TITLE PAGE

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

Protocol Number: BGBC020

Amendment Number: Amendment 2

Product: Bemcentinib

Study Phase: 2

Sponsor Name: BerGenBio ASA

Legal Registered Address: Jonas Lies vei 91
5009 Bergen
NORWAY

Date of Protocol: 08 October 2020

Version: Amendment 2, Final

Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly:

PPD BSc MB ChB MSc PhD FRCPE FRCP Date

PPD BerGenBio ASA

Medical Monitor name and contact information can be found in Appendix 2.

VERSION HISTORY

Name	Date	Summary of Changes
Original Protocol	05Aug2020	Creation
Original Protocol	26Aug2020	Modification of Inclusion/Exclusion criteria: exclusion patient with planned or current HIV and/or TB treatment, exclusion of Hep B and C positive patients, addition of Hep B and C viral serology at screening.
Amendment 2	08Oct2020	Addition and clarification on Steering committee, addition of IDMC (section 9.7.2 **Independent Data and Safety Monitoring Committee**), addition of stopping criteria (section 6.9 **Stopping Rules**), typographical corrections, addition of country-specific grade eligibility criteria (India – section 5.1 **Inclusion Criteria** and 5.2 **Exclusion Criteria**), addition of country target enrolment numbers, addition of procedures for handling protocol violations (section 7.4 **Protocol Violation**), addition of details on central laboratory assessments (section 8.2.3 **Clinical Safety Laboratory Assessments**), clarification of wording regarding adverse event of special interest (section 8.3.6 **Adverse Events of Special Interest**), addition of section on known adverse event serious adverse events (section 8.3.8 **Adverse events reported in non-COVID studies** and 8.3.9 **Expected Serious Adverse Events**), addition of details on study monitoring (section 10.0 **STUDY MONITORING**)

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

1.0 PROTOCOL SUMMARY

1.1 Synopsis

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

Rationale:

There are currently only 2 approved therapeutic agents available to treat coronavirus disease 2019 (COVID-19) in patients whose disease severity warrants treatment in hospital with supplementary oxygen (with or without ventilatory support).

- Remdesivir is an adenosine nucleotide prodrug indicated for the treatment of adults and adolescent patients hospitalised with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and severe disease.
- In the RECOVERY trial in the UK, dexamethasone reduced deaths by one-third in ventilated patients and by one-fifth in other patients receiving oxygen only. This has formed the basis for its inclusion in the SoC management of severe COVID-19 worldwide since June 2020, given its prior authorised posology for a broad range of non-endocrine corticosteroid responsive conditions.

Despite these advances in the therapeutic options for coronaviruses such as SARS-CoV-2 (causative agent of COVID-19), there is an urgent public health need for rapid development of additional interventions. The aim of this study is to rapidly assess bemcentinib as a treatment for COVID-19, in order to provide evidence of efficacy in this preliminary evaluation and to help with the design considerations of a later confirmatory stage. Hospitalised patients that may require either supplemental oxygen, non-invasive ventilation or high-flow oxygen devices would be considered for enrolment in the study. Patients in the need of intubation and invasive ventilation at the time of enrolment, would not be considered for this study.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of bemcentinib as add-on therapy 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). 9-point category ordinal scale: 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, non-invasive 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, extracorporeal membrane oxygenation 8. Death
Key Secondary	
• 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
Other Secondary	
• 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/heart rate/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: o [ascending order] The worst score o [ascending order] The last recorded score o [ascending order] The number of days at worst score o [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) o [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)
Exploratory	
• 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 be 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

Overall Design:

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 national study protocol in the United Kingdom in which bemcentinib is being evaluated.

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 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.
Participating sites in India will enrol only patients categorised as Grades 4 or 5 (hospitalised with moderate disease requiring oxygen supplementation, but not intubation). The reason for this is that, in accordance with India national COVID-19 management guidelines, patients who do not require supplementary oxygen therapy, would not generally be admitted to hospital. The effect of this is that Grade 3 patients in India, would only constitute a group of patients who had improved from more severe categories and were being prepared for discharge from hospital.

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 (1:1) to treatment arm to receive bemcentinib (as an add-on to standard of care [SoC]) or to control arm where only SoC will be administered.

Number of Investigators and Study Centres:

Study centres will be located in South Africa and India.

Number of Patients:

The expected number of patients for each treatment arm will be 60; for a total of 120 patients in this study. For each country, South Africa and India, an enrolment target of 60 patients (randomised 1:1) is in place.

Treatment Arms and Duration:

There will be 2 treatment arms-

- Patients receiving bemcentinib as an add-on to the SoC
- Patients receiving only SoC

The total study duration would be approximately 90 days.

Statistical Methods:

Sample size determination:

Note: the sample size calculation may re-evaluated as the treatment of COVID-19 evolves.

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.

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. To allow for uncertainty in the recruitment rates, 60 patients are planned to be randomised to each treatment arm in order to achieve the required number of events for this analysis.

Analysis sets:

- Intention to Treat (ITT) Set: All patients who are randomised and match the inclusion/exclusion criteria of the protocol will be included in the ITT.
- Safety Analysis Set: All patients who are randomised and receive study intervention (bemcentinib or SoC) will be included in the Safety Analysis Set.
- Pharmacokinetic Analysis Set (PKS): All patients who are randomised and take at least 1 dose of bemcentinib and have bemcentinib concentrations postdose without protocol deviations or events affecting the pharmacokinetic (PK) results will be included in the PKS.
- Pharmacodynamic Analysis Set (PDS): All patients who are randomised and receive study intervention (bemcentinib or SoC) and have evaluable results for at least 1 pharmacodynamic (PD) endpoint postdose. All analyses of the PDS will be based on each patient's randomised assigned treatment (not actual treatment received).

Efficacy, safety, pharmacokinetic, and pharmacodynamic results will be listed and summarised by stage, dose, and scheduled time for the respective analysis sets, where appropriate. Bemcentinib concentration versus response variables may be graphically displayed for selected endpoints.

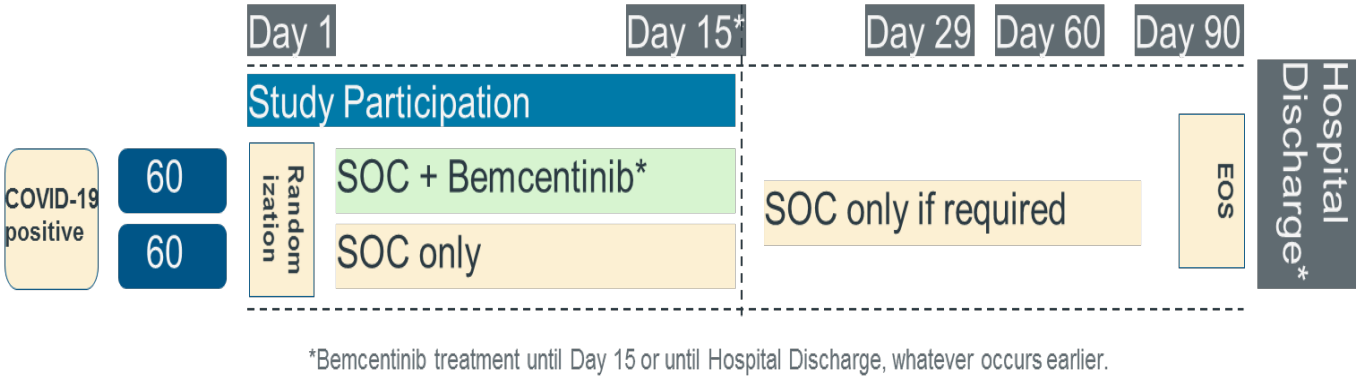
Exposure-response data obtained from this study may be combined with data from other studies and used for modelling and simulations.

Internal Sponsor Steering Committee: Yes

.

1.2 Schema

Figure 1 Study Schema



Abbreviation: COVID-19 = coronavirus disease 2019, EOS = end of study, SOC= Standard of care

1.3 Schedule of Activities

Table 1 Schedule of Activities

	Screening Visit	Baseline Visit	Inpatient Visit						Follow-up Visit	End of Study Visit
Day (± Window)	**Day-1 or Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Daily Until Hospital Discharge**	**Day 15[a] (±2 days)**	**Day 29[a] (±3 days)**	**Day 60[a] (±4 days)**	**Day 90[a] (±6 days)**
ELIGIBILITY										
Informed consent	X									
Demographics	X									
Relevant medical history[b]	X									
Review SARS-CoV-2 diagnostic tests	X									
Inclusion and exclusion criteria	X									
STUDY INTERVENTION										
Randomisation		X								
Administration of bemcentinib[c]		X	X	X	X	X	X			
Treatment with SoC	X	X	X	X	X	X	X	X		
STUDY PROCEDURES										
Clinical frailty score	X									
Diagnostic imaging (chest X-ray and/or computed tomography)[d]	X									
Physical examination (including presenting signs, height, weight)	X									
Targeted physical examination (To be performed as clinically indicated)			X	X	X	X				
Vital signs, including temperature, pulse rate, blood pressure, respiratory rate, SpO_2		X[e]	X	X	X	X	X	X		
Clinical assessments[f]		X[e]	X	X	X	X	X	X		
Targeted medication review (including use of vasopressors)		X[e]	X	X	X	X	X	X		
Adverse event evaluation (including adverse events of special interest)		X	X	X	X	X	X	X	X	X
Disease-related co-infection evaluation (including microbiologic/infectious agent assessment/results; bacteria, viral, fungi)		X	X	X	X	X				

	Screening Visit	**Baseline Visit**	**Inpatient Visit**						**Follow-up Visit**	**End of Study Visit**
Day (± Window)	**Day-1 or Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Daily Until Hospital Discharge**	**Day 15[a] (±2 days)**	**Day 29[a] (±3 days)**	**Day 60[a] (±4 days)**	**Day 90[a] (±6 days)**
Survival status		X	X	X	X	X	X	X	X	X
Blood gases and FiO_2 at worst PO_2[g]		X	X	X	X	X	X			
12-lead ECG[h]	***X***	***X***			X	X[h]	***X***			
LOCAL SAFETY LABORATORY[i]										
Haematology, chemistry, liver function tests, coagulation[i]	X[e,j,k]			X		Days 5, 8, 11 (all ±1 day)	***X[l]***	***X[l]***		
Hepatitis B and C virus serology	X[r]									
Pregnancy test for females of childbearing potential[m]	X[j]									
CENTRAL LABORATORY										
Blood (SST) for exploratory soluble factors analysis		X		X		Days 5, 8, 11 (all ±1 day)	X	X		
Blood (sodium heparin tube) for PBMC cellular immunity assays (optional)[n]		X		X		Day 8	X			
Blood (EDTA) for SARS-CoV-2 PCR (qualitative and/or quantitative)		X		X						
Oropharyngeal/nasal swab for SARS-CoV-2 PCR (qualitative and/or quantitative)		X		X		Days 5, 8, 11 (all ±1 day)	X	X		
Saliva for SARS-CoV-2 PCR (qualitative and/or quantitative)		X		X		Days 5, 8, 11 (all ±1 day)	X	X		
Blood (SST) for SARS-CoV-2 serology research[o]		X				Day 8	X	X	X	
Mid-turbinate nasal swab viral genome[p]		X								
Blood samples for PD[q]		X			X	Day 8	X	X	X	
PK sampling[q]		X			X	Day 8	X			

ECG=electrocardiogram; EDTA=ethylenediaminetetraacetic acid; FiO_2=fraction of inspired oxygen; PBMC=peripheral blood mononuclear cell; PCR=polymerase chain reaction; PD=pharmacodynamic; PK=pharmacokinetic; PO_2=partial pressure of oxygen; RT PCR=reverse transcription polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SoC=standard of care; SpO_2=oxygen saturation; SST=serum separator tube.

[a] These visits will be performed even if a patient has already been discharged. If discharged prior to scheduled visit, in-person visits are preferred, but recognising that quarantine and other factors may limit the patient's ability to return to the clinic, these visits may be conducted by telephone or with a home visit by study staff (blood samples scheduled for Days 15 and 29 will only be collected if the visit is conducted at the clinic). For visits conducted by telephone, it will not be possible to perform some scheduled assessments (eg, vital signs). The Day 29 assessments will also be performed, where possible, for patients who discontinue the study prematurely.

[b] Medical history includes estimated date and time of first signs and symptoms and number of co-morbidities (eg, respiratory, cardiovascular, metabolic, malignancy, endocrine, gastrointestinal, immunologic, renal).

[c] 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. Any exceptions to this must be authorised by the Medical monitor and/or Sponsor medical team. 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. Up to 15 days of bemcentinib treatment can be administered or until hospital discharge if less than 15 days. Bemcentinib should be taken once per day, in the morning, on an empty stomach or more than 2 hours after a light meal, with water. Patients should not consume anything other than water for at least 1 hour after taking study drug.
Patients will receive 400 mg loading doses on Days 1, 2, and 3 and 200 mg maintenance doses daily from Day 4 till the discharge or Day 15, whichever occurs earlier.

[d] Results obtained outside of the screening window are acceptable. If multiple assessments are performed during this time, the assessment closest to dosing will be regarded as the formal baseline assessment.

[e] Baseline assessments should be performed prior to study drug administration.

[f] Includes ordinal score, National Early Warning Score 2 (NEWS2), oxygen requirement, organ support, non-invasive or invasive ventilator requirement, including start and stop of low- or high-flow oxygen supply or of any form of ventilation etc.

[g] If done as part of SoC, blood gases results to be fully recorded with date and time.

[h] ECG to coincide with selected PK and PD sampling time points, ie, pre-loading dose (Day 1); then pre-maintenance dose and 6 hours postdose (Day 4). Subsequently predose on Days, 8 and 15. If QTcF is calculated from any ECG to be greater than or equal to 501 msec, then the ECG should be repeated after an interval of more than 10 minutes, to confirm this finding on a second ECG. If QTcF confirmed to be 501 msec or greater, bemcentinib should be permanently discontinued (see Section 7.0) by Investigator

[i] Please see Appendix 3.

[j] Laboratory tests performed in the 48 hours prior to first dose of study treatment will be accepted for determination of eligibility. If multiple tests are performed during this time, the test closest to dosing will be regarded as the formal baseline sample.

[k] Any laboratory tests performed as part of routine clinical care within the specified visit window can be used for safety laboratory testing.

[l] Additional safety laboratory evaluations to be performed on Days 15 and 29 only if patient is still hospitalised.

[m] Serum or urine pregnancy test.

[n] Samples collected for immediate laboratory processing and frozen storage.

[o] Samples collected on Day 1, Day 8 (if still an inpatient or at day of discharge, whichever comes first), Day 15 (if still an inpatient or at day of discharge, whichever comes first), Day 29 (if still an inpatient or at day of discharge, whichever comes first), and Day 60.

[p] Samples collected dependent on capacity of study centre, need for reduced study burden on staff, and potentially limited access to patients.

[q] Procedures for the collection, processing, storage and shipment of the PK and PD samples will be provided in the Study Laboratory Manual. When PK/PD sample is on the same day as ECGs, sample collection to coincide with the ECGs, ie, pre-loading dose (Day 1); then pre-maintenance dose and 6 hours postdose (Day 4). Subsequently predose on Days 8 and 15.

[r] Hepatitis B surface antigen and either Hepatitis C virus RNA PCR or Hepatitis C core antigen test as per standard screening by local laboratory.

2.0 INTRODUCTION

2.1 Study Rationale

There are currently only 2 approved therapeutic agents available to treat coronavirus disease 2019 (COVID-19) in patients whose disease severity warrants treatment in hospital with supplementary oxygen (with or without ventilatory support).

- Remdesivir is an adenosine nucleotide prodrug indicated for the treatment of adults and adolescent patients hospitalised with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and severe disease.
- In the RECOVERY trial in the UK, dexamethasone reduced deaths by one-third in ventilated patients and by one-fifth in other patients receiving oxygen only. This has formed the basis for its inclusion in the SoC management of severe COVID-19 worldwide since June 2020, given its prior authorised posology for a broad range of non-endocrine corticosteroid responsive conditions.

Despite these advancements in the therapeutic options for coronaviruses such as SARS-CoV-2 (the causative agent of COVID-19 disease), there is an urgent public health need for rapid development of additional interventions. The aim of this study is to rapidly assess bemcentinib as a treatment for COVID-19, in order to provide evidence for its efficacy in this preliminary evaluation and to help with design considerations of a later confirmatory stage. Hospitalised patients that may require either supplemental oxygen, non-invasive ventilation or high-flow oxygen devices would be considered for enrolment in the study. Patients in the need of intubation and invasive ventilation at the time of enrolment, would not be considered for this study.

2.2 Background

Coronaviruses are single-stranded RNA viruses, capable of causing life-threatening disease in humans and animals. The novel coronavirus SARS-CoV-2 was initially identified during an outbreak of viral pneumonia cases of unknown cause in China. Most of the initial infections outside of China were travel associated (ie, from people who had travelled from the infected regions of China to other countries), although person-to-person transmission in other countries was quickly established. The disease caused by the SARS-CoV-2 virus has been designated COVID-19.

SARS-CoV-2 binds via an angiotensin converting enzyme (ACE) receptor located on alveolar cells and intestinal epithelia.[1] The virus is mutating and showing diversity in critical surface protein; indicating that virulence and transmission will shift over time. New evidence suggests there are 2 groups of SARS-CoV-2; L-type and S-type.[1] S-type is the less aggressive (30%); the

L-type is now the most prevalent version (70%) and is more aggressive. Additionally, individuals appear to be affected to a different degree with varying symptoms and outcomes. These findings strongly support an urgent need for immediate comprehensive studies and robust validation of testing methods that combine genomic data, chart records, and clinical symptoms to help better understand the disease, enable risk assessment, and triage and support public health resource planning.

Due to the rapid global widespread increase in SARS-CoV-2 and COVID-19, there is an urgent need to develop efficacious treatments for the disease. Current clinical studies involve the use of already approved medications for other indications (repurposing) where it is thought that they might also be effective in the treatment of COVID-19 disease, as well as development of antibody-based therapies against the virus.

The current study will test bemcentinib with the aim of identifying potentially efficacious treatment in the shortest timeframe possible. In addition, it will support secondary research objectives that are critical for understanding the disease, spread of infection, and robust tests to diagnose it.

2.3 Benefit/Risk Assessment

2.3.1 Background/Rationale in Support of Bemcentinib for COVID-19

Bemcentinib is a clinical-stage, oral, selective small molecule AXL kinase inhibitor with well documented anti-viral effects in several systems. Bemcentinib is reported to block dengue, Ebola, and Zika virus infections in several cell types including epithelial, fibroblast, endothelial, neuronal and myeloid cell types in in vitro cell culture and organoid systems. Bemcentinib treatment is associated with increased interferon (IFN) signalling and reduced viral replication.[6,7,8]

During the 2013/2014 Ebola virus (EBOV) outbreak, bemcentinib was 1 of 60 compounds evaluated by Public Health England as an experimental therapy for EBOV, using its Biosafety Containment Level 4 facilities at Porton Down. Bemcentinib 200 mg/kg/day starting 6 hours post viral challenge protected 1/6 EBOV infected guinea pigs from weight loss and early mortality in an 18-day in vivo mortality study[7], compared with 1/6 untreated animals surviving to Day 18 but exhibiting weight loss during the observation period. The authors concluded that bemcentinib may have had some protective effect in this model.

Nonclinical in vitro and in vivo data suggest that bemcentinib might be useful for the treatment of early SARS-CoV-2 infection for which a few medical counter measures are currently approved. These data support testing the efficacy of bemcentinib treatment among hospitalised adults with COVID-19.

The AXL receptor tyrosine kinase promotes the infection of a wide range of enveloped viruses including pox-, retro-, flavi-, arena-, filo-, and alpha-viruses.[3,4,5,6,7] AXL increases viral infection through two mechanisms: 1) enhanced viral entry through "apoptotic mimicry"; and 2) suppression of anti-viral type I IFN responses.

The AXL receptor and related receptors (Tyro3 and MerTK, collectively TAM) are important for the clearance of apoptotic cells (efferocytosis) by macrophages.[8] Enveloped viruses co-opt this mechanism to expand tropism and enhance viral entry. Gas arrest-specific 6 (GAS6), the AXL ligand, binds PS exposed on the surface of the viral envelope, tethering the viral particle to the AXL receptor and promoting uptake by phagocytosis. This mechanism of viral entry, based on phosphatidylserine exposure, is common to most enveloped viruses and is termed viral "apoptotic mimicry".[10,11]

Binding of the viral particle to GAS6-AXL potently activates signal transduction through its tyrosine kinase domain to suppress type I IFN signalling and facilitate viral replication.[6,11] The AXL expression is induced by inflammation and serves as an innate immune checkpoint. AXL signalling suppresses viral-induced IFN responses via induction of protein synthesis suppressor of cytokine signalling 1 and 3 (SOCS1, SOCS3) leading to increased viral replication in infected cells and decreased anti-viral defences of neighbouring cells.[12,13,8] Consequently, AXL-null mice are resistant to Zika pathogenesis likely due to a combination of reduced virus entry and enhanced IFN responses [14], indicating a potential role for AXL inhibitors as therapeutics during viral infection.

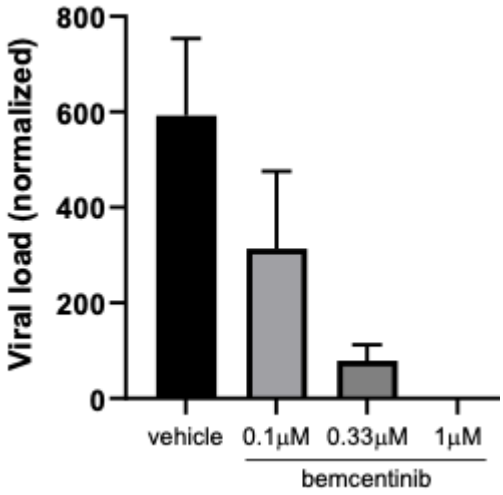
Therapeutic AXL receptor inhibition ameliorated pulmonary pathology resulting from primary viral infection in experimental models, indicating an important role for AXL within the lung.[15] During primary respiratory syncytial virus infection, AXL inhibition increased the number of IFNg–producing T cells and natural killer cells, suppressed respiratory syncytial virus replication and whole lung levels of interleukin (IL)-4 and IL-13. Also, the lethal effect of intrapulmonary H1N1 infection inflammation was reduced by AXL inhibition. AXL inhibition in infected mice increased the number of IFN-b–producing macrophages and dendritic cells and suppressed neutrophil infiltration.

2.3.2 Preliminary Efficacy Data vs With SARS-CoV-2 in Vitro

Professor Wendy Maury, University of Iowa, conducted a preliminary analysis of the anti-viral effects of bemcentinib on SARS-CoV-2 in a Vero E6 cell line. As shown in Figure 2, bemcentinib incubation starting 1 hour prior to virus inoculation potently inhibited SARS-CoV-2 infection of Vero E6 cells in a dose-dependent manner. Other studies using vesicular stomatitis virus pseudotyped with SARS-CoV spike protein and a mouse betacoronavirus (mouse hepatitis virus [MHV]) showed that bemcentinib may both inhibit uptake and activate the IFN-mediated antiviral gene, ISG15, to control viral infection. SARS-CoV-2 cell tropism is likely to include PS dependent viral uptake and may target critical immune cell populations (eg, macrophages,

dendritic cells) that produce IFN and mobilise antiviral immunity. Importantly, delayed IFN signalling is characteristic of pathogenic human betacoronaviruses and correlates with disease severity in animal models, suggesting that early intervention with IFN-activating treatment may provide therapeutic benefit.[16] Thus, AXL targeting is expected to attenuate SARS-CoV-2 pathogenesis both by limiting viral uptake and promoting innate antiviral immunity.

Figure 2 Bemcentinib Potently Inhibits Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection of Vero E6 Cells



Vero E6 cells (60,000) in a 48-well format were incubated (1 hour) with bemcentinib prior to addition of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (MOI 0.0005). Cells were lysed at 24 hours and viral load was analysed by quantitative reverse transcription polymerase chain reaction (RT PCR) for spike protein gene expression as normalised to the housekeeping gene *Cyclophilin*. W. Maury *et al*., unpublished results

Recent data that differentiate SARS-CoV-2 from severe acute respiratory syndrome (SARS) have emerged that support the hypothesis that AXL may have a more dominant role in SARS-CoV-2 infection, and therefore that bemcentinib may have specifically a more important role to play in inhibiting this viral infection:

SARS-CoV-2 has similar replication kinetics to SARS-CoV but demonstrates differential sensitivity to type I IFN treatment (1 of 2 mechanisms of action of bemcentinib through AXL inhibition).[17]

Structural analysis of the spike (S) protein of SARS-CoV-2 showed that its S protein has weaker binding to ACE2 receptor on human cells compared with strong affinity of human SARS coronavirus[18] – supporting the large magnitude effect observed for inhibition of viral replication using clinically appropriate doses of bemcentinib in ACE2 receptor +ve cells.

The currently approved therapeutic agents available (ie, dexamethasone and remdesivir) to treat coronaviruses such as SARS-CoV-2 and the severe disease manifestations in hospitalised

COVID-19 patients, have demonstrated benefits in reduced mortality risk and duration of hospitalisation. Despite the advances in available therapeutic interventions, there remains an unmet need in terms of mortality and morbidity due to SARS-CoV-2. Thus, while there may not be benefits for an individual patient participating in this study, there may be benefits to society if a safe and efficacious therapeutic agent can be identified during the global COVID-19 outbreak.

2.3.3 Cardiac Safety

Bemcentinib has shown in vitro evidence of antiviral effect against SARS-CoV-2 infection at concentrations below those achieved at the proposed dose regimen for use in this trial. This dose matches the recommended Phase 2 dose (RP2D) derived from multiple studies in various cancer populations. Treatment at this dose in 286 patients with cancer over a range of 6 weeks up to 2 years demonstrates that monotherapy or combination is largely well tolerated. Therefore, short term administration (15 days) in the context of hospitalised patients with SARS-CoV-2 infection is anticipated to be well tolerated. A non-severe, asymptomatic effect on QTc interval has been noted with bemcentinib treatment.

BerGenBio have amended the QTcF interval limit suggested in ICH E14, after taking specialist advice on pharmacometric characteristics and nonclinical toxicology of bemcentinib, and consultation with a clinical cardiac electrophysiology expert.

In order to mitigate the risk of drug-induced *Torsades de Pointes* (TdP) and drug-induced sudden cardiac death the following steps are enacted:

- Patients with a baseline QTcF interval >470 msec are excluded from the protocol.
- The cut off of 470 msec has been selected because this represents the estimated 99th percentile QTc values derived from otherwise healthy individuals (≤470 msec in men, and ≤480 msec in women).[19,20]. These QTc values are recommended by the American Heart Association consensus group for assessment of asymptomatic individuals for the presence of congenital long QT syndrome. In the absence of any exogenous QTc-aggravating factors, individuals with a QTc interval >470 msec have a higher probability of congenital long QT syndrome and therefore are at higher risk of QT-related ventricular arrhythmias if QT prolonging agents are administered;[21] for this reason, these patients are excluded from the study.

Additional risk mitigation steps will be in place:

- Regular electrocardiogram (ECG) monitoring is included in the clinical trial enabling early identification of prolonged QTc and early stopping rules (Appendix 6).
- Bemcentinib treatment will be withdrawn if QTcF interval prolongs to ≥501 msec. This is because population studies show that patients with a QTcF interval >500 msec are at increased risk of mortality.[22,23]

- Medication will be administered to participants while they are in hospital under medical supervision. Treatment is administered for a relatively short duration (maximum 15 days), ie, a relatively short exposure to any QTc prolonging effect of the medication.
- Bemcentinib treatment after stopping medication with potential for QT prolongation or concomitant with such medication which cannot be immediately discontinued, may be managed by increased frequency of QT evaluation and application of existing individual stopping rules. Coadministration of 2 medications with QT prolonging potential is not necessarily additive.[24]

Given the high morbidity and potential mortality of SARS-CoV-2 in hospitalised patients, there is a favourable balance of potential benefit: risk in the proposed clinical investigation of bemcentinib treatment for COVID-19 within the context of this clinical study. The QTcF cut-off criterion has been extended so that it represents the upper limit of normal values for otherwise healthy individuals. This will increase the number of patients who are eligible to take part in the study, while mitigating the risk of adverse effects due to potential QT prolonging effects of the treatment.

.

3.0 OBJECTIVES AND ENDPOINTS

Table 2 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• 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). 9-point category ordinal scale: 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, non-invasive 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, extracorporeal membrane oxygenation 8. Death
Key Secondary	
• 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
Other Secondary	

• 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/heart rate/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: o [ascending order] The worst score o [ascending order] The last recorded score o [ascending order] The number of days at worst score o [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) o [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)
Exploratory	
• 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 be 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

4.0 STUDY DESIGN

4.1 Overall Design

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. Bemcentinib was the first agent to be adopted to ACCORD-2 platform.

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). In India, only patients with Grade 4 or Grade 5 disease severity at screening, will be enrolled (per local guidelines Grade 3 patients would not typically be hospitalised). 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). Please refer to Figure 1 for further details.

Please refer to Appendix 8 for details of study procedures during special circumstances.

4.2 Scientific Rationale for Study Design

Bemcentinib is being assessed as a potential treatment for SARS-CoV 2 infection in this study, as there is an urgent public health need for rapid development of additional interventions. The study is randomised to minimise any kind of bias that could affect the study outcome.

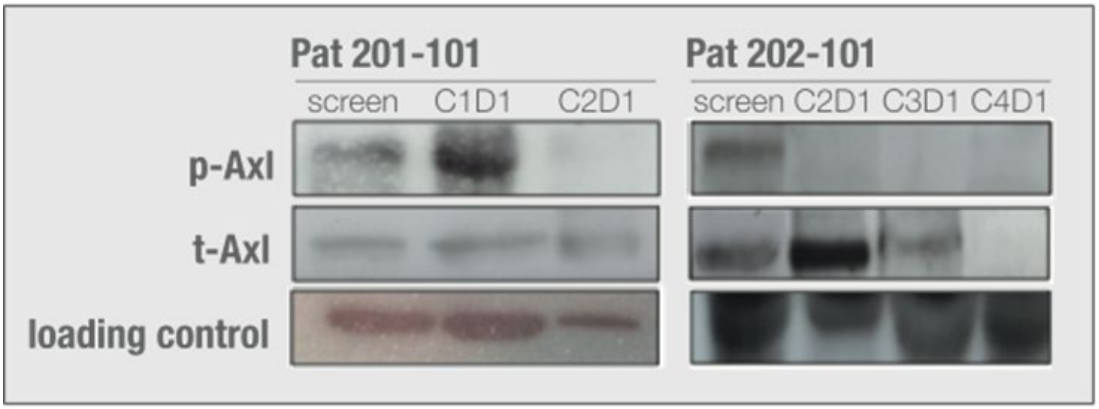
4.3 Justification for Dose

Bemcentinib's antiviral action stems from a cellular effect, inhibiting AXL kinase to prevent viral attachment and intracellular viral replication (through maximisation of the early type I interferon rather than a direct antiviral action). The target is AXL kinase inhibition rather than viral IC50, nevertheless, from estimates of pooled data, the half maximal inhibitory concentration (IC_{50}) at 24 hours for bemcentinib inhibition of viral load is approximately 140 nM and the approximate concentration required for 90% of maximum inhibition (IC_{90}) is 650 nM. This broadly corresponds to cancer cell data demonstrating high potency of bemcentinib to inhibit AXL. This high potency is reflected in translational data from clinical trials that demonstrate that at the RP2D steady state, AXL kinase is completely inhibited in myeloblasts from acute myeloid leukaemia (AML) patients on bemcentinib (Figure 3).

At RP2D, AXL kinase target demonstrates complete kinase inhibition (Figure 3), thus the maximal possible antiviral effect with this mechanism of action is accessed at the current clinical dose.

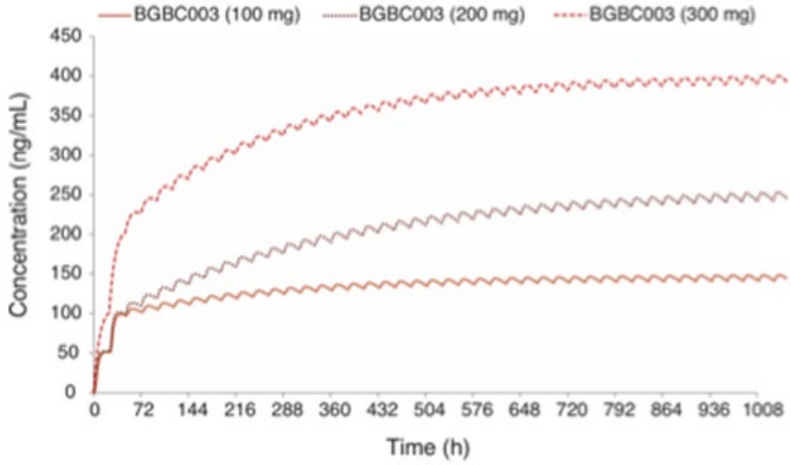
Frequent monotherapy complete responses are observed in AML at RP2D (Figure 3). Bemcentinib pharmacokinetic (PK) exhibits a prolonged enteral absorptive phase which overlaps with prolonged elimination kinetics after the second dose, to proportionately reduce peak to trough difference in plasma concentration-time profile, over a 24-hour dose interval, resulting in smooth steady state without noticeable peak to trough variation (Figure 4). Thus, at the clinical RP2D it is predicted that bemcentinib would be a highly potent antiviral against SARS-CoV-2, and potentially as efficacious as its main use an anticancer therapeutic.

Figure 3 Complete Inhibition of AXL Kinase Activation (p-AXL) in Two Acute Myeloid Leukaemia Patients Treated with Bemcentinib at the Recommended Phase 2 Dose (200 mg Maintenance Daily Dosing)



C=cycle; D=day; Pat=patient

Figure 4 Bemcentinib Plasma Pharmacokinetics in Acute Myeloid Leukaemia Patients



Bemcentinib is given orally as 100-mg capsules. Early clinical development in oncology patients identified the RP2D for that population; dose administration of bemcentinib in this study will utilise the same dosing regimen, ie, a loading dose (400 mg) given once daily for 3 days followed by a maintenance dose of 200 mg once daily. Planned duration of bemcentinib treatment is for a total of 15 days.

In preclinical and Phase 1 clinical studies, it was shown that systemic exposure to bemcentinib increased dose proportionately. The terminal half-life was 45.6 to 88.7 hours in man. Modelling of the PK data from this study indicated that the most effective approach to rapidly achieving steady state is to administer 3 daily loading doses followed by a lower daily maintenance dose.

4.4 Human Experience from Trials in Cancer Patients

Experience has been gained in the use of bemcentinib in the treatment of many types of cancer (including over 286 patients with AML, lung cancer, breast cancer, melanoma, and pancreatic cancer) in Phase 2 clinical studies. This has helped to define the safety profile, recommended dose and schedule as a monotherapy.[25] The safety profile of bemcentinib, initially ascertained in healthy human volunteers is tolerable and allows monotherapy approaches as well as combinations with chemotherapy (low dose cytosine arabinoside or with docetaxel), targeted therapy (epidermal growth factor receptor inhibitors) and immunotherapy (pembrolizumab). Bemcentinib is given as 2 oral capsules once daily (200 mg) following 3 daily 400 mg loading doses, to achieve steady state. Its principal significant AEs are a low incidence of diarrhoea (28%, with 6% Grade 3/4), asymptomatic QT prolongation (6% Grade 3/4), asthenia, and nausea at the RP2D.[25] Many patients have received bemcentinib without untoward effects for over 2 years at full dose. In particular, there were no QT prolongation related cardiac sequelae observed with either monotherapy or combination therapy in over 286 cancer patients, including elderly multimorbid patients (as presented in the Investigator's Brochure). Evidence of monotherapy efficacy has been documented in heavily pre-treated patients with AML. Complete response rates of approximately 40% have been observed in AXL expressing AML patients[25], indicating on target potency and specificity of bemcentinib as a monotherapy, through complete inhibition of the AXL kinase target. Treatment was well tolerated by most subjects, including the frail elderly. Bemcentinib was well tolerated when combined with pembrolizumab, demonstrating synergy with programmed cell death-1 antagonists through targeting of -AXLdependent immune suppressive mechanisms (M2 macrophages, suppressor dendritic cells, regulatory T cells, and myeloid derived suppressor cells). Collectively, bemcentinib- -mediated activation of innate immunity within the tumour microenvironment synergises with immune checkpoint therapy.[26]

4.5 End of Study Definition

The end of the study is defined as the date on which the last patient completes the last visit.

Once a patient has completed this study, there are no restrictions on them entering another study, subject to the eligibility criteria of that subsequent study, however, there will be ongoing requirement to adhere to the contraceptive conditions for 120 days after cessation of bemcentinib dosing.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

In order to enrol, a patient or legally authorised representative must sign an informed consent form (ICF) and meet all entry criteria for the protocol.

Concurrent participation in another clinical study of an investigational medicinal product while taking part in the current study (BGBC020) is not permitted, unless co-enrolment in the other study has been pre-approved by the Sponsor.

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria are met:

1. Adults (≥18 years) with SARS-CoV-2 infection confirmed by laboratory tests and/or point of care tests (which may include results from a test that was performed prior to hospital admission if, in the opinion of the Investigator, it is relevant to ongoing COVID-19).

2. Patients with symptoms and/or signs consistent with COVID-19, requiring treatment.

3. A score of Grade 3 to 5 on the 9-point ordinal scale (Section 8.1.1).
In India; only patients with a score of Grade 4 or 5 will be enrolled.

4. a) Male patients:

- A male patient must agree to use contraception as detailed in Appendix 5 during the treatment period and for at least 120 days after the last dose of study treatment and refrain from donating sperm during this period.

b) Female patients:

- A female patient is eligible to participate if she is not pregnant, not breastfeeding, and at least 1 of the following conditions applies:

i Not a woman of childbearing potential as defined in Appendix 5

OR

ii A woman of childbearing potential who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 120 days after the last dose of study treatment.

5. Women who are lactating who agree not to breastfeed their child during the study and for at least 120 days after termination of study therapy (they may continue to express milk away from the child during this period, but this milk must be discarded).

6. Ability to provide informed consent signed by the study patient or legally authorised representative.

5.2 Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

1. Patients who have previously had a score of 6 or 7 on the 9-point ordinal scale.

2. Inability to swallow capsules (administration via nasogastric tube is permitted in patients who become unable to swallow after starting the study drug)

3. History of the following cardiac conditions:

    a) Myocardial infarction within 3 months prior to the first dose

    b) Unstable angina

    c) History of clinically significant dysrhythmias (long QT features on ECG, sustained bradycardia [≤55 bpm]), left bundle branch block, or ventricular arrhythmia) or history of familial long QT.
    Patients with an implantable cardioverter defibrillator device in place, will be allowed to enrol. Atrial fibrillation will not be a reason for exclusion.

4. Screening 12-lead ECG with a measurable QT interval according to Fridericia correction (QTcF) >470 msec.
    In the presence of a cardiac pacemaker, QTcF will need to be calculated from an ECG which has been recorded during a period where ventricular (QRS) complexes without pacing are present. If no unpaced ventricular complexes are present to allow calculation of QTcF, the patient should not be enrolled in this protocol

5. Clinically significant hypokalaemia: Individuals who do not meet this criterion may be rescreened once, after correction of electrolyte abnormality.

6. Therapeutic anticoagulation with vitamin K antagonists. Note: Patients receiving low doses prescribed to maintain the patency of venous access devices may be included.

7. Previous bowel resection that would interfere with drug absorption.

8. Any patient whose interests are not best served by study participation, as determined by a senior attending clinician.

9. Alanine aminotransferase/aspartate aminotransferase >5 × the upper limit of normal.

10. Current treatment (or planned initiation of treatment during the first 15 days of the study) for human immunodeficiency virus (HIV) or tuberculosis (TB).
11. Positive serologic assay at screening for hepatitis B virus (Hep B surface antigen) or hepatitis C virus (hepatitis C PCR or hepatitis C core antigen) at local laboratory.
12. Stage 4 severe chronic kidney disease.
13. Anticipated transfer to another hospital that is not a study centre within 72 hours.
14. Allergy to any study treatment.
15. Experimental off-label usage of medicinal products as treatments for COVID-19 (except where the product has either been given a positive opinion under the Early Access to Medicines Scheme [EAMS] or is a SARS-CoV-2 vaccine) at the time of enrolment.
16. Patients participating in another clinical study of an investigational medicinal product.
17. Current or planned treatment for tuberculosis.

5.3 Lifestyle Considerations

Female patients are advised to avoid becoming pregnant during the study.

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

6.0 STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a patient according to the study protocol.

6.1 Study Treatment(s) Administered

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.

Bemcentinib should be taken once per day, in the morning, on an empty stomach or more than 2 hours after a light meal, with water. The first dose on Day 1 may be taken at any time before 1800 hours, with a subsequent loading dose on day 2 administered in the morning. Patients should not consume anything other than water for at least 1 hour after taking study drug.

The SoC will be based on appropriate local guidelines in place at the time of treatment during the study. The SoC may change during the course of the study as new information becomes available about treating COVID-19.

Where a patient is being treated with a product that has received a positive opinion under relevant local or global emergency use authorisation (eg, dexamethasone or remdesivir), appropriate clinical monitoring for that product should be adhered to (eg, daily renal or hepatic function testing).

6.2 Dose Modifications and Toxicity Management

Note: this modified guidance has been added to the Investigators' Brochure under relevant section of treatment of COVID-19.

Event	Recommended Bemcentinib Dose Modification
Estimated creatinine clearance decreases by more than ≥50% from baseline	Study medication should be withheld until estimated creatinine clearance returns to baseline
ALT or AST increases to >5 ULN	Study medication should be withheld until ALT and AST returns to baseline

Dose Modification of Bemcentinib Daily Dose for QTc Prolongation

QTcF	Recommended Bemcentinib Dose Modification
≥501 msec	
1st occurrence	Discontinue permanently
Ventricular arrhythmia	
1st occurrence	Discontinue permanently

ALT=alanine aminotransferase; AST=aspartate aminotransferase; QTcF= QTc interval according to Fridericia correction; ULN=upper limit of normal

Note: Serum calcium, magnesium and potassium should be measured regularly whilst receiving bemcentinib; all abnormal results should be corrected; check for use of concomitant medication that are associated with QT prolongation.

6.3 Preparation/Handling/Storage/Accountability

6.3.1 Bemcentinib Storage, Dispensing, and Destruction

Bemcentinib will be shipped to the participating site and must be stored at the site in a secure location under ambient temperature conditions (<25°C).

Site level accountability for study treatment is the responsibility of the Principal Investigator. The Investigator/designee must ensure that the bemcentinib will only be dispensed to patients in accordance with the dosing instructions in this protocol. Study staff should refer to the Bemcentinib Pharmacy Manual for specific instructions regarding the handling, storage, dispensing and destruction of bemcentinib.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for study treatment received and any discrepancies are reported and resolved before its use.

Only patients enrolled in the study may receive bemcentinib and only authorised study centre staff may supply or administer study drug. Study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions (see Bemcentinib Pharmacy Manual) with access limited to the Investigator and authorised study centre staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for bemcentinib accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused bemcentinib are provided in the Pharmacy Manual.

The Investigator, a member of the study centre staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of bemcentinib the Drug Accountability Form. These forms must be available for inspection at any time.

6.4 Measures to Minimise Bias: Randomisation and Blinding

No blinding will be used in this study.

The study will randomise participants to receive either bemcentinib as an add-on to SoC or to receive SoC alone. Randomisation will be stratified by baseline severity grade and by current use of approved agents in SoC.

6.5 Study Treatment Compliance

The prescribed dosage, timing, and mode of administration may not be changed, except as defined in Section 6.6. Any departures from the intended regimen must be recorded in the electronic case report forms (eCRFs).

Each dose of bemcentinib will be administered by a member of the clinical research team that is qualified and licensed to administer the study medication. Administration and date, time, and route will be entered into the eCRF.

6.6 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrolment (including screening) or receives during the study must be recorded in the eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Administration of bemcentinib is not recommended in patients requiring treatment with concomitant medications known to prolong QTc interval and promote TdP listed in Appendix 6. Patients already in receipt of such medications, where possible, should have these medications discontinued or replaced prior to starting bemcentinib; concomitant administration of 2 medications with potential for QT prolongation does not necessarily result in an additive effect on QTc.[24] If it is not clinically feasible to discontinue a specific medication, requiring its simultaneous short term use with bemcentinib, then patients may enrol as long as their baseline QTcF is not >470 msec. The Investigator should have a low threshold for initiating additional daily ECG monitoring, managing in accordance with the individual stopping rules (Section 6.2)

Medicines with both cytochrome P450 3A4 and TdP liabilities are particularly hazardous and their concomitant use should be subject to heightened caution, with a low threshold for additional ECG monitoring and discontinuation in line with individual stopping rules (Section 6.2).

Concomitant medications that are cytochrome P450 3A4 substrates are not reasons for exclusion of patients, however they should be discontinued, where possible, or used with caution.

Treatment with histamine receptor 2 inhibitors (cimetidine, ranitidine) or protein pump inhibitors (omeprazole) is permitted provided that administration is in the evening.

6.6.1 Citalopram – Specific Guidance for Use

Citalopram is a commonly prescribed medication, among the cohort of patients admitted to hospital for treatment of COVID-19. The product labels for citalopram, both European Summary of Product Characteristics 2019 and American product label (Celexa Proposed Labelling Text 2009), identify a specific risk of dose-dependent QT prolongation and TdP with contraindication against coadministration with other medicines with a potential for QT prolongation.

Following post-marketing reports of QT interval prolongation and TdP associated with citalopram, the Food and Drug Administration in 2012 evaluated formal thorough QT studies of citalopram and escitalopram in adults. These studies show that citalopram causes dose-dependent QT interval prolongation that is clinically significant with the 60 mg daily dose. In addition, clinical trials do not show any added effectiveness of citalopram at 60 mg/day compared with 40 mg/day. Therefore, citalopram should not be used at doses above 40 mg per day. Important safety information about the potential for QT interval prolongation and TdP with updated drug dosage and usage recommendations have been added to the citalopram drug label. Given that these findings were not observed with escitalopram, there are no changes planned for escitalopram at this time.

In accordance with the European Medicines Agency citalopram label, the maximum citalopram dose in patients over 60 years of age is limited to 20 mg daily.

Patients on citalopram, whose QTcF is not raised above 470 msec at screening, may continue on citalopram while on short term coadministration of study drug, but Investigators should have a low threshold for initiating additional ECG monitoring, managing in accordance with the individual stopping rules (Section 6.2).

6.6.2 Dosing with Remdesivir

No change in bemcentinib dose is recommended for patients taking both bemcentinib and remdesivir. Safety monitoring under current approval within each study region will apply and must be followed when remdesivir is used as standard of care; for example, the EAMS guidance in the UK, or any subsequent authorisation for its use, which supersedes this.

6.7 Dose Modification

The Sponsor will actively monitor interim data throughout the duration of the study to make recommendations about early study closure or changes to the study treatment arms.

6.8 Treatment after the End of the Study

This is a study in an acute severe respiratory disease and study treatment will not be continued/required following hospital discharge.

6.9 Stopping Rules

The stopping rules for this study pertain to assessments of the safety of bemcentinib use in the context of the protocol defined procedures for the treatment of patients hospitalised due to COVID-19. At this stage of development (exploratory clinical proof-of-concept in this indication) there is insufficient evidence on which to base a statistically robust futility analysis, therefore there are no defined stopping rules based on efficacy.

If any of the following events occur, the study enrolment will be paused with an urgent, ad hoc meeting of the IDMC convened in order to review the study data and make their recommendations (see IDMC charter):

- An unexpected Grade 5 event reported either with a possible or probable relationship to bemcentinib or reported as due to a study-related procedure
- Greater than 20% incidence of Grade 4 cardiac events (include ventricular arrhythmias and Torsade de pointes) reported in the bemcentinib treatment arm; a minimum enrolment of 1/3 of target patient number to the bemcentinib arm would be required to assess incidence rate.
- Incidence of QTcF ≥501 msec leading to discontinuation in the study of ≥ 25% in the bemcentinib treatment arm; a minimum enrolment of 1/3 of target patient number to the bemcentinib arm required to assess incidence rate.

If any of the above criteria were met, the IDMC will carefully review the totality of the data available at the time.

7.0 DISCONTINUATION OF STUDY TREATMENT AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

A patient in this study may discontinue from treatment for any of the following reasons:

1. Patient requests to discontinue study drug.
2. Occurrence of any medical condition or circumstance that does not allow the patient to adhere to the requirements of the protocol or patient fails to comply with protocol requirements or study-related procedures.
3. Any SAE, clinically significant AE, severe laboratory abnormality (including abnormal liver function test results), intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient.
4. Pregnancy recognised post start and prior to end of study treatment.

Unless the patient withdraws consent, those who discontinue study drug early should remain in the study for further acquisition of endpoint measurements. The reason for patient discontinuation of study drug should be documented in the eCRF.

7.2 Patient Discontinuation/Withdrawal from the Study

1. A patient may withdraw from study treatment or the study at any time at his/her own request or may be withdrawn from study treatment or the study at any time at the discretion of the Investigator for safety, behavioural, compliance, or administrative reasons.
2. If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
3. If a patient withdraws from the study, he/she may request destruction of any residual remaining samples taken and not tested, and the Investigator must document this in the study centre study records. However, any laboratory or test data generated from samples that have already been processed and included in any secondary research may not be recalled.
4. See Schedule of Activities (SoA, Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3 Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study centre.

The following actions must be taken if a patient fails to return to the study centre for a required study visit:

5. All efforts should be made to ascertain the vital status of the patient.
6. The study centre must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study. Recognising that quarantine and other factors may limit the patient's ability to return to the clinic, post-discharge visits may be conducted by telephone or with a home visit by study staff although patient visits to the site are preferred.
7. Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
8. Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

7.4 Protocol Violation

The investigator is accountable for protocol violations resulting from failure to adequately supervise the conduct of the clinical study.

All protocol violations will be recorded in CTMS and will be managed according to the Clinical Monitoring Plan and the Protocol Deviation Plan developed for the study. Protocol violations taken to guarantee subjects safety or other significant protocol violations will be reported according to local requirement. All violations will be reported in the clinical study report.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Note: Given the nature of the disease and the condition of the patients, it may not always be possible to perform all planned assessments at all time points; however, all efforts should be made to perform assessments as long as it considered clinically safe to do so.

The SoA is presented in Section 1.3.

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study design requirements is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

The maximum amount of blood collected from each patient over the duration of the study, including any extra assessments that may be required, will not exceed 350 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

All biological samples collected will be stored in a secure storage space in line with recommended guidelines for infectious substance handling, and with adequate measures to protect confidentiality. The samples will be retained while research on COVID-19 continues but no longer than 10 years or other period as per local requirements. For patients who withdraw consent to have their data analysed, samples will be destroyed.

8.1 Efficacy Assessments

8.1.1 Improvement on the 9-Point Scale

For the purposes of this study, the condition of each potential participant in the study will be assessed using a 9-point category ordinal scale:

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, non-invasive 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, extracorporeal membrane oxygenation
8. Death

For Grade 5, 'high-flow oxygen' consists of a heated, humidified high-flow nasal cannula delivering up to 100% heated and humidified oxygen at a maximum flow of 60 L/minute via nasal prongs or cannula to a patient at rates of flow higher than traditional low-flow therapy. In high-flow oxygen, the fraction of inspired oxygen (FiO_2) can be titrated from 21% to 100% independent of the flow rate.

Note: If initial data suggest that there are too few patients in certain categories, the decision may be made to combine parts of the ordinal scale, leading to a smaller number of categories.

To be considered for inclusion in the study, patients must be Grade 3 to 5 on this scale.

To be considered a "responder" to treatment with bemcentinib, a patient needs to show an improvement of at least 2 points (from randomisation) on this scale. For example, a patient who is Grade 5 (hospitalised - severe disease, non-invasive ventilation or high-flow oxygen) at randomisation but improves to Grade 3 (hospitalised - mild disease, no oxygen therapy) would be considered to be a responder. A patient with a live discharge from hospital or who is considered fit for discharge (a score of 0, 1, or 2 on the ordinal scale) will also be considered to be a responder.

The primary endpoint will be time to sustained clinical improvement of at least 2 points (from randomisation) by Day 29. Sustained clinical improvement is defined as improvement without subsequent worsening. The response rate (number and percentage of patients) will be determined for each treatment arm (bemcentinib) on Days 2, 8, 15, and 29 as a secondary endpoint.

In addition, a secondary endpoint will be proportion of patients not deteriorating according to the ordinal scale by 1, 2, or 3 points on Days 2, 8, 15, and 29.

Ranked trajectory over 29 days will be calculated, with trajectory ranked in the following order of the ordinal scale:

1. [ascending order] The worst score
2. [ascending order] The last recorded score

3. [ascending order] The number of days at worst score

4. [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)

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)

8.1.2 Other Efficacy Assessments

Overall mortality will be assessed on Days 15, 29, and 60, and, where applicable, time from treatment (bemcentinib) start date to death will be calculated.

The duration (days) of oxygen use and oxygen-free days (to Day 29) will be a secondary endpoint.

The duration of ventilator-free days (to Day 29) will be a secondary endpoint, as will be the incidence and duration (days) of new ventilation use.

The duration of overall organ support (eg, including respiratory, renal, and cardiac support) will be calculated.

The duration (days) of intensive care unit (ICU) and hospitalisation will also be a secondary endpoint.

The National Early Warning Score 2 (NEWS2 in Appendix 7) has demonstrated an ability to discriminate patients at risk of poor outcomes.[27] This score 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), and the overall score is uplifted by 2 points for patients requiring supplemental oxygen to maintain their recommended SpO_2. For patients confirmed to have hypercapnic respiratory failure on blood gas analysis, on either a prior or their current hospital admission, and requiring supplemental oxygen, the following are recommended: (i) a prescribed SpO_2 target range of 88% to 92%, and (ii) that the dedicated SpO_2 scoring scale (Scale 2) on the NEWS2 chart should be used to record and score the SpO_2 for the NEWS2.

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.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical Examinations

A general physical examination will be performed at screening, including assessment of presenting signs, height and weight.

As clinically indicated, a symptom-directed (targeted) physical examination will be performed from Day 2 through to hospital discharge.

8.2.2 Vital Signs and Blood Gases

Temperature, pulse rate, blood pressure, and respiratory rate will be assessed. Blood pressure and pulse measurements will be assessed with a completely automated device. SpO_2 will also be assessed. Manual techniques will be used only if an automated device is not available.

Blood gases (oxygen and carbon dioxide) and respiratory support will be recorded. FiO_2, the assumed percentage of oxygen concentration participating in gas exchange in the alveoli, will also be recorded.

Measurements will be taken in line with standard practices for the study centre.

Vital signs measurements will contribute to the NEWS2 score (see Section 8.1.2).

8.2.3 Clinical Safety Laboratory Assessments

Fasting is not required before collection of laboratory samples. See Appendix 3 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.

Local laboratories will be performing the test according to Appendix 3. These laboratories will be managed by the respective clinical trial site, reference ranges, accreditations and laboratory head Curriculum Vitae will be collected and filed in the site files accordingly.

The central laboratory will analyse the samples for the following:

Exploratory soluble factors, PBMC cellular immunity assays (optional test), blood for SARS CoV 2 PCR (qualitative and/or quantitative), oropharyngeal/nasal swab for SARS CoV-2 PCR (qualitative and/or quantitative), saliva for SARS¬ CoV 2 PCR (qualitative and/or quantitative), SARS-CoV-2 serology research, nasal swab viral genome, pharmaco-dynamics and pharmacological kinetics.

The involved central laboratories will be:

1. Q Squared Solutions301-A, Leela Business Park, M V Road, Andheri (East) Mumbai 400059, India
2. Q Squared Solutions Valencia 27027, Tourney Road, Suite 2EValencia, CA, 91000, USA

3. Myriad RBM 3300 Duval Td, Austin, Texas 78759
4. Alderly Analytical, UK, Alderly Park, Macclesfield, Cheshire, SK 10 4TG
5. Q Squared Solutions, Europe Alba Campus, Rosebank Livingston, West Lothian Scotland, EH54 7EG, UK
6. Expression Analysis, Q Squared Solutions 5927 South Miami, Blvd.Suite 100Morrisville, . NC, 27560, USA
7. CyteSpace 121 Amkor Road, Lyttelton Manor, Centurion, Gauteng, 0157, South Africa

8.3 Adverse Events

The definitions of an adverse event (AE) or SAE can be found in Appendix 4.

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the patient to discontinue the study treatment or the study (see Section 7.0).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from provision of informed consent until the final follow-up visit, at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs, and nonserious AESIs (see Section 8.3.6), will be followed until resolution, stabilisation, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 4.

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE (within 24 hours of becoming aware) is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, main research ethics committee (REC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the REC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female patients will be collected after the start of study treatment and until a time period that is at least 5 terminal half-lives after the last dose of the bemcentinib.

1. If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.
2. Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Adverse Events of Special Interest

There are no adverse events of special interest (AESI) in this study. Respiratory failure and QTc related AEs are not considered as AESI with bemcentinib treatment as respiratory failure is a sequelae of disease progression in Covid-19. QTc prolongation is minimised in this study through study inclusion/ exclusion criteria and as per Section 2.3.3 Cardiac Safety and Section 6.2 Dose Modifications and Toxicity Management.

8.3.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

Events that are typically associated with the disease under study will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE.

8.3.8 Adverse events reported in non-COVID studies

Investigators may refer to the current versions of the Investigator brochure (Section 6 – Summary of Data and Guidance for Investigators) for detailed information on adverse events. Summary information on adverse events for patients and/or legal representatives is provided in the relevant information sheets.

8.3.9 Expected Serious Adverse Events

The reference safety information is detailed in the current versions of the investigator brochure. Of those listed in the RSI, only serious adverse events due to gastrointestinal disorders (diarrhoea, nausea or vomiting) or infections and infestations (pneumonia) with a severity of Grade 3 and lower would be considered expected among patients with Covid-19.

8.4 Treatment of Overdose

In the event of an overdose of bemcentinib, the Investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the patient for any AEs/SAEs and laboratory abnormalities until bemcentinib can no longer be detected systemically.
3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

8.5 Pharmacokinetics

Venous blood samples for PK analysis will be collected according to the SoA (Section 1.3). The samples will be analysed for plasma concentrations of bemcentinib and bemcentinib metabolites. Detailed procedures for the collection, processing, storage and shipment of the samples will be provided in the Study Laboratory Manual.

Plasma samples for determination of bemcentinib concentration will be analysed by BerGenBio's Bioanalytical Services vendor using the validated liquid chromatography with tandem mass spectrometry method.

If a patient refuses blood collection for PK analysis or Investigator's judgement resolves that this blood collection is unsafe (eg, clinically significant anaemia), this will not be considered a protocol deviation as the PK is an exploratory endpoint in this study.

8.6 Pharmacodynamics

Blood samples for pharmacodynamic (PD) analysis will be collected according to the SoA (Section 1.3) and stored for future analysis in both the bemcentinib arm and the control arm. The samples will be analysed for soluble AXL, GAS6 (which could be predictive, PD, and mechanism biomarkers and hence require comparison with control arm not receiving bemcentinib), and other blood proteins. Detailed procedures for the collection, processing, storage and shipment of the samples will be provided in the Study Laboratory Manual.

If a patient refuses blood collection for pharmacodynamic analysis or Investigator's judgement resolves that this blood collection is unsafe (eg, clinically significant anaemia), this will not be considered a protocol deviation as the pharmacodynamic analysis is an exploratory endpoint in this study.

8.7 Virologic Load

Qualitative and/or quantitative polymerase chain reaction (PCR) determination of SARS-CoV-2 in oropharyngeal/nasal swab and in saliva (while hospitalised) on Days 1, 3, 5, 8, 11, 15, and 29 will be performed. A blood sample for PCR will be collected at baseline.

8.8 Immunology

Details regarding the type of sample and the specific soluble factors to be analysed and the analytical methods will be presented in the laboratory manual.

At time points indicated in the SoA (Section 1.3), an optional blood sample may be collected in a sodium heparin tube for immediate shipping to a central laboratory. Samples will be analysed for peripheral blood mononuclear cell cellular immunity assays.

If a patient refuses blood collection for immunology analysis or Investigator's judgement resolves that this blood collection is unsafe (eg, clinically significant anaemia), this will not be considered a protocol deviation as the immunology analysis is not a primary or secondary objective of the protocol.

8.9 Serology Research

At time points indicated in the SoA (Section 1.3), a whole blood sample will be collected in a serum separator tube to be processed to serum (within 48 hours) to be used in different antibody analysis methods for understanding immunity, antibody repertoire, and for validation of appropriate testing methods.

If a patient refuses blood for serology analysis, or Investigator's judgement resolves that this blood collection is unsafe (eg, clinically significant anaemia), this will not be considered a protocol deviation as the serology analysis are not a primary or secondary objective of the protocol.

9.0 STATISTICAL CONSIDERATIONS

9.1 Design Overview

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

9.2 Statistical Hypotheses

The primary hypothesis is time to response (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 arm is shorter than the SoC.

As the events are 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 test treatment with the control.

$$H_0: HR \leq 1 \text{ vs } H_A: HR > 1$$

9.3 Sample Size Determination

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.

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[28]). 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.

Safety data will also be assessed.

9.3.1 Sample Size Calculations

The calculations below (Table 3) are associated with time to improvement, discharge from hospital, or fit for discharge, and are associated with 80% and 90% power. The sample sizes are derived from a log-rank test, using a hazard ratio of 1.6 for the occurrence of the event, when comparing a bemcentinib with SoC.

Table 3 Sample Size for 80% and 90% Power for Time to Improvement, Discharge from Hospital, or Fit for Discharge Using Log-rank Test for a Hazard Ratio of 1.6 in Treatment Arm to Standard of Care

2-Point Improvement, Discharge from Hospital, or Fit for Discharge at Day 29				Patients/Arm [Total Events]		
SoC	Experimental Arm	Relative Improvement to SoC	Hazard Ratio	One-sided Alpha	Power	
					80%	90%
0.7	0.855	15.5%	1.6	0.1	54 [81]	79 [118]
	0.9	20%	1.9	0.1	29 [43]	42 [63]
0.7	0.855	15.5%	1.6	0.025	94 [141]	126 [188]
	0.9	20%	1.9	0.025	50 [75]	67 [100]

SoC=standard of care

9.4 Populations for Analyses

For purposes of analysis, the analysis sets are defined in Table 4.

Table 4 Analysis Sets

Analysis Set	Description
Intention to Treat (ITT)	All patients who are randomised and match the inclusion/exclusion criteria of the protocol.
Safety Set	All patients who are randomised and receive study intervention (bemcentinib or SoC).
Pharmacokinetic Analysis Set (PKS)	All patients who are randomised and take at least 1 dose of bemcentinib and have quantifiable bemcentinib concentrations postdose without protocol deviations or events affecting the pharmacokinetic results.
Pharmacodynamic Analysis Set (PDS)	All patients who are randomised and receive study intervention (bemcentinib or standard of care) and have evaluable results for at least 1 pharmacodynamic endpoint postdose. All analyses of the PDS will be based on each patient's randomised assigned treatment (not actual treatment received).

9.5 Statistical Analyses

The Statistical Analysis Plan (SAP) will describe the patient analysis sets to be included in the analyses and procedures for accounting for missing, unused, and spurious data.

Efficacy, safety, PK, and pharmacodynamic results will be listed and summarised by, dose, and scheduled time for the respective analysis sets, where appropriate. Bemcentinib concentration versus response variables may be graphically displayed for selected endpoints. Exposure-response data obtained from this study may be combined with data from other studies and used for modelling and simulations.

9.5.1 Efficacy Analyses

Please see Table 5.

Table 5 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Time to 2-point sustained improvement on the 9-point ordinal scale, live discharge, or fit for discharge (as analysed at Day 29), whichever comes first, will be compared with each treatment arm with standard of care (SoC) using log-rank test at the one-sided 0.1 alpha level. Intention to Treat (ITT) set will be used for the primary endpoint analysis. The time to 2-point sustained improvement on the 9-point ordinal scale, live discharge, or fit for discharge (as analysed at Day 29), whichever comes first, analyses will be conducted between the selected treatments plus SoC and SoC alone. The time to 2-point sustained improvement on 9-point ordinal scale, live discharge, or fit for discharge at Day 29 will be conducted between each selected treatment arm and control using the log-rank statistic, stratifying baseline severity grade, and the p-value associated with the log-rank statistic will be compared at the 2-sided 0.05 alpha level. The hazard ratio between treatment arm and SoC will be estimated using Cox regression, including treatment, age category (age <70 years vs ≥70 years), baseline severity, age category and treatment interaction, baseline severity and treatment interaction as fixed effect, and study centre as random effect.
Secondary	2-point sustained improvement on a 9-point ordinal scale will be analysed using CMH test, with stratification factors as covariates. Time to live discharge. Binary endpoints, including response rates at Days 2, 8, 15, and 29, and mortality rates at Days 15, 29, and 60, will be analysed using the same CMH test and logistic regression model as in the primary endpoint. Time-to-event endpoints, including time to sustained clinical improvement, time to worsening, time to death, and time to live discharge, from treatment start date will be plotted with Kaplan-Meier curves and will be tested with the log-rank test. Difference between treatment arms in the rank endpoints will be tested using the stratified Wilcoxon (van Elteren) test stratified by baseline ordinal score. Other continuous endpoints will be summarised with descriptive statistics such as mean, standard deviation, median, minimum, and maximum.
Exploratory	It will be described in the Statistical Analysis Plan finalised before database lock.

9.5.2 Safety Analyses

Analysis of Adverse Events

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities. Coding will be to lowest level terms. The preferred term (PT), and the primary system organ class will be listed.

Summaries of all treatment-emergent adverse events (TEAEs) by treatment arm will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by system organ class and PT
- TEAEs by severity, presented by system organ class and PT
- TEAEs by relationship to treatment (related, not related), presented by system organ class and PT
- Deaths and other SAEs will be listed and summarised by treatment arm.
- TEAEs leading to permanent treatment discontinuation will be listed and summarised by treatment arm.

Analysis of Clinical Laboratory Evaluations

The number and proportion of patients with normal/abnormal laboratory tests or different grades on Days 3, 5, 8, and 11 (or day of discharge) will be presented as shift tables by the baseline status (Day 1).

Analysis of Vital Signs

Potentially clinically significant abnormality values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review. The incidence of potentially clinically significant abnormality vital signs on Days 8, 15, and 29 (or day of discharge) will be summarised overall and by their baseline normality status (normal/abnormal).

9.5.3 Other Analyses

Where appropriate (if data collected), PK, pharmacodynamic, and biomarker exploratory analyses will be described in the SAP finalised before database lock. Drug concentration versus response variables may be graphically displayed for select endpoints. Exposure-response data may be obtained from this study and may be modelled and/or combined with data from other studies and used for modelling and simulations. If modelling and/or simulations are performed, these will be presented separately from the main clinical study report.

Subgroup analyses will be performed, and will include a repeat of the primary analysis by

- Severity at intervention;
- Comorbidity (cardiovascular; diabetes; any of chronic respiratory disease, hypertension or cancer; none of the above);
- Age group (up to 69 years of age; more than 69 years of age);

- Days from onset (less than 12 days; 12 or more days).

9.5.4 Missing Data

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

All patients recruited into the study will be accounted for, including those who did not complete the study along with the reasons for withdrawal from study and from study treatment. Patients who withdraw from the study and/or from the treatment will have the reasons of withdrawal collected in the eCRF. More details will be described in the SAP before database lock.

9.6 Interim Analyses

There is no plan for an interim efficacy analysis for this study. An Independent data and Safety monitoring committee will be established for this study (Section **9.7.2 Independent Data and Safety Monitoring Committee**).

9.7 Review Committees

9.7.1 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.

9.7.2 Independent Data and Safety Monitoring Committee

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.

10.0 STUDY MONITORING

10.1 Monitoring of the Study

Study Monitors will be responsible for the monitoring of the study. The Study Monitor will review the progress of the study on a regular basis to ensure adequate and accurate data collections. Monitoring visits to review eCRF, patient case notes, administrative documentation, including the Investigator Site File will be performed throughout the study.

Due to the current COVID-19 pandemic, any site training or monitoring methods may be conducted remotely (involving remote source data verification) with sites (via video calls and redacted source notes transferred to IQVIA via a secure file transfer method, or phone calls). Depending on the situation at each site over time, it is possible that the monitoring visits may be on-site visits at a later stage.

Before or during study initiation, representatives of the Sponsor or its designee(s) will review the protocol and eCRF with the investigators and their staff and perform study-specific training.

During the study, the IQVIA Biotech monitor and other IQVIA Biotech project team members, will check site specific documentation, either remotely or on-site, to confirm and ensure the following: completeness of records, accuracy of source data entries in the eCRFs, adherence to the protocol and ICH GCP, enrolment progress, and confirmation study drug supply/logistics.

Key study personnel must be available to assist the study monitor during remote or on-site visits. The investigator must maintain source documents for each subject in the study, which may consist of reports and visit notes (hospital or clinic medical records). All information on eCRFs must be traceable to these source documents in the subject's file.

For any on-site visits, the investigator must give the study monitor direct access to any relevant source documents to confirm their consistency with the eCRF entries, and compliance to the protocol. The investigator must also keep records documenting the informed consent process.

Information in source documents that could identify the subjects (such as the subjects' names) will not be forwarded to the Sponsor, IQVIA Biotech (or its designee(s)).

Once COVID-19 restrictions are lifted, the Sponsor or its representative(s) may visit the study facilities in order to maintain current knowledge of the study through review of the records, comparison with source documents, check of IP accountability, observation and discussion of the conduct and progress of the study. The clinical site will permit any trial related monitoring, audits, IRB/IEC review, and regulatory Clinical Trial Application inspection(s) by providing direct access to source data/documents.

10.2 Monitoring plan

For the current protocol, the study design and protocol details are strongly supportive of utilizing a 100% remote monitoring strategy, by managing or eliminating the unintended COVID 19 risk exposure to clinical monitoring staff.

From the monitor´s perspective, monitors will be conducting remote monitoring visits with sites and will be conducting Source data review over identified data points (detailed in the Clinical Monitoring Plan) including Informed consent review, inclusion/exclusion criteria, primary and secondary endpoints, contraception, pregnancy/lactation, COVID-19 testing, reasons for early discontinuation and AE/SAE review. Source documentation will be reviewed depending on the nature and capacities of each sites.

The use and access to validated electronic source documentation systems will be the preferred method if this exists at the site. Alternatively, sites will be able to upload source documentation to a secure platform/portal where monitors will review the mentioned data remotely. Additionally, monitor may be reviewing IP and reconciliation via teleconferencing as per study specifications, but this may change to be done at on-site visits when this is possible.

Remote monitoring includes subject safety, data quality, protocol compliance, endpoints and other reviews as identified during upfront risk assessment exercise. Detailed guidelines on monitoring activities are captured in the Clinical Monitoring Plan.

11.0 REFERENCES

1. Hamming I, Timens W, Bulthuis ML, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. 2004 Jun;203(2):631-7.
2. Tang X, Wu C, Li X, et al. On the origin and continuing evolution of SARS-CoV-2. National Science Review, https://doi.org/10.1093/nsr/nwaa036.
3. Shimojima M, Takada A, Ebihara H, et al. Tyro3 family-mediated cell entry of Ebola and Marburg viruses. *J Virol*. 2006 Oct;80(20):10109-10116.
4. Brindley MA, Hunt CL, Kondratowicz AS, et al. Tyrosine kinase receptor Axl enhances entry of Zaire ebolavirus without direct interactions with the viral glycoprotein. *Virology*. 2011 Jul 5;415(2):83-94.
5. Meertens L, Carnec X, Lecoin MP, et al. The TIM and TAM Families of Phosphatidylserine Receptors Mediate Dengue Virus Entry. *Cell Host and Microbe*. 2012 Oct 18;12(4):544-57.
6. Meertens L, Labeau A, Dejarnac O, et al. Axl Mediates ZIKA Virus Entry in Human Glial Cells and Modulates Innate Immune Responses. *Cell Rep*. 2017 Jan 10;18(2):324-333.
7. Dowall SD, Bewley K, Watson RJ, et al. Antiviral Screening of Multiple Compounds against Ebola Virus. *Viruses*. 2016 Oct 27;8(11):277.
8. Strange DP, Jiyarom B, Zarandi NP, et al. Axl Promotes Zika Virus Entry and Modulates the Antiviral State of Human Sertoli Cells. *mBio*. 2019 Jul 16;10(4):e01372-19.
9. Lemke G. How macrophages deal with death. *Nat Rev Immunol*. 2019 Sep;19(9):539-549.
10. Mercer J and Helenius A. Vaccinia Virus Uses Macropinocytosis and Apoptotic Mimicry to Enter Host Cells. *Science*. 2008 Apr 25;320(5875):531-5.
11. Bhattacharyya S, Zagórska A, Lew LD, et al. Enveloped viruses disable innate immune responses in dendritic cells by direct activation of TAM receptors. *Cell Host and Microbe*. 2013 Aug 14;14(2):136-47.
12. Huang MT, Liu WL, Lu CW, et al. Feedback regulation of IFN-α/β signaling by Axl receptor tyrosine kinase modulates HBV immunity. *Eur J Immunol*. 2015 Jun;45(6):1696-705.
13. Chen J, Yang YF, Yang Y, et al. AXL promotes Zika virus infection in astrocytes by antagonizing type I interferon signalling. *Nat Microbiol*. 2018 Mar;3(3):302-309.
14. Hastings AK, Hastings K, Uraki R, et al. Loss of the TAM Receptor Axl Ameliorates Severe Zika Virus Pathogenesis and Reduces Apoptosis in Microglia. *iScience*. 2019 Mar 29;13:339-350.
15. Shibata T, Habiel DM, Coelho AL, et al. Axl receptor blockade ameliorates pulmonary pathology resulting from primary viral infection and viral exacerbation of asthma. *J Immunol*. 2014 Apr 15;192(8):3569-81.
16. Channappanavar R, Fehr AR, Vijay R, et al. Dysregulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses Cause Lethal Pneumonia in SARS-CoV-Infected Mice. *Cell Host and Microbe*. 2016 Feb 10;19(2):181-93.
17. Lokugamage KG, Hage A, Vries Md, et al. Type I interferon susceptibility distinguishes SARS-CoV-2 from SARS-CoV, *bioRxiv*. 2020 Jan; (42), preprint 2020.03.07.982264.
18. Dong N, Yang X, Ye L, et al. Genomic and protein structure modelling analysis depicts the origin and pathogenicity of 2019-nCoV, a new coronavirus which caused a pneumonia outbreak in Wuhan, China. *F1000Res*. 2020 Feb;(9), preprint. 121–12.

19. Ackerman MJ, Zipes DP, Kovacs RJ, et al. Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Task Force 10: The Cardiac Channelopathies: A Scientific Statement From the American Heart Association and American College of Cardiology. *J Am Coll Cardiol. 2015 Dec;*66(21):2424–2428.
20. Giudicessi JR, Noseworthy PA, Friedman PA, et al. Urgent Guidance for Navigating and Circumventing the QTc-Prolonging and Torsadogenic Potential of Possible Pharmacotherapies for Coronavirus Disease 19 (COVID-19). *Mayo Clin Proc*. 2020 Jun;95(6):1213-1221.
21. Sharma S, Drezner JA, Baggish A, et al. International recommendations for electrocardiographic interpretation in athletes. *Eur Heart J*. 2018 Apr;39(16):1466-1480.
22. Haugaa KH, Bos JM, Tarrell RF, et al. Institution-wide QT alert system identifies patients with a high risk of mortality. *Mayo Clin. Proc*. 2013 Apr;88(4):315-25.
23. Priori SG, Schwartz PJ, Napolitano C, et al. Risk Stratification in the Long-QT Syndrome. *N Engl J Med*. 2003 May 8;348(19):1866-74.
24. Meid AD, Bighelli I, Mächler S, et al. Combinations of QTc-prolonging drugs: towards disentangling pharmacokinetic and pharmacodynamic effects in their potentially additive nature. *The Adv Psychopharmacol*. 2017 Dec;7(12):251-264.
25. Loges S et al. Comprehensive Analysis of the Dose Escalation, Expansion and Correlates in the Ph I/II Trial BGBC003 with the Selective Oral AXL Inhibitor Bemcentinib (BGB324) in Relapsed/Refractory AML and MDS ASH 2018, presentation.
26. Krebs M, Brunsvig PF, Helland A, et al. A phase II study of bemcentinib (BGB324), a first-in-class selective AXL inhibitor, in combination with pembrolizumab in patients with advanced NSCLC: Updated analysis. SITC 2019, oral presentation in High Impact Clinical Trials session.
27. National Early Warning Score (NEWS) 2: Standardising the Assessment of Acute-illness Severity in the NHS - Updated Report of a Working Party. Royal College of Physicians: London, 2017. https://www.rcplondon.ac.uk/file/8504/download [accessed 06 April 2020]
28. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med*. 2020;382(19):1787-1799.

12.0 APPENDICES

Appendix 1 Abbreviations

Abbreviation	Definition
ACE	Angiotensin-converting enzyme
AE	Adverse event
AESI	Adverse event of special interest
AML	Acute myeloid leukaemia
COVID-19	Coronavirus disease 2019
EAMS	Early Access to Medicines Scheme
EBOV	Ebola virus
ECG	Electrocardiogram
eCRF	Electronic case report form
FiO_2	Fraction of inspired oxygen
GAS6	Gas arrest-specific 6
ICF	Informed consent form
IFN	Interferon
IL	Interleukin
NEWS2	National Early Warning Score 2
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred term
REC	Research ethics committee
RP2D	Recommended phase 2 dose
SAE	Serious adverse evet
SAP	Statistical analysis plan
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SoA	Schedule of Activities
SoC	Standard of care
SpO_2	Oxygen saturation
TEAE	Treatment-emergent adverse event
TdP	Torsades de Pointes

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

Protocol Compliance

The Investigator agrees to comply with the requirements of the Protocol and Good Clinical Practice. Prospective, planned deviations or waivers to the protocol are not allowed under applicable regulations on Clinical Trials and must not be used; eg, it is not acceptable to enrol a patient if they do not meet the eligibility criteria or restrictions specified in the protocol. Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Medical monitor and Sponsor immediately.
Deviations from the protocol, which are found to frequently recur, are not acceptable and will require immediate action by the Sponsor. Frequent non-compliances could potentially be classified as a serious breach.

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the Protocol:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
    - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
    - Applicable local laws and regulations.
- The Protocol, protocol amendments, ICF, Investigator Brochures, and other relevant documents (eg, advertisements) must be approved by the appropriate regulatory body, local regulations, and REC before the study, or a new study arm introducing bemcentinib, is initiated.
- Any substantial amendments to the protocol will not be implemented until local regulations and REC have provided the relevant authorisations, except for changes necessary to eliminate an immediate hazard to patients.
- All correspondence with the local regulatory and the REC will be retained in the Trial Master File and the Investigator Site File (maintained by the site).
- An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.
- Within 90 days after the end of the study (as defined in Section 4.4), the Medical monitor and/or Sponsor medical team will ensure that the local regulatory and the main REC are notified that the study has finished. If the study is terminated prematurely, those reports will be made within 15 days after the end of the study.
- The Medical Monitor will supply the Sponsor with a summary report of the study, which will then be submitted to the main REC within 1 year after the end of the study.

- All results will be published on a publicly accessible database.
- After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 9). The study will not start at any study centre at which the Investigator has not signed the protocol.

Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Indemnity

The Sponsor of the study is BerGenBio ASA. Insurance certificate will be provided.

Informed Consent Process

Note: Informed consent from a patient will be obtained on paper and then scanned/photographed to retain an electronical copy, the original will be destroyed at site.

By consenting to participate in the study participants also consent to all the secondary research endpoints.

Some patients will be unable to give consent themselves and therefore consent can be given on their behalf by a legally authorised representative. If legally authorised representatives are unable to visit the patient in person due to COVID-19 restrictions, it may not be possible to obtain legally authorised consent in person; in these circumstances a legally authorised representative can give consent via a remote process. The legally authorised representative will be contacted by telephone to discuss the patient's condition and the consent documents; they will then be sent an e-mail invitation about the study, and they can sign the ICF remotely. Study staff will be available by telephone to answer questions.

The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorised representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Where they are able, patients or their legally authorised representative will be required to sign the ICF. If the patient is not able to read the text and/or sign the ICF for themselves but has capacity to give consent, an independent witness can witness the consent process and sign the ICF to confirm this. Where a legal representative is not able to sign the ICF but can provide verbal consent over the telephone, an independent witness can witness the consent process and sign the ICF to confirm this. In these instances, the patient or legally authorised representative must also sign the ICF within a reasonably practicable time frame.

The patient's medical record must include a statement that informed consent was obtained before the patient was entered in the study and the date the consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

If there are changes to the ICF, patients must be re-consented to the most current version of the ICF(s) during their participation in the study. The above-mentioned electronic processes will also apply in these instances if needed.

A copy of the signed ICF(s) must be provided to the patient or the patient's legally authorised representative.

Data Protection

- Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate REC members, and by inspectors from regulatory authorities.
- The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation, that also explains that his/her medical records (past and future) may be linked to their study data and accessed and examined for healthcare research, and that participant data may be stored and processed in the cloud or outside the country.
- The ICF will explain that the individual genotype results will not be returned to patients, provided to any insurance company, to any employer, their family members, general physician, or any other third party, unless required to do so by law.
- Participants will not receive any financial benefit from the use of their samples or data in research. Samples and data may be processed and used by commercial entities as well as government or academic entities.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, the Sponsor or representative physician or an Investigator might know a patient's identity and also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files.

Administrative Structure

The IQVIA Therapeutic Medical Advisor (Medical Monitor) is available for 24 hours a day/7 days a week urgent contact. If the IQVIA Therapeutic Medical Advisor is not able to provide 24/7 services for a period longer than 2 hours (eg, for international business travel) or during vacations, adequate back-up will be arranged and communicated.

The administrative structure will be documented in more detail in the Trial Master File.

Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to the European Union database a summary of the results of the clinical study within 1 year from the end of the clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

Data Quality Assurance

- All patient data relating to the study will be recorded on eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, REC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data review to confirm that data entered into the eCRF by authorised study centre personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study centre’s patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to

source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study centre.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the eCRF completion guidelines.

Study and Study Centre Closure

The Sponsor designee reserves the right to close the study centre or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centres will be closed upon study completion. A study centre is considered closed when all required documents and study supplies have been collected and a study centre closure visit has been performed.

The Investigator may initiate study centre closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study centre by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the REC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of patients by the Investigator.
- Discontinuation of further study treatment development.

Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available.

The publication policy with respect to the Investigator and study centre will be set forth in the Clinical Trial Agreement.

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre studies only in their entirety and not as individual study centre data. In this case, a Coordinating Investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 3 Clinical Laboratory Tests

- The minimum tests to be performed are detailed in Table 6. Clinical laboratory tests will be performed at a local laboratory.
- Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5.0 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Changes to some laboratory parameters are anticipated for any patients moving on to ECMO therapy.
- Investigators must document their review of each laboratory safety report.

Table 6 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Haematology	Platelet Count Haemoglobin White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Coagulation	D-dimer test Fibrinogen Activated partial thromboplastin time (aPTT) Prothrombin time International Normalised Ratio (INR)
Clinical Chemistry	Potassium Sodium Calcium Magnesium Phosphate Alkaline phosphatase Bicarbonate Creatinine Creatine kinase (including MB fraction if available) Glucose Total bilirubin Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Gamma-glutamyl transferase (GGT) C-reactive protein Ferritin Triglycerides Lactate dehydrogenase (LDH) Troponin
Additional laboratory serology	Hepatitis B and Hepatitis C

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An adverse event (AE) is any untoward medical occurrence in a patient or patient, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalisation for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening The term 'life-threatening' in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c) Requires inpatient hospitalisation or prolongation of existing hospitalisation In general, hospitalisation signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d) Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e) Is a congenital anomaly/birth defect
f) Other situations: • Medical or scientific judgement should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF. Each event must be recorded separately.
- It is **not** acceptable for the Investigator to send photocopies of the patient's medical records to the CRO/Sponsor in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the CRO/Sponsor. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the CRO/Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following Common Terminology Criteria for Adverse Events (CTCAE) grades:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental activities of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting selfcare activities of daily living (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe (Grade 3 and higher).

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The AE must be characterised as related or unrelated.
    - "Related" conveys that there are facts, evidence, and/or arguments to suggest a causal relationship for the individual case.
    - "Unrelated" is used if there is not a reasonable possibility that the study treatment caused the AE.
- The Investigator will use clinical judgement to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the CRO/Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the CRO/Sponsor.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the CRO/Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study or during a recognised follow-up period, the Investigator will provide the CRO/Sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to the CRO/Sponsor via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to the CRO/Sponsor will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the study centre will use the paper SAE data collection tool (see next section). • The study centre will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given study centre, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a study centre receives a report of a new SAE from a patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the study centre can report this information on a paper SAE form (see next section) or to the Medical Monitor/SAE coordinator by telephone.

SAE Reporting to CRO/Sponsor via Paper Case Report Form
• Facsimile transmission of the SAE paper case report form is the preferred method to transmit this information to the Medical Monitor or the SAE coordinator. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE eCRF pages within the designated reporting time frames.

Appendix 5 Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Fertile Male

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    a) Documented hysterectomy.
    b) Documented bilateral salpingectomy.
    c) Documented bilateral oophorectomy.

    Note: Documentation can come from the study centre personnel's: review of the patient's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
    a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-oestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Contraception Guidance

Male patients

- Male patients with female partners of childbearing potential are eligible to participate if they agree to ONE of the following:
    - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in the table below when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

- In addition, male patients must refrain from donating sperm for the duration of the study and for at least 120 days after the last dose of study treatment.
- Male patients with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for the duration of the study and for at least 120 days after the last dose of study treatment.

Female patients

Female patients of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That are User Dependent [a] *Failure Rate of <1% Per Year When Used Consistently and correctly.*
Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] Oral Intravaginal. Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation[b] Oral. Injectable
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] Intrauterine device (IUD). Intrauterine hormone-releasing system (IUS). Bilateral tubal occlusion.
Vasectomised Partner *A vasectomised partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.*

NOTES:
[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies.
[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilised during the treatment period and for at least 120 days after the last dose of study treatment.

Pregnancy Testing:

- WOCBP should only be included after a negative highly sensitive pregnancy test.
- Pregnancy testing will also be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information

Male subjects with partners who become pregnant (if required as per local country regulations).

- The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive bemcentinib.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of foetal status (presence or absence of anomalies) or indication for the procedure.

Female Subjects who become pregnant

Please refer to Section 8.3.5**.**

- The Investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a patient's pregnancy. The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.

- Any poststudy pregnancy-related SAE considered reasonably related to bemcentinib by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former patients, he or she may learn of an SAE through spontaneous reporting.

Continuation of study treatment may be allowed, as COVID-19 is a high mortality disease.

Appendix 6 Avoidance of Concomitant Medication with QT Prolongation Risk or CYP3A4 Interaction with Narrow Therapeutic Index

For any concomitant medication, please check the following website for the drug's *Torsades de Pointes* (TdP) risk: https://crediblemeds.org/oncosupport/.

If a medication can be discontinued, the 3-day bemcentinib loading regime may be started as long as the QTcF on prior therapy is not prolonged above that required for eligibility (470 msec).

While it is desirable to discontinue concomitant medications with QT prolonging liability prior to trial entry, and replace where indicated with non-QT prolonging medications, where it is not clinically feasible to immediately discontinue, concomitant administration will not exclude the patient, but Investigators should have a low threshold for applying additional ECG monitoring (daily) in this setting as clinically indicated, and discontinue bemcentinib permanently if QTcF becomes ≥501 msec.

For drugs with a conditional risk, please review the product label and correct any abnormalities, eg, hypokalaemia.

Sensitive Cytochrome P450 3A4 Substrates With A Narrow Therapeutic Margin THESE MEDICATIONS SHOULD BE **DISCONTINUED** BEFORE ENROLMENT		
Alfentanyl 90-111 minutes	Dihydroergotamine & ergotamine 2 hours	Quinidine 6 hours
Astemizole 7 – 9 hours	Fentanyl 8 – 10 hours	Sirolimus 63 hours
Cisapride 12 hours	Fluticasone[a] 3 – 8 hours	Tacrolimus (FK506) 12 hours
Cyclosporine 8.4 hours	Pimozide 55 hours	Terfenadine 3.5 hours

[a] Fluticasone, administered either nasally or inhaled, has limited systemic exposure and may continue without interruption.

Common medication Associated with a Risk of QT Prolongation and TdP – USE NOT RECOMMENDED AS CONCOMITANT MEDICATION		
Amiodarone 50 days[$]	Erythromycin 2 hours[$]	Pimozide 55 hours **
Astemizole 24 hours **	Escitalopram 30 hours[$a]	Procainamide 2.5-4.75 hours[$]
Azithromycin 2-4 days[$]	Fluconazole 30 hours[$]	Quinidine 6 hours **[$]
Chloroquine 1-2 months[$]	Haloperidol 15 – 27 hours[$]	Sotalol 10 – 20 hours[$]
Citalopram 35 hours[$a]	Ketoconazole 3 – 10 hours[$]	Terfenadine 3.5 hours**
Clarithromycin 3-4 hours[$]	Methadone 25 – 55 hours[$]	Thioridazine 21 – 24 hours[$]
Cocaine 0.6 – 1.3 hours[$]	Moxifloxacin 12 hours[$]	Voriconazole 6 hours[$]
Disopyramide 6.7 hours[$]	Ondansetron 3 hours[$]	
Droperidol 2 hours[$]	Petamidine 10 – 14 days[$]	
***also CYP3A4 substrates*	[$] also TdP risk	

RECOMMENDED ACTION

1. QTcF >470 msec (on above medication) → patient is **not eligible** for enrolment in the subprotocol
2. QTcF ≤470 msec (on above medication):

a) Stop drug, if possible, for duration of study dosing and consider alternatives
3-day bemcentinib loading regime may be initiated and consider enhanced frequency of ECG monitoring

b) If drug cannot be stopped, may be continued with enhanced ECG monitoring frequency (daily)

In either case bemcentinib must be discontinued permanently if QTcF is calculated at ≥501 msec (see Section 6.2)

For specific advice on citalopram or escitalopram, see Section 6.5.1.

Woosley RL, Heise CW, Gallo T, Tate J, Woosley D and Romero KA, www.CredibleMeds.org, QTdrugs List, [14Apr2020], AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755

[a] Citalopram/escitalopram may be continued with short term coadministration of bemcentinib, in accordance with guidance in Section 6.5.1.

Guidance on other concomitant medication	
Use of gastric acid-reducing agents	Treatment with histamine receptor 2 inhibitors (cimetidine, ranitidine) or protein pump inhibitors (omeprazole) is permitted provided that administration is once daily, in the evening,
Anti-diarrhoeal	Loperamide use is permitted at up to a maximum dose of 16 mg in a 24-hour period
Nausea/anti-emetic	No evidence for specific restrictions on coadministration of anti-emetic medication, but Investigators should note QT prolongation potential associated with ondansetron and should not be newly initiated

Appendix 7 The 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	

Appendix 8 Study Procedures During Special Circumstances

During special circumstances (eg, COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For the duration of such special circumstances, the following measures may be implemented for enrolled subjects:

- Safety follow-up may be made by a telephone call, other means of virtual contact, or home visit, if appropriate.
- Diary cards may be transmitted from and to the site by electronic means and/or conventional mail.
- Biological samples may be collected at a different location* other than the study site or at subject's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- If despite best efforts it is not possible to collect blood samples within the interval predefined in the protocol, then the interval for blood sampling may be extended up to a maximum length of 30 days before the next blood sampling. Impact on the per protocol set for analysis of immunogenicity will be determined on a case-by-case basis.
- A limited number of subjects may be recruited in the active arms, should there be a high rate of missed visit and/or visit outside of planned interval and/or withdrawal due to the current exceptional and unpredictable circumstances.

*It is the Investigator's responsibility to identify an alternate location. The Investigator should ensure that this alternate location meets International Council for Harmonisation Good Clinical Practice requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on subjects by Investigator and staff at a site other than the designated study site.

Appendix 9 Signature of Investigator

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

PROTOCOL NO: BGBC020

VERSION: Original Protocol

This protocol is a confidential communication of the Sponsor. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study centre in which the study will be conducted. Return the signed copy to the CRO/Sponsor.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Centre: _____

_____

_____