PDS) will contain all patients who are randomised and receive study intervention (bemcentinib or standard of care) and have evaluable results for at least 1 pharmacodynamic endpoint post-dose. All analyses of the PDS will be based on each patient's actual treatment received.

5.5. PROCESS FOR ANALYSIS SET ASSIGNMENT

For the PKS and the PDS, the identification and agreement of protocol deviations or events which affect PK and/or PD results will be performed between the PK analyst, biostatistician, and the sponsor, prior to DBL, with sponsor authorisation of any excluded patients or their data.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

For efficacy and safety analyses, unless otherwise stated, the reference start date will be the date of randomisation. Study Day will be calculated from the reference start date to the date of start/stop day of assessments and events.

Study Day will be derived as follows:

- Study Day = (Date of event –Date of randomisation) + 1 if the date of the event is on or after the date of randomisation
- Study Day = (Date of event – Date of randomisation) if the date of the event is prior to the date of randomisation.

In the situation where the event date is partial or missing, Study Day and any corresponding durations will appear missing in the listings and dates will be presented as partial or missing.

6.2. BASELINE

Unless otherwise specified, Baseline is defined as the last non-missing measurement taken prior to the date and time of randomisation (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide and time of measurement is not available, that measurement will be considered -Baseline unless the assessment was scheduled to be post-randomisation in the protocol.

6.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

For by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries but will contribute to the Baseline timepoint and/or worst-case value where required (e.g. shift tables or summaries involving worst-case values at any time post-Baseline).

Early termination data will be mapped to the next available visit number for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.4. WINDOWING CONVENTIONS

No visit windowing will be performed for this study, except for early termination data (refer to Section 6.3)

6.5. COMMON CALCULATIONS

Change from Baseline will be calculated as:

- Change from Baseline = Test value at post-Baseline visit – Baseline value

Percent change from Baseline will be calculated as:

- Percent change from Baseline (%) = (Change from Baseline at post-Baseline visit / Baseline value) * 100%

7. STATISTICAL CONSIDERATIONS

7.1. SAMPLE SIZE CONSIDERATIONS

Approximately 60 patients will be randomised into each arm of the study, whereby patients will receive either bemcentinib (with SoC) or SoC alone. The chosen endpoint to compare treatments will be the time to a sustained 2-point improvement on a 9-point category ordinal scale, discharge from hospital, or considered fit for discharge at Day 29.

It is expected that 54 patients are needed per arm, which will provide 80% power to detect a hazard ratio of 1.6 for the occurrence of the event, when comparing bemcentinib with SoC. This calculation is based on a 1-sided test and a 10% significance level, and assumes 85.5% of patients will improve, be discharged from hospital, or considered fit for discharge at Day 29 for bemcentinib versus 70% of patients for the SoC (the estimate of SoC was taken from Cao (2020)). To allow for uncertainty in the recruitment rates, it is expected that up to 60 patients (rather than 54 patients) will be randomised to each arm in order to achieve the required number of events for the preliminary analysis.

The sample size calculation may be re-evaluated as the treatment of COVID-19 evolves.

7.2. MISSING DATA

Missing safety data will not be imputed other than if the severity or relationship to study treatment of an AE is missing (see Sections 17.1.1.1 and 17.1.1.2). Partial or completely missing AE and concomitant medication dates will be handled as described in APPENDIX 1.

Missing efficacy data will be handled as described in Sections 16.1.2 and 16.2.2. Missing bioanalytical data (PK data) will be handled as described in Section 18.1.

7.3. STATISTICAL TESTS

Statistical tests of the primary endpoint will be one-sided at the 10% significance level, with a one-sided p-value provided.

Two-sided p-values will be provided for the secondary efficacy endpoints if applicable and no formal inference will be made based on these endpoints.

No statistical testing will be performed for the safety endpoints.

All Confidence Intervals (CIs) will be two-sided with 80% coverage or 95% coverage as specified in the relevant efficacy analysis sections.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

No multiplicity adjustments will be made for the fact that multiple endpoints will be analysed at multiple timepoints.

7.5. MULTICENTRE STUDY

The study will be conducted at multiple centres in India and South Africa. At sites in India, hospitalised patients will only include baseline severity grades 4 or 5, in accordance with national treatment guidelines.

Randomisation to study treatment is stratified by baseline severity grades (grade 3, 4 and 5). Patients with baseline severity grade 4 and 5 will be further stratified by intended steroid use (none vs. dexamethasone or alternative steroid).

In the primary efficacy endpoint, centre or pooled centre will be included as a random factor in sensitivity analyses.

7.6. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following factors are used in the primary efficacy analyses. For details of their inclusion in the models, see the specific analysis sections.

- Study treatment (bemcentinib plus SoC vs SoC alone)
- Age category (age <70 years vs ≥70 years)

- Baseline severity grade (ordinal Grades 3, 4, or 5)
- Age category and treatment interaction
- Baseline severity grade and treatment interaction
- Study centre or pooled study centre

If the use of all 3 levels Baseline severity grade causes sparsity and inestimable model parameters in the primary efficacy analysis, the Baseline levels will be pooled as follows for the purpose of inclusion in analyses:

- If Grade 3 has the least patients it will be pooled with Grade 4
- If Grade 5 has the least patients it will be pooled with Grade 4
- If Grade 4 has the least patients it will be pooled with the Grade (3 or 5) with the least patients. If Grade 3 and 5 have the same number of patients, Grade 3 will be pooled with Grade 4.

If the use of all study centres causes sparsity and inestimable model parameters in the primary efficacy analysis, the study centres will be pooled according to country for the purpose of inclusion in analyses. A centre with less than 8 patients will be pooled with its most adjacent centre.

7.7. EXAMINATION OF SUBGROUPS

Subgroup analyses will be performed for the primary efficacy analysis (see Section 16.1.3) by:

- Comorbidity
  - Heart disease (yes/no)
  - Diabetes (yes/no)
  - Chronic lung disease (yes/no)
  - Chronic liver disease (yes/no)
  - Asthma (yes/no)
  - HIV (yes/no)
  - Tuberculosis (yes/no)
  - Hypertension (yes/no)
  - Cancer (yes/no)
  - Any of comorbidities (yes/no)

- Age group (<70 years/≥70 years)
- Days from symptoms onset (<12 days/≥12 days)
- Intended steroid use (none/dexamethasone or alternative steroid) at baseline, among patients with baseline Grade 4 or 5 only

Note that a) the study is not powered to detect statistically significant differences between treatment arms within subgroups; b) due to sparsity, only the covariates factors described in Section 7.6 will be included in the model.

7.8. HANDLING MODEL CONVERGENCE OR ESTIMATION ISSUES

If there are convergence or estimation issues with any statistical models or analyses due to the number of patients at baseline severity levels or centre/pooled study centre, then the baseline severity levels will be pooled as described in Section 7.6. If there are still issues, the centre/pooled study centre effect will be removed from the model, and if there are still issues, then baseline severity levels will also be removed. Additional covariates or factors may be removed if there are still issues.

7.9. SOFTWARE VERSION

All analyses will be conducted using SAS Enterprise Guide 7.1 (64-bit).

8. OUTPUT PRESENTATIONS

The presentation of data in outputs will follow IQVIA Biotech Data Display Standards. See TFL shells for additional information.

9. DISPOSITION AND WITHDRAWALS

All patients who were randomised to study treatment in this protocol will be accounted for.

9.1. DISPOSITION

Number of patients in intention to treat analysis set, safety analysis set, PK analysis set and PD analysis set will be presented by treatment arm and overall. Number and percentages of patients who completed/discontinued early from treatment (including reason for withdrawal) and who completed/discontinued early from the study (including reason for withdrawal) will be provided by treatment arm and overall based on the ITT analysis set.

- Complete full course of study treatment
- Treatment discontinued early
  - Adverse event
  - Death
  - Lack of efficacy

  - Lost to follow up
  - Non-compliance with study drug
  - Pregnancy
  - Progressive disease
  - Protocol deviation
  - Physician decision
  - Recovery
  - Study terminated by sponsor
  - Withdrawal by patient
  - Other
- Complete study
- Study discontinued early
  - Adverse event
  - Death
  - Lack of efficacy
  - Lost to follow up
  - Non-compliance with study drug
  - Pregnancy
  - Progressive disease
  - Protocol deviation
  - Physician decision
  - Recovery
  - Study terminated by sponsor
  - Withdrawal by patient
  - Other

A listing of patient disposition will be provided. Additionally, a listing showing inclusion and exclusion of each patient from each analysis population, including reason for exclusion, will also be provided.

9.2. PROTOCOL DEVIATIONS

Number and percentage of patients with important protocol deviations, as identified by the study team, will be provided by treatment arm and overall based on the ITT analysis set for each category specified by PK analyst, biostatistician, and the sponsor, prior to DBL.

A listing of protocol deviations identified by the study team (important or not) will be provided. For protocol deviations which may impact the quality of the PK or PD data, see Section 18.1.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The following demographic data and baseline characteristics will be presented for the ITT analysis set:

- Age (years) – calculated relative to date of consent, as a continuous variable
- Age categories (age <70 years/≥70 years)
- Sex (male/female/undifferentiated/unknown)
    - Childbearing potential for female patients only (yes/no)
    - Reasons if not of childbearing potential (post-menopausal/premenarchal/surgically sterile/other)
- Race
- Ethnicity
- Clinical frailty score (very fit/well/managing well/vulnerable/mildly frail/moderately frail/severely frail/very severely frail/terminally ill)
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI) (kg/m^2)
- Resident in care home (yes/no)
- Randomisation strata (grades 3/grades 4 and none/grades 4 and intended steroid use/grade 5 and none/ grade 5 and intended steroid use)
- Actual strata (grades 3/grades 4 and none/grades 4 and SoC intervention use (Remdesivir vs Dexamethasone)/grade 5 and none/ grade 5 and SoC intervention use (Remdesivir vs Dexamethasone))

Continuous demographic and baseline characteristics will be summarised using descriptive statistics by treatment arm and overall. Categorical demographic and baseline characteristics using number and percentages of patients in each category by treatment arm and overall. No statistical testing will be carried out for demographic or baseline characteristics.

10.1. DERIVATIONS

BMI, in kg/m^2, will be calculated as BMI (kg/ m^2) = weight (kg)/ [height (m)^2].

11. COVID-19 CO-MORBIDITIES AND MEDICAL HISTORY

COVID-19 co-morbidities as captured on the *Medical History* page of the eCRF will be summarised for the ITT analysis set by treatment arm and overall, via the number and percentage of patients with each of the following:

- History of diabetes
- History of heart disease
- History of chronic lung disease
- History of chronic liver disease
- History of asthma
- History of HIV
- History of tuberculosis
- History of hypertension
- History of cancer
- Any of above

Medical History will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0 or above. Medical history will be summarised by SOC and PT by treatment arm and overall based on the ITT analysis set. A patient having more than one reported medical diagnosis within the same SOC/PT will be counted only once for that SOC or PT.

All medical history data will be listed.

12. DISEASE HISTORY

The following disease history characteristics will be summarised by treatment arm and overall based on the safety analysis set:

- Time since symptoms onset (days) – calculated relative to date of randomisation
- Time since symptoms onset (<12 days/≥12 days)
- Time since diagnosis (days) – calculated relative to date of randomisation
- Presence or absence, and severity (mild/moderate/severe/unknown) of each of the following COVID-19 symptoms at study entry:
  - Cough
  - Fever
  - Myalgia
  - Diarrhoea
  - Dyspnoea
  - Fatigue
  - Malaise
  - Loss of appetite

- Loss of smell
- Loss of taste

- Time since hospital admission (days) for patients already hospitalised at study entry – calculated relative to date of randomisation
- On supplemental oxygen at study entry (yes/no)
- Type of supplemental oxygen for patients receiving supplemental oxygen at study entry (Non-Invasive Mechanical Ventilation/Nasal Cannula/Venturi Mask - 24% FiO2 flow rate/Venturi Mask - 28% FiO2 flow rate/Venturi Mask - 35% FiO2 flow rate/Venturi Mask - 40% FiO2 flow rate/Venturi Mask - 60% FiO2 flow rate/Simple Face Mask/Nonrebreathing Face Mask with Reservoir and One-Way Valve/Reservoir Cannulas/Other)
  - if on non-invasive mechanical ventilation
    - Continuous positive airway pressure
    - Bilevel positive airway pressure
- Time since start of supplemental oxygen (days) for patients on supplemental oxygen at study entry - calculated relative to date of randomisation
  - Time since start of non-invasive mechanical ventilation (days) for patients on non-invasive mechanical ventilation at study entry - calculated relative to date of randomisation.

All disease history characteristics will be listed.

12.1. DERIVATIONS

Time since endpoints, in days, will be calculated as follows:

- Time since symptoms onset (days) = (Date of randomisation – Date of symptoms onset)
- Time since diagnosis (days) = (Date of randomisation - Date of diagnosis)
- Time since hospital admission (days) = (Date of randomisation – Date of hospitalisation admission) if patient is already hospitalised at study entry. Time since hospitalisation admission will not be computed for patients who are not hospitalised at study entry
- Time since start of supplemental oxygen (days) = (Date of randomisation – Date of start of supplemental oxygen) if patient is already on supplemental oxygen at study entry. Time since start of supplemental oxygen will not be computed for patients who are not on supplemental oxygen at study entry
- Time since start non-invasive mechanical ventilation (days) = (Date of randomisation – Date of start of ventilation) if patient is already on non-invasive mechanical ventilation at study entry. Time since start of non-invasive mechanical ventilation will not be computed for patients who are not on non-invasive mechanical ventilation at study entry.

13. MEDICATIONS

All medications will be coded using the World Health Organisation (WHO) Drug Global dictionary, version B3 March 2020. Prior medications are defined as any medication that stopped before the date of randomisation. Concomitant medications are defined as any medication that were ongoing or ended at the date of randomisation, or any medication that started on or after the date of randomisation.

Partially or completely missing medication start and stop dates will be handled as described in APPENDIX 1.

Prior and concomitant medications will be summarised separately by Anatomical Therapeutic Class (ATC) level 2 and preferred drug name by treatment arm and overall based on the safety analysis set. A patient having more than one medication within the same ATC Level 2 or preferred drug name will be counted only once for that ATC Level 2 or preferred drug name.

All medications (prior and concomitant) will be listed.

14. EXPOSURE TO STUDY TREATMENT

Duration of bemcentinib exposure (days) will be summarised for the bemcentinib plus SoC arm. To provide an approximate equivalent exposure duration for the SoC arm, the duration of exposure up to Day 15 for SoC arm patients will be summarised. Additionally, treatment duration will also be summarised for the safety analysis set.

14.1. DERIVATIONS

Duration of bemcentinib exposure (days) = Date of last bemcentinib dose – Date of first bemcentinib dose + 1

Duration of exposure to SoC for patients who receive SoC is Minimum of (Date of last treatment – Date of randomisation) +1, or 15

Total duration of exposure to either arm is Date of last treatment – Date of randomisation +1

Interruptions and dose changes (increases or decreases) will not be considered for duration of exposure. The dates of first and last bemcentinib administration will be taken from the eCRF *Oral Drug Administration* page. The date of last treatment will be taken from the *Date of treatment completion/discontinuation* on the eCRF *End of Study Treatment* page.

15. STUDY MEDICATION COMPLIANCE

Bemcentinib will be administered as a 400 mg oral loading dose on Days 1, 2, and 3, followed by 200 mg once daily oral maintenance dose from Day 4, for a total of 15 days. Compliance with bemcentinib, in percentage, will be summarised based on the safety analysis set of bemcentinib plus SoC arm only.

15.1. DERIVATIONS

Bemcentinib compliance (%) = (Total dose received/Dose planned to be received) * 100%.

- Total dose received = the sum of "Dose per administration" in mg recorded on the *Oral Drug Administration* eCRF page, across all study days

- Dose planned to be received = 400 mg × the duration of bemcentinib exposure, if the duration of bemcentinib exposure is 3 days or less
- Dose planned to be received = 1200 mg + [(duration of bemcentinib exposure - 3) × 200 mg], if the duration of bemcentinib exposure is more than 3 days

Bemcentinib compliance will be summarised as a continuous variable as well as a categorical variable for the categories of <80%, 80% to <90%, 90% to 100% and >100%.

16. EFFICACY OUTCOMES

16.1. PRIMARY EFFICACY

16.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy variable is the time to sustained clinical improvement of at least 2 points (from randomisation) on a 9-category ordinal scale, or live discharge from the hospital or fit to be discharged (e.g., a score of 0, 1, or 2), whichever comes first, by Day 29 (this will also define the "responder" for the rate of 2-point sustained improvement response).

Time to response = (the date of response event – date of randomisation) +1, where the day of randomisation is Day 1.

Sustained clinical improvement is defined as improvement without subsequent worsening, e.g. if a patient improves from an ordinal scale grade of 5 at Baseline to a grade of 3, but subsequently has a grade greater than 3 this would be considered as subsequent worsening and the patient would be a non-responder at that timepoint. If a patient is a responder based on being fit for discharge with a score of 0 or 1, which later increases but is still a score of 2 or less, this patient would still be considered as a responder.

The 9-point category ordinal scale, used to assess patients is as follows:

0. Uninfected, no clinical or virological evidence of infection
1. Ambulatory, no limitation of activities
2. Ambulatory, limitation of activities
3. Hospitalised – mild disease, no oxygen therapy
4. Hospitalised – mild disease, oxygen by mask or nasal prongs
5. Hospitalised – severe disease, noninvasive ventilation or high-flow oxygen
6. Hospitalised – severe disease, intubation and mechanical ventilation
7. Hospitalised – severe disease, ventilation and additional organ support – vasopressors, renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO)
8. Death

Patients who are alive and who have not met the sustained 2-point improvement in the 9-point ordinal scale, or live discharge from hospital, or considered fit for discharge at Day 29 will have their time to response censored at the study Day that their last ordinal scale assessment was made, i.e. either Day 29 or earlier.

Patients who die before they meet the criteria for response, will be included in the analysis with a censored time to response of Day 29.

16.1.2. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLE(S)

Missing data will be minimised, with outcomes collected after premature withdrawal of treatment. The estimand will therefore be a "treatment policy" one.

For the purpose of a supplementary analysis, for patients who withdraw from treatment and also withdraw from the study (i.e. who refuse to have further data collected), their missing ordinal scores after treatment discontinuation will be multiply imputed for a visit based on patients who withdrew from treatment but did not withdraw from the study, allowing the estimate of post-withdrawal treatment effect to vary by last observed visit on treatment. Thus, for example, if post-treatment withdrawal outcomes tend to get steadily worse over time, this proposed model could fully reflect this in imputations of post-withdrawal visit outcomes. For the MI model,100 imputations will be generated using PROC MI with the MNAR statement and the MODELOBS option to base the imputation model on patients who withdraw from treatment but did not withdraw from the study. Fully Conditional Specification (FCS) model using the regression method will be used with the baseline ordinal score, the scores at prior post-baseline visits, and the time of treatment discontinuation as covariates. The ROUND and MINIMUM options will be utilized to ensure imputed values are non-negative integers. The seed to be used in all MI model is 20201012.

If this model is not estimable due to the potentially small numbers of patients discontinuing at a visit, the imputation will not take account of time of treatment discontinuation in modelling the imputations for a visit, but will base the model for imputations for a visit on all outcomes observed at the visit in patients who discontinued treatment, irrespective of when they discontinued treatment. This model would reflect post-discontinuation worsening via an average post-treatment-discontinuation worsening, applied to all imputed visit outcomes.

For all patients, intermittent missing data would be imputed assuming that the data are missing at random using the Markov Chain Monte Carlo (MCMC) method.

Note that prior to any imputation, ordinal severity scores will be set to 8 for all visits after a patient died, and for patients discharged live from hospital, any missing ordinal score data post-discharge will be set to their most-recent score.

16.1.3. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The primary efficacy analysis will be performed for ITT analysis set.

The primary hypothesis of this study is time to response (sustained 2-point improvement in the 9-point ordinal scale, live discharge from hospital, or considered fit for discharge, as analysed at Day 29) of the bemcentinib plus SoC arm is shorter than the SoC. This endpoint of sustained 2-point improvement in the 9-point ordinal scale or live discharge from hospital, or considered fit for discharge at Day 29, are referred to as the response, and patients with this response, are referred to be as responders.

As the events are sustained 2-point improvement in 9-point ordinal scale, live discharge, or considered fit for discharge, a hazard ratio (HR) larger than 1 is favourable to the test treatment, with the HR comparing the bemcentinib plus SoC arm with the SoC.

$$H0{:}HR \leq 1 \; vs \; HA{:}HR > 1$$

No multiplicity adjustment will be made for the fact that bemcentinib plus SoC arm will be compared with the control arm (SoC).

A Kaplan-Meier curve (product-limit estimate) will be provided along with a summary of the associated statistic for time to response including the 25th percentile, 50th percentile (median), and 75th percentile and their corresponding two-sided 80% CI and two-sided 95% CI. These CIs will be calculated according to Brookmeyer and Crowley (1982).

One-sided p value and two-sided p value of time to events between the bemcentinib plus SoC arm and the SoC arm will be calculated using a log-rank test stratified by age category, baseline severity grade (3, 4 or 5) and study centre/pooled study centre. HR will be estimated based on a Cox regression model. The analyses will be stratified by study treatment, age category, baseline severity grade, age category and treatment interaction, baseline severity grade and treatment interaction, and study centre/pooled centre. Ties will be handled using the exact method.

16.1.4. Sensitivity Analysis of Primary Efficacy Variable

If the severity at beginning of treatment does not match the baseline severity, the primary analysis will be re-run using the severity at beginning of treatment.

16.1.5. Supplementary Analysis of Primary Efficacy Variable

The following supplementary analyses will be performed for the primary efficacy endpoint:

- The same analysis as for the primary analysis of the primary efficacy endpoint (refer to Section 16.1.3) will be repeated but with only treatment arm in the models (unadjusted)
- The same analysis as for the primary analysis of the primary efficacy endpoint (refer to Section 16.1.3) will be repeated but the following factor (s) will be removed from the models
  - Centre/pooled centre
  - Age category
  - Age category and Centre/pooled centre
- The same analysis as for the primary analysis of the primary efficacy endpoint (refer to Section 16.1.3) will be repeated but the model will include factors relating to use of particular concomitant medications. The details of identifying and handling concomitant medications likely to affect COVID outcomes in analysis will be finalized before database lock.
- The same analysis as for the primary analysis of the primary efficacy endpoint (refer to Section 16.1.3) will be repeated but with the derivation of the endpoint involving imputed ordinal severity grade data (see Section 16.1.2 for details).
- The same analysis as for the primary analysis of the primary efficacy endpoint (refer to Section 16.1.3) will be repeated in each of the subgroups described in Section 7.7 but without centre/pooled centre in the model (as described in Section 7.7).
- A forest plot will be produced for the hazard ratio and its 95% CI within each of the subgroups, and for the primary analysis.

On each imputed dataset, the primary efficacy analysis will be repeated, and the log-rank test statistics, hazard ratios and standard errors will be combined using Rubin's rules, to obtain an overall hazard ratio, p-value and derived 80%

and 95% confidence intervals for the hazard ratio. A combined Kaplan-Meier (product-limit estimate) will be provided from the multiply imputed time to event analysis, along with a summary of the associated statistic for time to response including the 25th percentile, 50th percentile (median), and 75th percentile calculated as the median of these statistics across the multiply imputed analyses. The Kaplan-Meier curve will be combined across the multiply imputed analyses as in Moscovici (2017). The estimate of the standard error (SE) used in combining the multiply imputed results will be computed using Greenwood's formula.

16.2. SECONDARY EFFICACY

The secondary efficacy analyses will be performed on the ITT analysis set.

16.2.1. KEY SECONDARY EFFICACY VARIABLES & DERIVATIONS

16.2.1.1. The proportion of patients not deteriorating according to the ordinal scale by 1, 2, or 3 points on Days 2, 8, 15, 22, and 29

For each patient, deterioration by 1 point at each of these study days will be defined as an increase in ordinal scale score of at least 1 point compared to Baseline. Similarly, for each patient, deterioration by each of 2 points or 3 points at each of these study days will be defined as an increase in ordinal scale score of at least 2 point or 3 points respectively compared to Baseline.

16.2.1.2. Duration (days) of oxygen use and oxygen-free days

The duration of each occurrence of oxygen use will be derived based on the start date and time, and end date and time of the use of any type of supplemental oxygen (including mechanical ventilation) as captured on the *Supplemental Oxygen and Mechanical Ventilation* page of the eCRF. For each patient, the duration in days of oxygen use will be derived as the sum of the duration (in minutes) of each occurrence of oxygen use, divided by 1440 (24*60).

The number of oxygen-free days will be derived as the number of unique 24-hour days for which no oxygen was used while hospitalized.

To account for the different durations of the study for patients, including those who die and may therefore have less oxygen use recorded than other patients, the duration of oxygen use and the number of oxygen-free days will also be converted into percentages based on the total time in hospital for a patient, from randomisation to the *Stop date of admission* as captured on the *Hospitalization* page of the eCRF. If a patient dies and the stop date of admission is missing, the date of death will be used instead.

16.2.1.3. Qualitative and quantitative PCR determination of SARS-CoV-2 in oropharyngeal/nasal swab on Days 1, 3, 5, 8, 11, 15, and Day 29

PCR determination of SARS-CoV-2 in oropharyngeal/nasal swab on Days 1, 3, 5, 8, 11, 15, and Day 29 will be performed.

Results from for determination of SARS-CoV-2 will be available as either Positive, or Negative.

For quantitative results, change from Baseline will be derived at each visit as per Section 6.5. Quantitative results will also be log (base 10)-transformed, and change from Baseline in the log-transformed data will also be derived as per Section 6.5.

16.2.2. Missing Data Methods for Key Secondary Efficacy Variables

For the analysis of deterioration of 1, 2 or 3 points, patients with no ordinal score measured at Days 2, 8, 15, 22, or 29, and who have been discharged from hospital prior to that Day will have their ordinal score used from the most recent value recorded prior to the relevant Day.

Patients who have died prior to Day 2, 8, 15, 22 or 29, will have a score of 8 used for all Days after death.

All other occurrences of patients with missing ordinal score at Days 2, 8, 15, 22 or 29, will result in the patient being classified as having deterioration at that Day.

16.2.3. Analysis of Key Secondary Efficacy Variables

16.2.3.1. Analysis of the proportion of patients not deteriorating according to the ordinal scale by 1, 2, or 3 points on Days 2, 8, 15, 22, and 29

For each Day and for each of the three binary variables (non-deterioration of 1, 2 or 3 points), the number and percentage of patients with deterioration will be presented and the proportion of patients will be analysed using a Cochran-Mantel-Haenszel (CMH) test, with Baseline severity grade and centre/pooled centre.

The odds ratio (bemcentinib plus SoC vs SoC) for having deterioration and its two-sided 95% Wald CI and associated p-value, from a logistic regression model with treatment and the factors used in the CMH test will also be presented.

In addition, the risk difference (difference in proportions) between treatment arms at each Day will be presented along with the 95% CI of the risk difference obtained using the Newcombe hybrid score method (Newcombe 1998).

16.2.3.2. Analysis of duration (days) of oxygen use and oxygen-free days

The duration in days, the number of days and the percentage of each of these relative to days in hospital will be summarised descriptively for each treatment arm using N, mean, standard deviation, median, minimum, maximum and 1st and 3rd quartiles.

For each of these parameters, these summaries will be further broken down by whether patients died in hospital or not.

16.2.3.3. Analysis of qualitative and quantitative PCR determination of SARS-CoV-2

The number and percentage of patients with a positive and negative result for SARS-CoV-2 based on oropharyngeal/nasal swab, blood and saliva will be provided by treatment arm and visit based on the Intention to Treat Analysis Set for PCR test results only.

PCR test quantitative values for SARS-CoV-2 based on oropharyngeal/nasal swab, blood and saliva will be summarised at Baseline and each of Days 3, 5, 8, 11, 15 and 29, and their change from Baseline will be summarised at each of Days 3, 5, 8, 11, 15, and Day 29. These summaries will include N, arithmetic mean, standard deviation, median, minimum, maximum and 1st and 3rd quartiles. Log (base 10)-transformed, and change from Baseline in the log-transformed data will be summarised with geometric mean and geometric standard deviation.

Any SARS-CoV2 data not obtained from oropharyngeal/nasal swab, blood or saliva, or not analysed via PCR will be listed only.

16.2.4. Other Secondary Efficacy Variables & Derivations

16.2.4.1. Duration (days) of ventilation and ventilation-free days

The duration of ventilation will be derived based on the start date and time, and end date and time of either *Invasive Mechanical Ventilation* or *Non-Invasive Mechanical Ventilation* as the *Type of Supplemental Oxygen* captured on the *Supplemental Oxygen and Mechanical Ventilation* page of the eCRF.

The number of ventilation-free days will be derived as the number of unique 24-hour days for which no ventilation was provided.

To account for the different durations of the study for patients, including those who die and may therefore have less ventilation recorded than other patients, the duration of ventilation and the number of ventilation-free days will also be converted into percentages based on the total time in hospital for a patient, from randomisation to the *Stop date of admission* as captured on the *Hospitalization* page of the eCRF. If a patient dies and the stop date of admission is missing, the date of death will be used instead.

16.2.4.2. Incidence of any form of new ventilation use and duration (days) of new ventilation use

New ventilation use is defined as ventilation other than that occurring at the time of randomisation, i.e. for patients who are on ventilation at the time of randomisation, new ventilation use would be ventilation after the end of the ventilation at the time of randomisation. For patients who are not on ventilation at the time of randomisation, any ventilation use after randomisation would be considered as new ventilation use.

The duration in days, of new ventilation use would be derived in a similar manner as for duration of ventilation in Section 16.2.4.1 but excluding the initial period of ventilation for patients who were being ventilated at the time of randomisation.

16.2.4.3. Duration (days) of organ support

Duration of organ support (eg, including respiratory, renal, and cardiac support) will be derived from the duration of the AESIs defined in Section 17.1.5. For each patient the duration of AESIs will be summed, noting that if there are any overlapping dates of AESIs, days will only be counted once for a patient. Only AESIs for which *Was treatment given?* = Yes on the *Adverse Events* page of the CRF, will be included when deriving the durations.

To account for the different durations of the study for patients, including those who die and may therefore have less organ support than other patients, the duration of organ support will also be converted into percentages based on the total time in hospital for a patient, from randomisation to the *Stop date of admission* as captured on the *Hospitalization* page of the eCRF. If a patient dies and the stop date of admission is missing, the date of death will be used instead.

16.2.4.4. Response rate at Days 2, 8, 15, 22 and 29

The definition of responder is provided in Section 16.1.1. Patients who have not been discharged and who have no ordinal scale assessment on a particular study day, (including patients who have died prior to that study day) will be considered as non-responders. Patients who have not been discharged on a study day will be considered as responders at all subsequent time-points.

16.2.4.5. Time to live discharge from the hospital by Day 29

Time to live discharge from hospital will be defined as the number of days between randomisation and discharge. It will be derived as: (date of discharge - date of randomisation) +1.

Date of discharge will be taken from the *Stop date of admission*, recorded on the *Hospitalization* page of the eCRF.

Patients who are alive and still in hospital at the time of analysis will have their time to discharge censored at the data cut-off date for the analysis. Patients who have died at the time of analysis, without having been discharged from hospital, will have their time to live discharge censored at Day 29

16.2.4.6. Mortality at Days 15, 29, and 60

For patients who have died, date of death will be taken from the *Death Details* page of the eCRF. Day of death will be derived as (Date of death - date of randomisation) +1. Patients will be counted as having died at each of Days 15, 29 and 60 if they died on or prior to each of those respective study Days. Patients who died after each of Day 15, Day 29 or Day 60 will be counted as alive at each of these respective study Days.

Patients who are no longer in the study at each of these days and for whom there is not information available to say they are alive at that study day, will not be included in the denominator the mortality rates at the timepoints.

16.2.4.7. Time from randomisation to death

Date of death will be taken from the *Death Details* page of the eCRF. Time from randomisation to death will be defined as: (date of death – date of randomisation) +1.

Patients who are not known to have died at the time of analysis will have their time to death censored at the last date the patient was known to be alive. The last date the patient was known to be alive will be the latest date from the following:

- The *Date of completion/discontinuation* on the *Disposition* page of the eCRF
- The *Date of Procedures* from *Related Procedures* page of the eCRF
- The *Date contact was made* from *Contact* page of the eCRF when *Patient Status* is *Alive*
- The last *Date of Ordinal Scale for Clinical Severity* from *the Ordinal Scale for Clinical Severity* page of the eCRF.

The last study day known to be alive for such patients will be derived as (date last known to be alive – date of randomisation +1).

16.2.4.8. SpO_2/FiO_2 from randomisation to Day 15, hospital discharge, or death

SpO_2 (Oxygen Saturation) and FiO_2 (Fraction of Inspired Oxygen) will be taken from *Blood Gas Measurements* page of the eCRF. The ratio SpO_2/FiO_2 will be derived based on daily measurement. Change from Baseline in SpO_2/FiO_2 will be derived at each visit as per Section 6.5.

16.2.4.9. Duration (days) of ICU and hospitalisation

Duration of ICU and hospitalisation (days) will be derived based on start/stop date of admission and start/stop date of ICU/HDU stay in the *Hospitalization* page of the eCRF. Duration of hospitalization is derived as stop date of admission - start date of admission +1. Duration of ICU is the sum of duration (days) of each episode of ICU/HDU

stay. If a patient dies and the stop date of admission is missing, the date of death will be used instead.

To account for the different durations of the study for patients, including those who die and may therefore have less hospitalisation than other patients, the duration of ICU will also be converted into percentages based on the duration of hospitalisation for a patient.

16.2.4.10. NEWS2 assessed daily while hospitalised and on Days 15 and 29

The NEWS2 is based on 6 physiological measurements (respiration rate, oxygen saturation [SpO_2], systolic blood pressure, pulse rate, level of consciousness or new confusion, and temperature). Each of these physiological parameters is rated using a 4-point Likert scale (0= no risk to 3 = high risk). The NEWS2 score is obtained by summing the 6 physiological parameter individual scores, with higher score indicating higher risk of deterioration and need for escalation in clinical care, including transfer of the patient to a higher level of care hospital unit. The NEWS2 score is set to missing if at least one physiological parameter individual score is missing, and the overall score is uplifted by 2 points for patients requiring supplemental oxygen to maintain their recommended SpO_2. The range of NEWS2 score, taking into account this potential 2 point uplifting, is 0-20.

The scoring system for NEWS2 is provided in APPENDIX 2.

NEWS2 will be assessed daily while hospitalised and on Days 15 and 29. This should be evaluated at the first assessment of a given study day.

NEWS2 score data will be captured on the *National Early Warning Score (NEWS2)* page of the eCRF. Although the NEWS2 score is also captured on this page of the eCRF in addition to the individual 6 physiological parameters scores, the NEWS2 score will be re-calculated by IQVIA Biotech Biostatistics and the re-calculated NEWS2 scores will be used in the analysis. Both the captured and re-calculated NEWS2 scores will be listed.

Change from Baseline in NEWS2 will be derived as per Section 6.5.

16.2.4.11. Time to a NEWS2 of ≤2, maintained for at least 24 hours

NEWS2 will be derived as described in Section **Error! Reference source not found.**. Time to a NEWS2 of ≤2, maintained for at least 24 hours will be derived as follows:

- (The date of the first post-Baseline assessment where NEWS2 is ≤ 2 and sustained for at least 24 hours) – date of randomisation +1.

Note: To be sustained for at least 24 hours, the most recent NEWS2 score after a score of ≤ 2 must also be ≤ 2 AND there must also be at least 24 hours between the two NEWS2 assessments.

Patients who are alive at the time of analysis and have not had the event will have their time to event censored at the date of the last non-missing post-Baseline NEWS2 assessment. Patients who have died without having the event, will have their time to event censored at the same day as the maximum known time to event or censored observation.

16.2.4.12. Ranked trajectory over 29 days

For all patients across both treatment arms combined, trajectory will be ranked in the following order of the ordinal scale:

1. [ascending order] The worst (highest) score up to and including Day 29
2. [ascending order] The last recorded score up to and including Day 29
3. [ascending order] The number of days at worst score up to and including Day 29
4. [ascending order] The best (lowest) score up to and including Day29 that occurs after the worst score (this will equal the worst score if the worst score is the last score)
5. [descending order] The number of days the patient is at 4), counting only days after the last occurrence of the worst score (the number of days for this item will be 0 if the worst score is the last score).

Each of the orderings performed at steps 2, 3, 4 and 5 above are used to resolve any tied ranks resulting from the previous step, and each patient will have one overall rank for their trajectory compared to all other patients (across both treatment arms). Lower ranks will represent a better trajectory.

The rankings will be performed on each of the 100 imputed datasets obtained using the multiple imputation of ordinal scores data described in Section 16.1.2.

16.2.5. Analysis of Other Secondary Efficacy Variables

16.2.5.1. Analysis of duration (days) of ventilation and ventilation-free days

The duration of ventilation and ventilation-free days, and the percentage of days relative to days in hospital will be summarised descriptively for each treatment arm using N, mean, standard deviation, median, minimum, maximum and 1st and 3rd quartiles.

For each of these parameters, these summaries will be further broken down by whether patients died in hospital or not.

16.2.5.2. Analysis of Incidence of any form of new ventilation use and duration (days) of new ventilation use

The number and percentage of patients with any form of new ventilation use will be presented and the proportion of patients will be analysed using the same methodology as described in Section 16.2.3.1.

The duration of new ventilation use, and the percentage of days relative to days in hospital will be summarised descriptively for each treatment arm using N, mean, standard deviation, median, minimum, maximum and 1st and 3rd quartiles. For each of these parameters, these summaries will be further broken down by whether patients died in hospital or not.

At each Day up to Day 29, patients were classified as one of the following: Died; discharged (alive) from hospital; in hospital receiving ventilation; in hospital not receiving ventilation. The percentage of each category will be plotted with Day.

16.2.5.3. Analysis of duration (days) of organ support

The duration of organ support, and the percentage of days relative to days in hospital will be summarised descriptively for each treatment arm using N, mean, standard deviation, median, minimum, maximum and 1st and 3rd quartiles.

16.2.5.4. Analysis of response rate at Days 2, 8, 15, 22 and 29

Response rate at each of Days 2, 8, 15, 22 and 29 separately will be analysed using the same methodology as described in Section 16.2.3.1.

16.2.5.5. Analysis of time to live discharge from the hospital by Day 29

The analyses of time to live discharge will be the same as the primary analysis of the primary efficacy endpoint as described in Section 16.1.3.

16.2.5.6. Analysis of mortality at Days 15, 29, and 60

The number and percentage of patients alive, dead or with unknown mortality status at each of Day 15, 29 and 60 will be summarised for each treatment arm.

For each Day separately, the mortality rate will be analysed using the same methodology as described in Section 16.2.3.1.

16.2.5.7. Analysis of time from randomisation to death

The analyses of time from randomisation to death will be the same as the primary analysis of the primary efficacy endpoint as described in Section 16.1.3.

16.2.5.8. Analysis of SpO_2/FiO_2 from randomisation to Day 15, hospital discharge, or death

Ratio of SpO_2/FiO_2 will be summarised descriptively for each treatment arm using N, mean, standard deviation, median, minimum, maximum and 1st and 3rd quartiles. Change from Baseline in SpO_2/FiO_2 ratio will be summarised similarly at each post-Baseline study day at which SpO_2/FiO_2 ratio was assessed.

16.2.5.9. Analysis of duration of ICU and hospitalisation

Duration of ICU, percentage of duration of ICU and duration of hospitalisation will be summarised descriptively for each treatment arm using N, mean, standard deviation, median, minimum, maximum and 1st and 3rd quartiles.

16.2.5.10. Analysis of NEWS2 assessed daily while hospitalised and on Days 15 and 29

NEWS2 at Baseline and each day from Day 1 to Day 29 at which NEWS2 was assessed will be summarised descriptively as a continuous variable using number of observations, mean, standard deviation, median, minimum, maximum and 1st and 3rd quartiles. Change from Baseline in NEWS2 will be summarised similarly at each post-Baseline study day at which NEWS2 was assessed.

16.2.5.11. Analysis of time to a NEWS2 of ≤2, maintained for at least 24 hours

The analysis of time to a NEWS2 of ≤2, maintained for at least 24 hours will be the same as the primary analysis of the primary efficacy endpoint as described in Section 16.1.3, but with the following additions:

- For the stratified log-rank test, an additional stratum will be included based on whether the baseline NEWS2 score is:
    - < the 1st quartile Baseline NEWS2 score across all patients

- ≥ the 1st quartile and < the median Baseline NEWS2 score across all patients
- ≥ the median and < the 3rd quartile Baseline NEWS2 score across all patients
- ≥ the 3rd quartile Baseline NEWS2 score across all patients.

- For the Cox regression, an additional continuous covariate of baseline NEWS2 score will be included in the model.

If there are convergence or estimation issues with either the log-rank test or the Cox regression model, the Baseline NEWs score will remain in the model, and the other factors will be removed, as described in Section 7.8. If convergence or estimation issues still remain, then for the log-rank test, a simplified strata based on values being < or ≥ the median baseline NEWs score across all patients will be used.

16.2.5.12. Analysis of Ranked trajectory over 29 days

The ranks of all patients will be compared between treatment arms using the stratified Wilcoxon (van Elteren) test (using "Row mean scores differ" test in SAS PROC FREQ with the CMH option, with scores=modridit), stratified by Baseline severity and centre/pooled centre.

17. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the safety analysis set. There will be no statistical comparisons between the treatment arms for safety data, unless otherwise specified with the relevant section.

17.1. ADVERSE EVENTS

Prior AEs are defined as any AE that started or worsened in severity on or after the date of signed informed consent but before randomisation.

Treatment emergent AEs (TEAEs) are defined as any AE that started or worsened in severity on or after randomisation. For AEs with onset on the day of randomisation, if time of onset of the AE is not recorded, or is recorded and is on or after the time of randomisation, the AE will be considered TEAEs. All other AEs with onset on the day of randomisation will be considered as prior AEs.

See APPENDIX 1 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

If there are any patients randomised to SoC who received bemcentinib, a separate listing of AEs will be provided for these patients, denoting whether AE onset was before or after first administration of bemcentinib.

AEs will be coded using MedDRA version 23.0 or above.

An overall summary of number and percentage of patients within each of the categories described in the sub--sections below will be provided by treatment arm and overall based on the safety analysis set. Should a patient experience multiple events within a category, the patient will be counted only once for that category unless otherwise stated.

17.1.1. ALL TEAEs

Incidence of TEAEs will be presented by System Organ Class and Preferred Term and broken down further by maximum severity and relationship to study medication.

17.1.1.1. Severity

Severity will be classified according to the Common Terminology Criteria for AEs (CTCAE) grades, version 5. TEAEs with a missing severity will be classified as Grade 3 (severe) unless the outcome of the AE was Fatal in which case the missing severity would be classified as Grade 5 (fatal).

A patient experience multiple TEAEs within a System Organ Class or PT, only the patient's worst CTCAE grade will be counted for that System Organ Class or PT.

17.1.1.2. Relationship to Study Treatment

Relationship to study treatment, as indicated by the Investigator, will be classified as not related or related.

TEAEs with a missing relationship to study drug will be regarded as related to study drug. A patient experience multiple TEAEs within a System Organ Class or PT, only the patient's worst relationship will be counted for that System Organ Class or PT.

17.1.1.3. Relationship to Non-Study Drug

Relationship to non-study drug, as indicated by the Investigator, will be classified as not related or related.

TEAEs with a missing relationship to non-study drug will be regarded as related to non-study drug. A patient experience multiple TEAEs within a System Organ Class or PT, only the patient's worst relationship will be counted for that System Organ Class or PT.

17.1.1.4. Relationship to Study Procedure

Relationship to study procedure, as indicated by the Investigator, will be classified as not related or related.

TEAEs with a missing relationship to study procedure will be regarded as related to study procedure. Should a patient experienced multiple TEAEs within a System Organ Class or PT, only the patient's worst relationship will be counted for that System Organ Class or PT.

17.1.2. ADVERSE EVENTS WITH AN OUTCOME OF DEATH

TEAEs with an outcome of death are those events which are recorded as "Fatal" on the *Adverse Events* page of the eCRF. A summary of TEAEs with an outcome of death by System Organ Class and Preferred Term will be prepared.

A listing of all AEs with an outcome of death will be provided.

17.1.3. SERIOUS ADVERSE EVENTS

Serious AEs (SAEs) are those events recorded as "Serious" on the *Adverse Events* page of the eCRF. A summary of serious TEAEs by System Organ Class and Preferred Term will be prepared. Should a patient experience multiple

serious TEAEs within a System Organ Class or PT, the patient will be counted only once for that System Organ Class or PT.

A listing of all SAEs will be provided.

17.1.4. TEAEs Leading to Discontinuation of Study Treatment

TEAEs leading to permanent discontinuation of study drug are those events recorded as "Drug withdrawal" on the *Adverse Events* page of the eCRF. A summary of TEAEs leading to permanent discontinuation of study drug by System Organ Class and Preferred Term will be prepared. Should a patient experience multiple events within a System Organ Class or Preferred Term, the patient will be counted only once for that System Organ Class or Preferred Term.

A listing of all TEAEs leading to discontinuation of study treatment will be provided.

17.1.5. Adverse Events of Special Interest (AESIs)

17.2. There are no adverse events of special interest (AESI) in this study. Deaths

If any patients die during the study as recorded on the *Death Details* page of the eCRF, the number and percentage of patients who died due to COVID-19 as primary cause of death and those who died due to any other primary cause will be summarised by treatment arm based on the safety analysis set. Similarly, the number and percentage of patients who died due to COVID-19 as secondary cause of death and those who died due to any other secondary cause will be summarised by treatment arm based on the safety analysis set.

A listing of all deaths will be provided.

17.3. Laboratory Evaluations

A serum or urine pregnancy test will be performed at the screening visit. Chemistry, haematology, coagulation tests and blood gas assessments will be performed as per the schedule of events (refer protocol Section 1.3). A list of laboratory parameters to be included in the outputs is included in APPENDIX 3.

Quantitative laboratory parameters reported as "< X", i.e. below the lower limit of quantification (BLQ) or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summary will be provided by treatment arm based on the safety analysis set for blood gas parameters:

- Observed and change from Baseline in Standard International (SI) units by visit

The following summaries will be provided by treatment arm based on the safety analysis set for chemistry, haematology and coagulation parameters:

- Observed and change from Baseline in SI units by visit (for selected quantitative parameters, see parameters with an asterisk in APPENDIX 3)
- Shift from Baseline to the worst post-Baseline value according to the CTCAE toxicity grades (CTCAE

toxicity grades for applicable quantitative parameters are defined per CTCAE grading system, v5.0: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm [accessed 12-Oct-2020])

- Listing of patients with laboratory value meeting a CTCAE toxicity grade ≥ 3
- Shift from Baseline to the minimum post-Baseline value according to normal range criteria (for selected quantitative parameters, see parameters with an asterisk in APPENDIX 3)
- Shift from Baseline to the maximum post-Baseline value according to normal range criteria (for selected quantitative parameters, see parameters with an asterisk in APPENDIX 3)
- Listing of patients with abnormal laboratory values not meeting the normal range criteria (for selected quantitative parameters, see parameters with an asterisk in APPENDIX 3)
- Number and percentage of patients with maximum post-Baseline ALT/AST observed value categorised as < 3 x upper limit of normal (ULN), ≥ 3 to < 5 x ULN, ≥ 5 to < 10 x ULN or ≥ 10 ULN by maximum post-Baseline total bilirubin observed value categorised as < 2 x ULN or ≥ 2 x ULN
- A listing of patients with at least one observed post-Baseline ALT value > 3 x ULN, AST value > 3 x ULN or TBL value ≥ 2 x ULN will be provided.

17.3.1. LABORATORY NORMAL RANGES

Quantitative laboratory parameters will be compared with the relevant laboratory normal ranges in SI units and categorised as:

- Low: Below the lower limit of the laboratory normal range.
- Normal: Within the laboratory normal range (upper and lower limit included).
- High: Above the upper limit of the laboratory normal range.

17.4. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (SBP) (mmHg)
- Diastolic Blood Pressure (DBP) (mmHg)
- Heart Rate (bpm)
- Respiratory Rate (breaths/min)
- Body Temperature (ºC)
- Oxygen Saturation (SpO_2) (%)

The following summaries will be provided by treatment arm for vital signs data based on the safety analysis set:

- Incidence of potentially clinically significant abnormalities (PCSAs) at Days 8, 15 and 29 (or day of discharge), and at any time post-Baseline, overall and by Baseline normality status (low/normal/high)

- Listing of patients meeting PCSA criteria.

17.4.1. VITAL SIGNS POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITY (PCSA) CRITERIA

PCSA values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review.

Vital Signs measurements will be identified as normal/abnormal at Baseline, or as PCSA in accordance with the following predefined markedly abnormal criteria:

Variable	Unit	Low	High
SBP	mmHg	Baseline: ≤ 90 PCSA: ≤ 90 and CFB ≤ -20	Baseline: ≥ 180 PCSA: ≥ 180 and CFB ≥ 20
DBP	mmHg	Baseline: ≤ 50 PCSA: ≤ 50 and CFB ≤ -15	Baseline: ≥ 105 PCSA: ≥ 105 and CFB ≥ 15
Heart rate	bpm	Baseline: ≤ 50 PCSA: ≤ 50 and CFB ≤ -15	Baseline: ≥ 120 PCSA: ≥ 120 and CFB ≥ 15
Body temperature	˚C	NA	Baseline: ≥ 38.3 PCSA: ≥ 38.3 and CFB ≥ 1.1
Oxygen saturation	%	Baseline: < 94 PCSA: < 94	NA

CFB = change from Baseline.

17.5. ECG EVALUATIONS

The following electrocardiogram (ECG) parameters will be measured for this study as per the schedule of events (refer to protocol Section 1.3):

- Heart rate (bpm)
- PR interval (msec)
- RR interval (msec)
- QRS interval (msec)
- QT interval (msec)
- QTc interval (msec)
- QTcF interval (msec)
- QTcB interval (msec)
- Overall ECG interpretation (Investigator's judgment):
  - Normal
  - Abnormal, not clinically significant (NCS)

- Abnormal, clinically significant (CS).

The following summaries will be provided by treatment arm based on the safety analysis set for each ECG parameter:

- Shift from Baseline to worst-case markedly abnormal result (for quantitative parameters) post-Baseline for the observed values markedly abnormal criteria (refer to Section 17.5.1). In these shift tables values, the categories will be ≤470 msec, >470-<501 msec and ≥501 msec
- Incidence of any markedly abnormal change from Baseline values (for quantitative parameters) at any time post-Baseline. Patients will be counted in all relevant categories based on their highest post-Baseline change from Baseline, e.g. a value of > 60 will also be counted as > 30
- Listing of patients meeting markedly abnormal criteria
- Shift from Baseline in overall ECG interpretation to the worst post-Baseline interpretation
- Listing of patients with an abnormal overall ECG interpretation, including the finding(s) for each patient.

All ECG data will be listed.

17.5.1. ECG Markedly Abnormal Criteria

Markedly abnormal quantitative ECG parameters will be identified in accordance with the following predefined markedly abnormal criteria:

- Observed values for QT, QTc, QTcF, and QTcB intervals will be classified as:
  - > 470 msec
  - ≥ 501 msec.
- Change from Baseline for QT, QTc, QTcF, and QTcB intervals will be classified as:
  - >30 msec increase from Baseline
  - >60 msec increase from Baseline.

17.6. Other Safety Data

17.6.1. General Physical Examination

Physical examinations will be conducted as per the schedule of events (refer to protocol Section 1.3). At screening a general physical examination will be performed, and at post-Baseline visits a targeted physical examination of the chest will be performed.

All physical examination data will be listed only.

17.6.2. Diagnostic Imaging

Diagnostic imaging (chest X-ray and/or computed tomography) will be performed at Screening as per the schedule

of events (refer to protocol Section 1.3).

All diagnostic imaging data, including findings, will be listed only.

17.6.3. DISEASE-RELATED CO-INFECTION EVALUATION

Disease-related co-infection evaluation data will be listed only.

18. PHARMACOKINETICS

Because only sparse blood sample collections are planned for determination of bemcentinib (and metabolite, to be defined) concentration in plasma, non-compartmental analysis is not planned.

Pharmacokinetic data summaries are limited to concentration-time summary statistics.

18.1. DEVIATIONS OR EVENTS AFFECTING PK RESULTS

Changes to the procedures or events which may impact the quality of the PK data will be considered important protocol deviations or events and will be documented in the PK results. These changes or events will include any circumstances that will alter the evaluation of the PK. Examples of deviations/events for PK include, but may not be limited to, sample processing errors that lead to inaccurate bioanalytical results, inaccurate dosing on or prior to the day of PK sampling, and/or predose samples collected after the administered dose (see specifications below). Note that vomiting or diarrhoea are generally considered events that would result in exclusions from the Primary PKS set. However, the primary analysis set will include data potentially impacted by vomiting or diarrhoea. A secondary PK analysis set will exclude data potentially impacted by vomiting or diarrhoea.

18.2. PLASMA CONCENTRATION DATA

All bemcentinib (and metabolites, to be defined) plasma concentration data received will be listed by patient, and summaries for both the primary and secondary PKS will be presented by nominal time for patients included in the respective analysis sets.

In addition, for the primary PKS only, summaries will be presented based on further stratification by gender and age groups. The descriptive summary will include number of patients/non-missing observations (N/n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median), and maximum (Max). In cases with n ≤2, only n, Min, and Max will be reported. Plasma concentrations below the lower limit of quantification (LLOQ) will be set to 0 for calculation of the descriptive statistics. Mean and median values falling below the LLOQ will be presented as <LLOQ. Missing plasma concentration data will not be imputed, data will be treated as missing for descriptive statistics.

For both the primary and secondary PKS, there will be no exclusion of concentration-time data related to deviations from the scheduled sampling time for the 6-hour sample. Trough samples will be included in the concentration summary as long as they are collected no later than 30 minutes after dose administration.

A listing of individual PK blood sample collection times as well as derived sampling time deviations will be provided.

For the primary PKS only, the individual plasma bemcentinib (and metabolites) concentrations will be plotted versus actual time as an x-y scatter plot; the arithmetic mean (±SD, if appropriate) plasma candidate agent

concentrations will be plotted for each treatment versus nominal (or scheduled) time. Plots will be included with the y-axis presented on both a linear and a log scale.

Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data and will be rounded for reporting purposes only. The following conventions will be applied when reporting descriptive statistics of PK concentration data:

Mean, Min, Median, Max:	Same as source data
SD:	One more than source data
CV%	1 decimal place

For the metabolite concentration data, individual and summary metabolite concentration-time tables, listings, and figures will be generated as described above for parent bemcentinib. Depending on the metabolite data generated, additional tables, listings and figures may be generated. Also depending on the data, the generated metabolite tables, listings, and figures may not be presented in the CSR; however, all metabolite concentration time data will be maintained in the applicable SDTM and ADaM datasets.

19. PHARMACODYNAMICS

19.1. EXPLORATORY PD ANALYSIS

Pharmacodynamics analysis will be performed using the PDS.

A listing of PD sample collection times as well as derived sampling time deviations (as appropriate) will be provided.

Patient listings of all available PD endpoint-time data will be presented for observed values and baseline-corrected values. Baseline will be defined as the closest observation prior to the first dose of study medication. Concentrations for blood-based PD endpoints which fall below the LLOQ will be set to the LLOQ for any summary and/or inferential analyses.

The following will be listed:

- PBMC Phenotyping
- Cytokine analysis
- Soluble AXL, GAS6, and other blood proteins.

19.2. EXPLORATORY PK/PD ANALYSIS

Exploratory PK/PD correlations may be performed as part of the Stage 1 analysis using appropriately paired evaluable bemcentinib concentration - PD endpoint data sets for each analysis. If sufficient data is available, the following will be assessed using an appropriate plot or figure and/or regression analysis:

- Concentration - QTcF analysis: Bemcentinib plasma exposure to QT (C-QT)

- Soluble AXL levels to bemcentinib exposure
- Viral load to bemcentinib plasma concentration
- Log drop of viral load to bemcentinib plasma exposure
- Bemcentinib agent plasma exposure by prior therapy.

Some modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during study conduct.

20. REFERENCES

Brookmeyer R, Crowley J. A (1982) Confidence Interval for the Median Survival Time. Biometrics 38:29-41.

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Moscovici J.L, Ratitch B (2017) Combining Survival Analysis Results after Multiple Imputation of Censored Event Times, PharmaSUG 2017 – Paper SP05.

Newcombe, R.G. (1998) Interval Estimation for the Difference between Independent Proportions: Comparison of Eleven Methods. Statistics in Medicine 17:873–890.

APPENDIX 1. PARTIAL DATE CONVENTIONS

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS

START DATE	END DATE	ACTION
Known	Known/Partial/ Missing	If AE start date < date of randomisation then not a TEAE; If AE start date = date of randomisation and time of onset of AE is available and is before the time of randomisation then not a TEAE; Otherwise, TEAE.
Partial, but known components show that AE started before date of randomisation	Known/Partial/ Missing	Not TEAE.
Partial and known components show that AE started on or after date of randomisation OR Missing	Known	If AE end date < date of randomisation then not TEAE; If AE end date = date of randomisation and time of end of AE is available and is before the time of randomisation then not a TEAE; Otherwise, TEAE
	Partial	If known components of AE stop date show that AE stopped before date of randomisation), then not TEAE; Otherwise, TEAE
	Missing	Assume TEAE.

Note: If an AE started prior to randomisation but worsened after randomisation, it will be reported as a separate adverse event with new AE start date.

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS

START DATE	STOP DATE	ACTION
Known	Known	If medication stop date < date of randomisation, assign as prior; Otherwise, assign as concomitant
	Partial	If known components of medication stop date show that medication stopped before date of randomisation, assign as prior; Otherwise, assign as concomitant
	Missing, or ongoing	Can never be assigned as prior, therefore assign as concomitant.
Partial	Known	If medication stop date < date of randomisation, assign as prior; Otherwise, assign as concomitant.
	Partial	If known components of medication stop date show that medication stopped before date of randomisation, assign as prior; Otherwise, assign as concomitant.
	Missing, or ongoing	Can never be assigned as prior, therefore assign as concomitant.
Missing	Known	If medication stop date < date of randomisation, assign as prior; Otherwise, assign as concomitant
	Partial	If known components of medication stop date show that medication stopped before date of randomisation, assign as prior; Otherwise, assign as concomitant;
	Missing, or ongoing	Assign as concomitant.

APPENDIX 2. NEWS2 SCORING SYSTEM

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Source: https://www.rcplondon.ac.uk/file/9434/download [accessed 16 June 2020]

Note: SpO_2 Scale 1 corresponds to the eCRF *National Early Warning Score (NEWS2)* item *If Hypercapnic respiratory failure is NO.*

SpO_2 Scale 2 corresponds to the eCRF *National Early Warning Score (NEWS2)* item *If Hypercapnic respiratory failure is YES.*

Air or oxygen corresponds to the eCRF *National Early Warning Score (NEWS2)* item *Room air or Supplemental O2?*

CVPU corresponds to eCRF *National Early Warning Score (NEWS2) Consciousness* item response of *New-onset confusion (or disorientation/agitation), responds to voice, responds to pain, or unresponsive*

APPENDIX 3. LABORATORY ASSESSMENTS

Chemistry (SI unit)

- Sodium (mmol/L) *
- Potassium (mmol/L) *
- Calcium (mmol/L)
- Magnesium (mmol/L)
- Glucose (mmol/L) *
- Creatinine (µmol/L) *
- Creatine kinase (CK) (µkat/L) *
- MB Isoenzyme Fraction of CK (%)
- Direct bilirubin (µmol/L)
- Indirect bilirubin (µmol/L)
- Total bilirubin (µmol/L) *
- Gamma glutamyl transferase (GGT) (µkat/L) *
- Alkaline phosphatase (ALP) (IU/L)
- Aspartate transaminase (AST) (IU/L) *
- Alanine transaminase (ALT) (IU/L) *
- Carbon dioxide (CO_2) (mmol/L)
- Albumin (g/L)
- C-Reactive protein (CRP) (nmol/L)
- Bicarbonate (mmol/L)
- Triglycerides (mmol/L)
- Ferritin (µg/L)
- Lactate dehydrogenase (LDH) (IU/L)
- Phosphate (mmol/L)
- Chloride (mmol/L)
- Troponin (µg/L) I * and Troponin T (µg/L) *
- Creatine Clearance Calculation (mL/min)

* Selected parameter to be used in particular laboratory data summaries/analyses : Refer to Section 17.3 for details.

Haematology (SI unit)	
• Haemoglobin (g/L) *	• Absolute basophils count (x10E9/L)
• Platelet count (x10E9/L)	• Relative neutrophils count (%) *
• White blood cell (WBC) count total (x10E9/L) *	• Relative lymphocyte count (%)
• Absolute neutrophils count (x10E9/L) *	• Relative monocyte count (%)
• Absolute lymphocyte count (x10E9/L)	• Relative eosinophils count (%)
• Absolute monocyte count (x10E9/L)	• Relative basophils count (%)
• Absolute eosinophils count (x10E9/L)	

* Selected parameter to be used in particular laboratory data summaries/analyses : Refer to Section 17.3 for details.

Coagulation (SI unit)	
• International normalised ratio (INR) *	• Fibrinogen (g/L)
• Prothrombin time (PT) (s) *	• D-dimer (µg/L DDU)
• Activated partial thromboplastin time (aPTT) (s) *	

* Selected parameter to be used in particular laboratory data summaries/analyses : Refer to Section 17.3 for details.

Blood Gas (SIunit)	
• Arterial pH	• Capillary pH
• Arterial partial pressure of oxygen (PaO2) (kPa)	• Capillary PaO2 (kPa)
• Arterial partial pressure of CO2 (PaCO2) (kPa)	• Capillary PaCO2 (kPa)
• Arterial base excess/deficit (mEq/L)	• Capillary base excess/deficit (mEq/L)
• Arterial Oxygen Saturation (SpO2, %)	• Capillary Oxygen Saturation (SpO2, %)
• Arterial Fraction of Inspired Oxygen (FiO2, %)	• Capillary Fraction of Inspired Oxygen (FiO2, %)