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Intervention Specific Appendix Title:

Efficacy and safety of AXL-inhibitor bemcentinib for the treatment of moderate COVID-19

Intervention Specific Appendix Protocol to Master Protocol EU-SolidAct: European DisCoVeRy for Solidarity: An Adaptive Pandemic and Emerging Infection Platform Trial.

Intervention Specific Appendix Protocol Number: 1.5 dated 24 January 2023

Refers to EU-SolidAct Master Protocol Number: 3.1 dated 28 November 2022

Amendment Number: 3

Compound: Bemcentinib (BGB324)

Brief Title: AXL-SolidAct

Study Phase: 2b

Sponsor Name: Oslo University Hospital

Legal Registered Address:

P. O. Box 4950 Nydalen

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Manufacturer: BerGenBio ASA [study identifier BGBIL022]

Regulatory Agency Identifier Number(s)

EU CTR: 2022-500385-99-00 (EU-SolidAct Reference trial)

EU CTR: 2022-500363-12-00 (AXL-SolidAct)

WHO UTN: U1111-1278-1806 (AXL-SolidAct)

Approval Date:

Sponsor Signatory: DocuSigned by: Morten Tandberg Eriksen F3AD66A29FF34D4... 24 January 2023

Morten Tandberg Eriksen, MD PhD **Date**

Head - Division of Surgery, Inflammatory Diseases and Transplantation, Oslo University Hospital

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Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amdendment 3 protocol version 1.5	*24 January 2023*
Amendment 2 protocol version 1.4	*10 July 2022*
Amendment 1 protocol version 1.3	*22 June 2022*
Original Protocol v 1.2	*30 March 2022*

This is amendment 3 protocol version 1.5 dated 24 January 2023

This amendment is considered to be substantial based on the criteria set forth in Article 2(2)(13) of The Clinical Trials Regulation (CTR).

Overall Rationale for the Amendment:

This amendment includes the following updates to allow the inclusion of participants who have been infected by COVID-19 in the hospital.

Section # and Name	Description of Change	Brief Rationale
First page	Reference to a new version 3.1 of the master protocol	The master protocol has been changed to be consistent with this protocol on the primary endpoint for phase 2 investigations.
5.2 Exclusion Criteria	SE-02: updated to not exclude patients developing nosocomial pulmonary COVID-19 during hospitalisation SE-16: Updated to specify that the “hospitalised > 4 days” exclusion criteria only applies if the hospitalisation is with COVID-19.	The changes in the exclusion criteria maintain the intended population of participants in an equivalent stage of their disease evolution but clarify to the investigator that the same criteria apply whether the participant develops pulmonary COVID in a community setting or in a hospital setting. The rationale is increased inclusion.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: Efficacy and safety of AXL inhibitor bemcentinib for the treatment of moderate COVID-19

Brief Title: AXL-SolidAct

EU CTR: 2022-500385-99-00 (EU-SolidAct Reference trial)

EU CTR: 2022-500363-12-00 (AXL-SolidAct)

Rationale: The AXL pathway is a well-described mechanism used by several enveloped viruses to enter host cells and dampen the anti-viral immune response. AXL is part of a tyrosine kinase receptor complex that recognises phosphatidyl serine, and which may enhance viral infection through two mechanisms: 1) facilitated viral entry through "apoptotic mimicry"; and 2) suppression of anti-viral type I interferon (IFN) responses[1]. Bemcentinib (BGB324) is an orally bioavailable, potent and highly selective inhibitor of AXL tyrosine kinase currently being studied for the treatment of various cancers[1]. Bemcentinib has been investigated in two Phase 2a clinical studies in hospitalised COVID-19. Exploratory results from these studies indicate that bemcentinib has a potential antiviral effect, and a favourable effect on limiting disease progression, including the avoidance of invasive ventilation or death, shortening time to recovery or discharge, and potentially increasing overall survival at day 29, with only mild and reversible adverse events being observed. Bemcentinib represents a novel class of drug with a mechanism independent of the spike protein and mutations. The potential of blocking the AXL-dependent interferon suppression could be of particular importance in patients with a sub-optimal immune response to vaccines, in particular in a setting with emerging variants of concern. There is a clear rationale to further study the safety and efficacy of bemcentinib in a phase 2b trial of hospitalized patients with moderate COVID-19.

Objectives and Endpoints:

The primary objective is to evaluate the efficacy of bemcentinib + SoC vs placebo + SoC on disease state in hospitalised patients with moderate COVID-19

Primary endpoint: Disease state on the 11-point WHO progression scale at day 8

The core secondary objective is to examine the efficacy of bemcentinib + SoC vs placebo + SoC on disease progression within 14 days, in hospitalized patients with moderate COVID-19 pulmonary disease.

Core secondary endpoint: Occurrence of disease progression, defined as a progression of disease state from moderate (WHO score 4-5) to severe/critical (WHO score 6-9) or death (WHO score 10) within 14 days of enrolment.

Additional Secondary endpoints:

- Occurrence of disease progression by at least 1 point increase on the 11-point WHO clinical progression scale from baseline within 14 days and 28 days of enrolment.
- Disease state on the 11-point WHO scale at D15 and D29
- SpO_2/FiO_2 ratio at day 8.
- Occurrence of death within 28 and 60 days
- Time from randomization to sustained recovery, defined as being discharged from the index hospitalization, followed by being alive and home for 14 consecutive days within 90 days

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- Time from randomization to first hospital discharge within 90 days
- Occurrence of serious adverse events leading to study treatment discontinuation or death
- Occurrence of any treatment emerging adverse events, including adverse events of special interest
- Viral clearance as assessed by SARS-CoV2 PCR in naso/oropharyngeal and saliva samples during hospitalization
- Inflammatory biomarkers (CRP, ferritin, LDH, leukocyte subsets, D-dimer, suPAR, cytokine panels) during hospitalisation
- Patient related outcome measures (PROM) by the Oslo COVID-19 QLQ-PW80 questionnaire after 90 days

Overall Design:
Double blind, multicentre, **r**andomized, placebo-**c**ontrolled **t**rial (RCT)

Trial Population:
The trial will include hospitalised adult patients with moderate pulmonary COVID-19, but without cardiac conditions such as a recent history of myocardial infarction, unstable angina or cardiac arrythmia; on medical treatment affecting the cardiac rhythm; severe kidney disease; or are pregnant or breastfeeding.

Number of Participants enrolled:
Approximately 550 participants will be screened to achieve 500 randomly assigned to bemcentinib or placebo to end up with 450 evaluable participants (225 per arm).

Intervention Groups and Duration:

- Loading dose 400 mg bemcentinib daily for 2 days, followed by a maintenance dose of 100 mg daily (200 mg if concomitant use of proton pump inhibitors - PPI) up to a total of 14 days + SoC
- Matching placebo to bemcentinib (similar loading dose and maintenance dose as above up to 14 days + SoC

The study duration will be up to 90 days (± 14 days) for each participant. Bemcentinib or placebo will be provided for up to 14 days, as long as the patient is hospitalized. Patients progressing to a need for ventilation via non-invasive positive pressure ventilation or via high-flow oxygen delivery, may continue daily oral therapy up to 14 days as long as oral medication intake remains feasible. However, patients who progress to a need for intubation should permanently discontinue study investigational treatment.

Risk assessment and conclusion:
Participation in this trial may have benefits for the individual patients, as bemcentinib may prevent disease progression and improve prognosis for patients with moderate COVID-19. Potential benefits also include contributing to the process of developing new therapies for moderate COVID-19 patients, including individuals afflicted by new virus variants.

Taking into account the measures taken to minimize risk to participants participating in this study, including the scheduled ECG monitoring, the potential risks identified in association with bemcentinib are justified by the anticipated benefits that may be afforded to participants with moderate COVID-19.

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1.2. Study outline

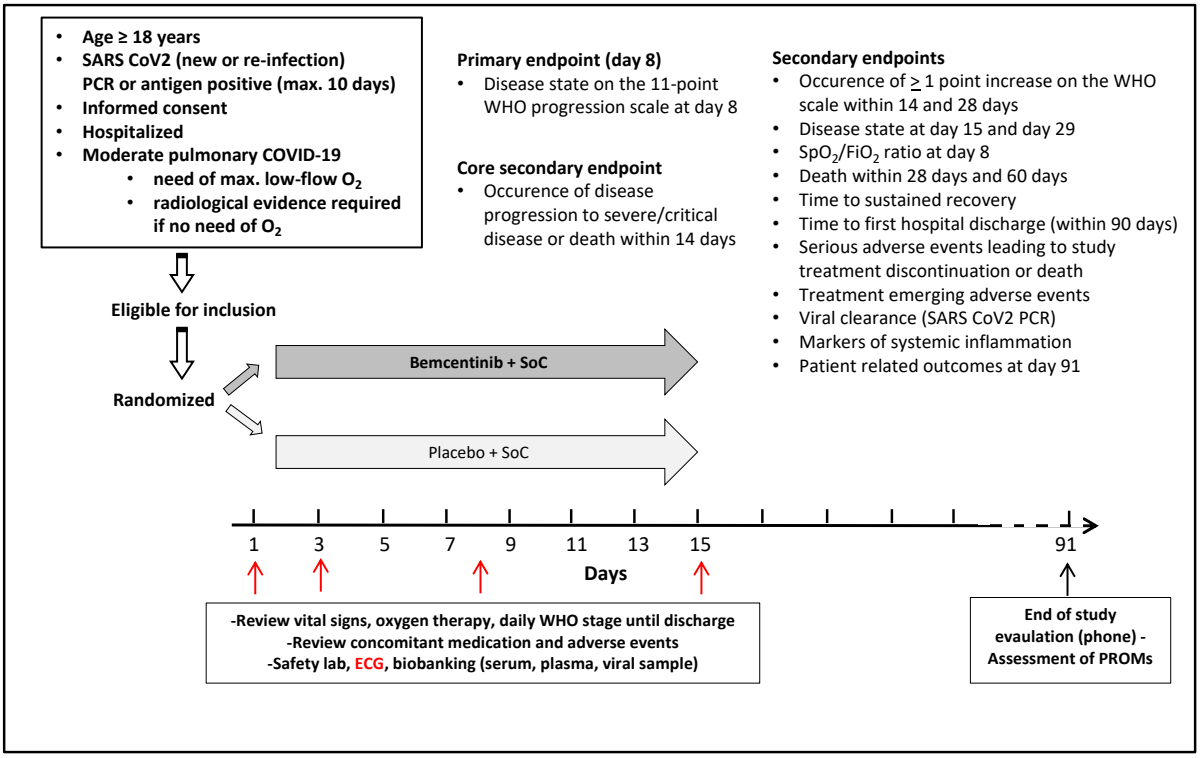

Figure 1 Outline of Study Design

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1.3. Schedule of Assessments (SoA)

Procedure	**Screening**	**Baseline**	**Assessments during hospitalisation**	**Core secondary endpoint**	**Secondary endpoint**	**Secondary endpoint**	**End of study**[12]
Day ± window		1	Day 3, 5, 8 (all ±1 day), then weekly (±3 d), or until discharge	15±3	29±3	61±7	91±14
Screening for eligibility[1]							
Demographics and medical history	X						
Vaccination history	X						
Review SARS-CoV-2 status (documented positive in the last 10 days)	X						
Informed consent	X						
Baseline procedures							
Randomization		X					
Standard of care (SoC)[2]		X					
Intervention (bemcentinib/placebo)		X	Note doses given				
Safety procedures							
Safety biochemistry[3]	X	(X)	D3, D5, D8	X[4]	X[4]	X[4]	X[4]
ECG[5]	X	(X)	D3, D8	X[4]			
Pregnancy test[6]		X[6]					X[6]
Study procedures							
Vital signs		X	D3, D5, D8	X[4]	X[4]	X[4]	X[4]
Oxygen therapy and SpO_2/FiO_2-ratio[7]		X	D3, D5, D8	X[4]	X[4]	X[4]	X[4]
Review WHO stage[8]		X	Daily until discharge up to D8	X[4]	X[4]	X[4]	X[4]
SARS-CoV2 serology		X[9]					
Concomitant medication[10]		X	Note changes daily until discharge up to D15, note on occurrence[10]	X[4]	X[4]	X[4]	X[4]
AE and SAE evaluation			On occurrence	X[4]	X[4]	X[4]	X[4]
PROM							X
Endpoints assessment							
Endpoint assessment[11]		X	D8	X	X	X	X
Biobanking (level II) [13]							
Serum, EDTA & Heparin plasma		X	D 3, D8	X[4]			
Naso/oropharyngeal swab/ Saliva		X	D 3, D8	X[4]			

Modular data capture according to level of commitment (level I and level II will be implemented in this protocol). Assessments in level I are mandatory. Biobanking (level II) is necessary for virological and inflammatory end points, refer to section 8.2 and biobank manual for details.

1. Screening/baseline assessments should be performed prior to study drug administration. Time between screening and randomisation should be registered in the eCRF.
2. Standard of Care (SoC) details, including remdesivir (or other direct acting antivirals), anti-SARS-CoV2 monoclonal antibodies, dexamethasone (or other systemic steroids) and other COVID-specific medication.
3. The following laboratory results should be collected: Hb, leukocytes, lymphocytes, neutrophils, platelets, creatinine, glucose, total bilirubin, INR, ALT, AST, amylase, LDH, D-dimer, CRP, ferritin.
   - Repeat at baseline if >24 hours since screening. If not, enter laboratory results from screening.
   - If ferritin is not routinely gathered at a site for clinical follow-up, analyses should be prioritized at baseline, D8 and D15. The other laboratory parameters are considered necessary for safety assessment and should be performed according to time points in SoA table.
4. Register if still hospitalized. At discharge or early discontinuation, register SpO_2/FiO_2-ratio, WHO disease progression scale (Table 2), review concomitant medication and adverse events as detailed in section 8 (sub protocol and master protocol). AE and SAE should be collected after discharge as well.
5. ECG should be performed at screening or baseline (triplicate at baseline), after loading dose of IMP (D3), at D8, and at end of treatment (D15, if still hospitalized) for assessment of QTcF. In patients with significant QTcF prolongation from baseline, additional measurements could be indicated. ECG should be obtained pre-dose of IMP so that IMP can be stopped in case of significant QTc prolongations triggering discontinuation.
6. Pregnancy test should be performed before randomization and at least 28 days after last dose of IMP (home based urine dip stick if discharged) and reviewed at end of study evaluation by phone, as detailed in section 10.1.4.

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7. If possible and patient is stable, record SpO_2/FiO_2-ratio while patient has been on room air for five minutes (on room air, FiO_2 equals 0.21). If oxygen is needed during measurement, specify oxygen therapy: a) Nasal prongs, b) Face mask, c) Face mask with reservoir, d) High flow oxygen e) Non-invasive ventilation (NIV) f) Mechanical ventilation/Extracorporeal membrane oxygenation (ECMO). Enter SpO_2, number of litres of O_2 provided or fraction of inspired O_2 (FiO_2), unless on ECMO. These measurements must be performed at the same time point to calculate SpO_2/FiO_2-ratio.
8. Review WHO daily stage including mode of oxygen therapy (disease state on WHO scale, Table 2). Record the highest daily score within a 24-hour period (0000-2359). Note that daily scores may be entered retrospectively to the CRF by study staff, to cover the days when no other assessments are scheduled.
9. If available, SARS-CoV2 antibodies (total, anti S, anti N) should be measured at baseline. If all SARS-CoV2 antibodies are negative, patient is considered seronegative.
10. Register the start and discontinuation of concomitant medication. If it is not feasible to register all changes in concomitant medication, the priority should be to register start and discontinuation in concomitant medication that could interfere with safety or efficacy of the tested drug, as detailed in section 6.7. For bemcentinib, particular focus should be on drugs known to prolong QTc-interval., Changes in COVID-specific therapy, including tocilizumab, baricitinib or increased steroid dose as rescue therapy (see section 6.7.1), will be specifically asked for in eCRF.
11. If discharged, endpoint assessments including sustained recovery, will be conducted by telephone contact with the patient at end of study and/or by reviewing patient records and/or contacting primary caretaker and/or relatives.
12. End of study assessment will be performed by telephone contact at end of study (D91±14) to complete assessment of all end points (D8, D15, D29, D61, D91), safety, pregnancy status and that patient has completed patient related outcome measures (PROM).
13. Biobanking at D1, D3, D8 and D15 or following discharge,. Note: PK sampling should be obtained before dosing of IMP, as detailed in section 8.2.

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2. Introduction

The Intervention Specific Appendix (ISA) Protocol, "AXL-SolidAct", refers to the Master Protocol "EU-SolidAct": An Adaptive Pandemic and Emerging Infection Platform Trial. The following terms are used throughout the master protocol and this ISA and are defined below:

• Participant refers to the common term subject.

• Study intervention refers to common term study agent.

• A platform study is a study with multiple targeted therapies investigated in a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm. A platform study will typically consist of a master protocol and 1 or more ISAs.

• The master protocol is the document which describes the overall clinical trial design applicable to all related interventions, such as the clinical trial rationale, objectives, endpoints, benefit-risk assessment, shared procedures regarding safety monitoring and reporting, and a common screening platform dictating participant eligibility and/or treatment allocation.

• The ISA is the appendix to the related master protocol which describes the specific features of the intervention and treatment of participants randomized to that intervention. Each intervention will have a separate ISA. Together, a master protocol and an ISA define all the elements needed to conduct a study.

• Intervention cohort refers to the group of participants who receive a specific investigational intervention or an intervention-specific comparator (i.e., placebo and/or an active comparator) and in whom that intervention is evaluated. In the event of a shared comparator group described in the master protocol, the intervention cohort refers to the group of participants who receive the investigational intervention. The intervention cohort is described in the ISA.

• The investigational treatment arm refers to the group of participants in an intervention cohort who receive the investigational intervention of interest being evaluated in the ISA.

2.1. Study Rationale

The AXL pathway is a well-described mechanism used by several enveloped viruses to enter host cells and dampen the anti-viral immune response. AXL is part of a tyrosine kinase receptor complex that recognises phosphatidyl serine, and which may enhance viral infection through two mechanisms: 1) facilitated viral entry through "apoptotic mimicry"; and 2) suppression of anti-viral type I interferon (IFN) responses. Bemcentinib (BGB324) is an orally bioavailable, potent and highly selective inhibitor of AXL tyrosine kinase currently being studied for the treatment of various cancers. Bemcentinib has been investigated in two Phase 2a clinical studies in hospitalised COVID-19. Exploratory results from these studies indicate that bemcentinib has a potential antiviral effect, and a favourable effect on limiting disease progression, including the avoidance of invasive ventilation or death, shortening time to recovery or discharge, and potentially increasing overall survival over 29 days, with only mild and reversible adverse events being observed. Clinical benefit of bemcentinib correlated with reduced viral load and systemic modulation of cytokine signalling. Bemcentinib represents a novel class of drug with a mechanism independent of the spike protein and mutations. Pre-clinical data indicates that bemcentinib both blocks viral entry and modulates the interferon response in a cell line specific manner which locally could contribute to enhanced anti-viral responses. The potential of blocking the AXL-dependent interferon suppression could be of

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importance in patients with a sub-optimal immune response to vaccines, in particular in a setting with emerging variants of concern. There is a clear rationale to further study the safety and efficacy of bemcentinib in a phase 2b trial of hospitalized patients with moderate COVID-19.

2.2. Background

SARS-2 CoV-2 was identified in December 2019 as the cause of COVID-19, as detailed in the master protocol. Despite advances in both vaccines and therapeutic options for COVID-19, there remains an urgent need for development of innovative and personalized interventions. The AXL pathway is a well-described mechanism used by several enveloped viruses (e.g. Ebola, Zika) to enter host cells and dampen the anti-viral immune response. AXL is part of a tyrosine kinase receptor complex that recognises phosphatidyl serine, and which may enhance viral infection through two mechanisms: 1) facilitated viral entry through "apoptotic mimicry"; and 2) suppression of anti-viral type I IFN responses[1].

Type I IFN response is important in mediating an early anti-viral host response, but can, if unresolved, drive inflammation resulting in tissue damage and immunopathological conditions. Reports have pointed towards the complexity of the Type I IFN response in SARS-CoV-2 infection with peripheral blood data analysis showing impaired Type 1 IFN activity and inflammatory responses, while increased amounts of Type 1 IFN mRNA were found in naso-oropharyngeal specimens and bronchioalveolar lavage [2,3]. Hence, it is not conclusively established what role Type 1 IFN responses play in COVID-19 patients and systemic effects might differ from local effects in the lung tissue. Bemcentinib (BGB324) is an orally bioavailable, potent, and highly selective inhibitor of AXL kinase inhibitor currently being studied for the treatment of various cancers. Bemcentinib treatment has been reported to block dengue, Ebola, and Zika virus infections, and is associated with increased interferon (IFN) signaling and reduced viral replication in several cell types including epithelial, fibroblast, endothelial, neuronal, and myeloid cell types[4-6].

Preclinical data confirm that bemcentinib inhibits SARS-CoV-2 host cell entry [1] and modulates anti-viral Type I IFN response in a cell line specific manner that does not correlate to a classical upregulation [Maury et al., unpublished data]). Bemcentinib robustly inhibited virus infection of multiple human lung cell lines that expressed AXL. This inhibition correlated well with inhibitors that block endosomal acidification and cathepsin activity, consistent with AXL-mediated uptake of SARS-CoV-2 into the endosomal compartment[1]. Its mechanism of action is independent of direct interaction with spike protein, which is of relevance given the emergence of new variants like omicron.

Bemcentinib has been investigated in two randomised, open-label Phase 2a clinical studies (BGBC020 and ACCORD2 [BGBIL019]) in which patients were randomly allocated to treatment with bemcentinib in addition to current standard-of-care (SoC) treatment, or SoC alone. These studies enrolled a total of 179 hospitalised COVID-19 patients (half of whom were allocated to bemcentinib treatment) in three different countries from three continents (UK, South Africa and India). Exploratory results from these studies indicate that bemcentinib has a favourable effect on limiting progression of disease, including the avoidance of invasive ventilation or death, shortening time to recovery or discharge, and potentially increasing overall survival over 29 days[7]. Clinical benefit of bemcentinib correlated with reduced viral load and systemic modulation of cytokine signalling [8]. The effect seemed even more promising in

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patients with CRP-levels > 30 mg/L[7]. Overall safety and tolerability in COVID-19 patients was consistent with the oncology program for bemcentinib, with only mild and reversible adverse events being observed. From oncology studies, asymptomatic QTcF prolongation has been reported in 6% of study patients[9]. In the two Phase 2a COVID-19 studies (BGBC020 and ACCORD2), there was one report of QTcF prolongation > 500 ms, and one report of change from baseline of QTcF ≥60 ms[7].

Bemcentinib represents a novel class of drug with an oral means of administration suitable for use in hospitalised patients with moderate disease. The potential antiviral mechanism is independent of the spike protein, and local effects on the interferon response could potentially contribute to enhanced anti-viral responses if kept constrained. Systemic consequences are hard to predict based on cell culture data, but importantly, the translational biomarker data from BGBC020 show that clinical benefit of bemcentinib correlates to reduced viral load and systemic modulation of cytokine signalling[8]. Overall, the putative viral inhibitory mechanism of action from nonclinical studies, if confirmed in clinical studies, may be of both direct benefit to the infected patient, but also has the potential of limiting onward transmission; if confirmed this could be an epidemiologically important feature of therapy, particularly when highly transmissible variants develop over time.

2.3. Benefit/Risk Assessment

Detailed information about known and expected benefits, risks and reasonably expected adverse events of bemcentinib, including QTc prolongation and elevated transaminase levels, can be found in the Investigator's Brochure (IB). The benefit/risk supports inclusion of patients ≥ 65 years old based on previous safety information, the thorough baseline/screening inclusion/exclusion criteria and safety monitoring in place for the study.

For treatment modifications due to drug interactions and decreased renal function, refer to section 6.5.

For discontinuation (temporarily or permanent) of study medication, refer to section 7.1.

For adverse event classification and reporting, refer to section 8.2.

Risks / adverse events that are likely to occur during the limited therapeutic intervention timespan and the mitigation strategies are described below.

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2.3.1. Risk Assessment

Table 1 Risk Management Strategy

Potential Risk of Clinical Significance	Mitigation Strategy
Risk of QTc-prolongation	Investigators and patients will be informed about this risk. ECG with QTcF measurement will be obtained at screening or baseline, after loading dose (D3), D5 and D15 if still hospitalized, and even more frequently if QTcF increases significantly. Patients with screening QTcF >470 msec will not be eligible for the study. Bemcentinib/placebo will be permanently discontinued if QTcF > 500 ms or if QTcF increases more than 60 ms from screening/baseline. Patients with screening QTcF >470 msec will not be eligible for the study
Hepatotoxicity	1. Monitoring of Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) will be performed at baseline, D3, D5, D8 and D15 if still hospitalized. Bemcentinib/placebo will be permanently discontinued if: a. AST and/or ALT levels increase to >5 times upper limit of normal (ULN) b. AST and/or ALT levels increase to >3 times ULN in addition to increase of bilirubin or INR. 2. Discontinuation criteria as criteria as described in section 7.1 should be followed.
Serious infection	No notable risk of infection linked to bemcentinib was identified in patients treated for COVID-19 in phase 2a trials. However, if a severe infection occurs, study drug interruption criteria as described in section 7.1 should be respected.

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Decreased renal function.	No notable risk of renal dysfunction linked to bemcentinib was identified in patients treated for COVID-19 in phase 2a trials. However, if renal function decreases significantly after IMP is initiated, study drug interruption criteria as described in section 7.1 should be respected. Bemcentinib/placebo will be permanently discontinued if eGFR < 30 mL/min/1.73 m^2.
Diarrhoea	Diarrhoea is a commonly reported side effect of bemcentinib administration. It is recommended that patients who begin to show this symptom are treated early with loperamide or another anti-diarrhoeal agent.

Refer to section 7.1 for levels of neutrophils, lymphocytes, QTcF, ALT and AST leading to interruption and mitigation strategies.

2.3.2. Benefit Assessment

Participation in this trial may have benefits for the individual patients, as bemcentinib may prevent disease progression and improve prognosis for patients with moderate COVID-19. Potential benefits also include contributing to the process of developing new therapies for moderate COVID-19 patients, including individuals afflicted by new virus variants.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, including the scheduled ECG monitoring, the potential risks identified in association with bemcentinib are justified by the anticipated benefits that may be afforded to participants with moderate COVID-19.

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3. Objectives and Endpoints

Objectives	Endpoints*
Primary	
• The primary objective is to evaluate the efficacy of bemcentinib + SoC vs placebo + SoC on disease state in hospitalised patients with moderate COVID-19.	• Disease state on the 11-point WHO progression scale at Day 8.
Core secondary	
• The core secondary objective is to examine the efficacy of bemcentinib + SoC vs placebo + SoC on disease progression within 14 days, in hospitalized patients with moderate COVID-19 pulmonary disease.	• Occurrence of disease progression, defined as a progression of disease state from moderate (WHO score 4-5) to severe/critical (WHO score 6-9) or death (WHO score 10) within 14 days.
Secondary	
Secondary objectives are	
To compare the time to any disease progression by WHO-scale from baseline status between bemcentinib or placebo	• Occurrence of disease progression by at least 1 point increase on the 11-point WHO clinical progression scale from baseline within 14 days and 28 days of enrolment.
To compare the efficacy of bemcentinib + SoC vs placebo + SoC on disease state for up to 28 days after study enrolment	• Disease state on the 11-point WHO scale at D15 and D29
To examine the efficacy of bemcentinib vs placebo on respiratory dysfunction within 7 days in hospitalised COVID19 patients receiving oxygen at study entry	• SpO_2/FiO_2 ratio at day 8.
To compare the efficacy of bemcentinib vs. placebo on occurrence of death	• Occurrence of death within 28 and 60 days
To compare the efficacy of bemcentinib vs. placebo on time to sustained recovery	• Time from randomization to sustained recovery, defined as being discharged from the index hospitalization, followed by being alive and home for 14 consecutive days within 90 days
To compare the efficacy of bemcentinib vs. placebo on time to first hospital discharge	• Time from randomization to first hospital discharge within 90 days

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To compare bemcentinib vs. placebo on major serious adverse events	• Occurrence of serious adverse events leading to study treatment discontinuation or death
To compare the general safety and tolerability of bemcentinib vs. placebo	• Occurrence of any treatment emerging adverse events, including adverse events of special interest
To compare the efficacy of bemcentinib vs. placebo on viral clearance	• Viral clearance as assessed by SARS-CoV2 PCR in naso/oropharyngeal specimens and saliva during hospitalization
To compare the efficacy of bemcentinib vs. placebo on markers of systemic inflammation	• Inflammatory biomarkers (CRP, ferritin, LDH, leukocyte subsets, D-dimer, suPAR, cytokine panels) during hospitalisation
To compare the efficacy of bemcentinib vs. placebo on patient reported outcomes (PROM)	• Patient related outcome measures (PROM) by the Oslo COVID-19 QLQ-PW80 questionnaire after 90 days

* Disease state variables will be adjusted by baseline value in the statistical analysis.

Table 2 Modified WHO clinical progression scale from section 8.1 in the master protocol

Disease Stage	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory: mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy needed*	4
	Hospitalised; need of oxygen by mask or nasal prongs	5
Hospitalised: Severe disease	Need of oxygen by NIV or high flow, re-breather mask, OR SpO2<90% on room air OR SpO2 90-94% with a downwards trend and/or signs of respiratory distress**	6
Hospitalised: Critical disease	Intubation and mechanical ventilation, pO_2/ FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation pO_2/FiO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2<150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

ECMO = extracorporeal membrane oxygenation, FiO_2 = fraction of inspired oxygen,
NIV = non-invasive ventilation, pO_2 = partial pressure of oxygen, SpO_2 = oxygen saturation
*If hospitalised for isolation only, record status as for ambulatory patient.

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**persistently increased respiratory rate, use of accessory muscles, inability to complete full sentences. Clinical judgement must be applied to determine whether a low oxygen saturation is indicative of disease progression or severity or is habitual for a given patient (i.e., with underlying chronic lung disease).

A slightly modified version of the original scale[10] will be applied for end point assessment by setting WHO score 6 as a separate stage (severe, not requiring mechanical ventilation) as opposed to WHO score 7-9 (critical, requiring mechanical ventilation), in accordance with WHO treatment guideline[10]. In addition, the term "need of" is included to account for a situation where the required oxygen therapy is needed but not available. In this case, the WHO score should be based on the level of support needed rather than the level of support received. For assessing indication of oxygen therapy, we refer to recommendations for respiratory support for
COVID-19 patients from NIH as well as Surviving sepsis campaign[11] for guidance:

- Supplemental oxygen recommended: peripheral SpO2 < 92% on room air.
- NIV or high flow oxygen recommended: acute hypoxemic respiratory failure despite conventional oxygen therapy.
- Invasive mechanical ventilation recommended: worsening of respiratory status in patients receiving NIV or high flow oxygen OR NIV/high flow oxygen considered insufficient by treating physician.

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4. Study Design

4.1. Overall Design

A double blind, multicentre, randomized, placebo-controlled, phase 2b trial to investigate the safety and efficacy of bemcentinib + standard of care (SoC) compared with placebo + SoC on respiratory dysfunction and disease progression in male and female participants aged ≥ 18 years with moderate COVID-19.

4.1.1. Trial Population:

The trial will include hospitalised adult patients with moderate pulmonary COVID-19, but without cardiac conditions such as a recent history of myocardial infarction, unstable angina or cardiac arrythmia; on medical treatment affecting the cardiac rhythm; severe kidney disease; or are pregnant or breastfeeding.

4.1.2. Number of Participants enrolled:

Approximately 550 participants will be screened to achieve 500 randomly assigned to bemcentinib or placebo to end up with 450 evaluable participants (225 per arm).

Intervention Groups and Duration:

- Loading dose 400 mg bemcentinib daily for 2 days, followed by a maintenance dose of 100 mg daily (200 mg if concomitant use of proton pump inhibitors - PPI) up to a total of 14 days + SoC
- Matching placebo to bemcentinib (similar loading dose and maintenance dose as above up to 14 days + SoC

The study duration will be up to 90 days (± 14 days) for each participant. Bemcentinib or placebo will be provided for up to 14 days, as long as the patient is hospitalized. Patients progressing to a need for ventilation via non-invasive positive pressure ventilation or via high-flow oxygen delivery, may continue daily oral therapy up to 14 days as long as oral medication intake remains feasible. However, patients who progress to a need for intubation should permanently discontinue study investigational treatment.

4.1.3. Risk assessment and conclusion:

Participation in this trial may have benefits for the individual patients, as bemcentinib may prevent disease progression and improve prognosis for patients with moderate COVID-19. Potential benefits also include contributing to the process of developing new therapies for moderate COVID-19 patients, including individuals afflicted by new virus variants.

Taking into account the measures taken to minimize risk to participants participating in this study, including the scheduled ECG monitoring, the potential risks identified in association with bemcentinib are justified by the anticipated benefits that may be afforded to participants with moderate COVID-19.

Refer to master protocol for further details on the platform trial design and implications to this and other sub-protocols.

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4.2. Scientific Rationale for Study Design

Refer to master protocol for an overall scientific rationale for the platform trial design and the implications to this and other sub-protocols.

4.3. Justification for Dose

The study dose (400 mg loading dose and 100 mg or 200 mg maintenance dose depending on the concomitant use of PPI) and treatment duration (up to 14 days, as long as patient is hospitalized) is based on dosing studied in two previous phase 2a trials[7]. The potential benefit of this dosing in reducing disease progression in moderate COVID-19, and the short duration of treatment provides the rationale for the benefit/risk assessment in the setting of a RCT. Since patients are being monitored in a hospital environment and will be treated for a short period of time, a dose reduction is not considered appropriate. For treatment management of patients with decreased renal function, see section 6.5.

These doses were selected for the acute, short-term finite treatment of patients hospitalized for the treatment of COVID-19, on the basis of both non-clinical evidence of bemcentinib pharmacokinetics and pharmacodynamics, and evidence generated on clinical therapeutic effect, pharmacokinetic exposure and pharmacodynamic responses (viral kinetics) in the phase 2a COVID-19 studies.

Data generated from non-clinical and clinical studies indicate that bemcentinib engages and inhibits the biological target as well as reduces viral load (both preclinical and clinical evidence) at clinically relevant concentrations. The relationship between the pharmacokinetic exposure of bemcentinib and response is understood, and the planned dose of 400 mg loading dose for 2 days followed by 100 mg maintenance has been shown to provide the maximal benefit with respect to efficacy with minimal risk in relation to safety; for detail, refer to bemcentinib Investigator Brochure.

4.4. End of Study Definition

The study duration will be up to 90 days (± 14 days) for each participant. A participant is considered to have completed the study if he/she has completed all periods of the study including the last scheduled evaluation at Day 90 shown in the Schedule of Assessments (SoA, section 8.11.3). End of study is defined as last visit for the last patient.

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5. Study Population

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

5.1. Inclusion Criteria

All participants must be eligible based on the master protocol inclusion criteria (EU-SolidAct Part A). Only the general inclusion criteria (GI) for moderate COVID-19 are applicable:

GI1. ≥18 years of age

GI2. Documented laboratory-confirmed SARS-CoV-2 infection (new infection or reinfection) as determined by PCR or antigen test in any specimen not more than 10 days old

GI3. Admitted to hospital

GI4. Informed consent by the participant.

GI5. Moderate disease state defined as hospitalisation without need of supplemental oxygen, or supplemental oxygen only by nasal prongs or mask.

In addition, the following specific inclusion (SI) criterion applies:

SI-01: Moderate pulmonary COVID19 disease defined as mainly lower respiratory symptoms and either:

i. need of oxygen by mask or nasal prongs, or
ii. current radiologic evidence of new pulmonary infiltrates consistent with COVID pneumonitis

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following general exclusion criteria (GE) apply:

GE1. Anticipated transfer to another non-trial hospital within 72 hours.

In addition, participants are excluded from being eligible for the bemcentinib intervention cohort if any of the additional specific exclusion (SE) criteria below apply:

SE-01. Unable to swallow capsules.

SE-02. Hospitalised for reasons other than pulmonary COVID19 disease, unless developing nosocomial pulmonary COVID-19 during hospitalisation.

SE-03. History any of the following cardiac conditions:

- Myocardial infarction within 3 months prior to the first dose
- Unstable angina
- History of clinically significant dysrhythmias (long QT features on ECG, sustained bradycardia [≤55 bpm]), left bundle branch block, or ventricular

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arrhythmia) or history of familial long QT. Note: Patients with an implantable cardioverter defibrillator device in place, will be allowed to enrol. Atrial fibrillation will not be a reason for exclusion

SE-04. Screening 12-lead ECG with a measurable QT interval according to Fridericia correction (QTcF) >470 msec (triplicate at baseline).

SE-05. Treatment with a concomitant medication with increased risk of Torsade-de-Pointes arrhythmia or significant electrocardiographic QT prolonging effect that cannot be safely discontinued.

Note: The list includes but is not limited to (in alphabetical order) Amiodarone, Astemizole, Azithromycin, Chloroquine, Citalopram, Clarithromycin, Cocaine, Disopyramide, Droperidol, Erythromycin, Escitalopram, Fluconazole, Haloperidol, Ketoconazole, Methadone, Moxifloxacin, Ondansetron, Petamidine, Pimozide, Procainamide, Quinidine, Sotalol, Terfenadine, Thioridazine, Voriconazole.

Concomitant treatment with CYP 3A4 substrates that have a narrow therapeutic window should also be discontinued (with the exception of fluticasone detailed below). The following should be discontinued (in alphabetical order) Alfentanyl, Cisapride, Cyclosporine, Ergotamine/ Dihydroergotamine, Fentanyl , Sirolimus, Tacrolimus. Fluticasone may continue without interruption when administered either nasally or inhaled.

Note: If a medication can be safely discontinued, the 2-day bemcentinib loading regime may be started as long as the QTcF on prior therapy is not prolonged above that required for eligibility (470 ms).

SE-06. Therapeutic anticoagulation with vitamin K antagonists.

SE-07. Previous bowel resection/ bowel dysfunction that would interfere with drug absorption.

SE-08. Alanine aminotransferase/aspartate aminotransferase ≥ 5 × the upper limit of normal.

SE-09. Severe chronic kidney disease. Subjects with estimated glomerular filtration rate (eGFR) <30 millilitre/minute/1.73 meters squared are excluded.

SE-10. Individuals with clinically significant hypokalaemia (<3.0 mmol/l) are excluded.
Note: Individuals who do not meet this criterion may be rescreened once, after correction of electrolyte abnormality.

SE-11: Patients on current or planned pharmaceutical treatment for tuberculosis.

SE-12. Are pregnant or breastfeeding or intend to become pregnant or breastfeed during the study.
Note: Women of childbearing potential (WOCBP) can only be included based on a negative pregnancy test and WOCBP must comply with requirements regarding highly effective contraception. Refer to section 10.1 for contraception requirements for women and men.

SE-13. Participation in other therapeutic clinical trial for COVID-19.

SE-14. Allergy to any component of the study treatment.
Note: Bemcentinib or placebo capsules contain

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Capsule core: lactose monohydrate, microcrystalline cellulose, crosspovidone, polyvinylpyrrolidone, colloidal silicon dioxide and magnesium stearate.
Capsule: hypromellose, red iron oxide, titanium dioxide

Note: Participants who are lactose intolerant should not be included.

SE-15. Severe COVID-19, defined as SpO_2 < 90% on room air, and/or need of high flow oxygen, non-invasive ventilation, mechanical ventilation or ECMO.

SE-16. Had COVID-related symptoms > 10 days or hospitalised with COVID-19 > 4 days.

SE-17. Experimental off-label usage of medicinal products as treatments for COVID-19 at the time of enrolment unless these are defined as SOC.

SE-18. Neutrophil count <500 cells/uL

SE-19. Known uncontrolled chronic viral infection (including HIV, HBV, HCV).

Note: Screening for viral infections is not mandatory.

5.3. Lifestyle Considerations

Not applicable. For pregnancy and contraception, refer to section 10.1.

5.4. Screen Failures

Refer to the master protocol for screen failure considerations. Participants who meet the entry criteria for inclusion per the master protocol but do not meet the entry criteria for participation in this intervention cohort may be rescreened to another intervention cohort.

5.5. Criteria for Temporarily Delaying Enrolment, Randomization or Administration of Study Intervention

If there is new or emerging safety information affecting the benefit/risk assessment of bemcentinib negatively, pausing enrolment to the bemcentinib trial should be initiated, and the sub protocol discontinued if necessary. Refer to master protocol for general criteria and procedures.

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6. Study Intervention and Concomitant Therapy

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

6.1. Study Intervention Administered (added to SoC)

Table 3 Study Intervention

ARM Name	BEMCENTINIB	PLACEBO
Intervention Name	Bemcentinib plus SoC	Placebo plus SoC
Type	Drug	Placebo for bemcentinib
Dose Formulation	Hypromellose (HPMC) capsules Capsule core: lactose monohydrate, microcrystalline cellulose, crosspovidone, polyvinylpyrrolidone, colloidal silicon dioxide and magnesium stearate Capsule: hypromellose, red iron oxide, titanium dioxide	HPMC capsules Capsule core: lactose monohydrate, microcrystalline cellulose, colloidal silicon dioxide and magnesium stearate Capsule: hypromellose, red iron oxide, titanium dioxide
Unit Dose Strength(s)	100 mg capsules	100 mg capsules
Dosage Level(s)	Loading dose 400 mg (4 capsules of 100 mg once daily) for 2 days followed by a maintenance dose of 100 mg once daily (200 mg if concomitant use of PPI) up to a total of 14 days after randomisation For treatment management related to drug interaction and decreased renal function, refer to section 6.5.	Loading dose 400 mg (4 capsules of 100 mg once daily) for 2 days followed by a maintenance dose of 100 mg once daily (200 mg if concomitant use of PPI) up to a total of 14 days after randomisation For treatment management related to drug interaction and decreased renal function, refer to section 6.5.
Route of Administration	Oral	Oral
Use	Experimental	Placebo comparator
IMP and NIMP	IMP	IMP

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Sourcing	Provided centrally by the manufacturer.	Provided centrally by the manufacturer.
Packaging and Labelling	Study Intervention will be provided in bottles and labelled according to country requirement	Study Intervention will be provided in bottles and labelled according to country requirement
[Current/Former Name(s) or Alias(es)]	Bemcentinib (BGB324, R428)	Placebo for bemcentinib

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee will confirm that appropriate temperature conditions have been maintained during transit, and during storage at site/pharmacy, for all study intervention received. Any discrepancies will be reported to sponsor and the manufacturer (BGB) and resolved before use of the study intervention.
2. Only participants enrolled in the study will receive study intervention and only authorized site staff will supply or administer study intervention. All study intervention will be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Information for the final disposition of unused study interventions will be provided on a site-basis where applicable and by the sponsor where the required disposal facilities are not available.
5. Administration: bemcentinib capsules are given orally once daily, within four hours after oral food intake.

   Alternate administration is not possible. The intervention and placebo will be administered to the patients by the treating nurses.

6.3. Measures to Minimize Bias: Randomization and Blinding

The general randomization procedure is described in the master protocol. Participants will be randomly assigned to treatment with either bemcentinib or matching placebo in a 1:1 allocation. Since IMP includes placebo, the allocation to treatment will be performed as follows: When a participant is deemed eligible and ready for randomization, the electronic Case Report Form (eCRF) system will reveal the treatment kit number available at the clinical site. The corresponding kit number will be registered in the medical records, and the corresponding kit will exclusively be used to treat the patient. The kits will be prepared according to a computer-generated random list permuted with block-size of 8. The allocation list and kit list will be aligned in the eCRF system to provide the patient with the allocated treatment.

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The eCRF will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable. Lifting the treatment blinding during the course of the study should be an exceptional measure with the sole aim to preserve the safety of the trial participants.

6.4. Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Dose Modification

6.5.1. Proton-pump inhibitor (PPI) use

The maintenance dose will need to be modified in patients prescribed a concomitant PPI for reduction of gastric acidity:

IMP (bemcentinib or placebo) will be administered at a

i. loading dose of 400 mg (4 capsules of 100 mg once daily) for 2 days followed by
ii. a **maintenance dose of 200 mg (2 capsules of 100mg)** once daily up to a total of 14 days after randomisation.

If a PPI is newly prescribed during the maintenance phase, in a patient previously treated at the standard dose, the maintenance dose of bemcentinib or placebo should be increased from 100mg to 200mg once daily.

6.5.2. Management of Laboratory Toxicity

- Evaluate baseline eGFR, liver enzymes, and complete blood count to determine treatment suitability and dose. Monitor closely patients with abnormal baseline and post-baseline laboratory values. For treatment interruptions, refer to section 2.3.1.
- Treatment management of patients with renal impairment:
    - eGFR ≥30 to <60 mL/min/1.73 m^2: monitoring of renal function.
    - eGFR below 30 mL/min/1.73 m^2: withdraw treatment.

6.5.3. Continued Access to Study Intervention after the End of the Study

Not relevant.

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6.6. Treatment of Overdose

For this study, the period for an overdose is considered up to 20 hours following any dose of study drug; if total intake of bemcentinib in this period exceeds 400mg during loading (days 1 and 2) or is greater than 100 mg (without PPI) or 200 mg (with PPI) during maintenance from day 3 onwards, this event will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator will:

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or discontinued.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until bemcentinib can no longer be detected systemically (at least 21days). Any case of overdose will be collected in the eCRF and notified immediately to the pharmacovigilance team even without occurrence of AE.
- Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.

6.7. Concomitant Therapy

Prohibited medication related to increased risk of Torsade the Points (TdP) arrhythmia and QT prolongation are mentioned under exclusion criteria (section 5.2). More details (including drug half-life and CYP3A4 substrate) is given in Table 4 below. If a medication can be discontinued, the 2-day bemcentinib loading regime may be started as long as the QTcF on prior therapy is not prolonged above that required for eligibility (470 ms).

Table 4 Common medication Associated with a Risk of QT Prolongation and TdP

IF IN USE, THESE MEDICATIONS SHOULD BE **DISCONTINUED** BEFORE ENROLMENT

Amiodarone 50 days[$]	Erythromycin 2 hours[$]	Petamidine 10 – 14 days[$]
Astemizole 24 hours	Escitalopram 30 hours[$]	Pimozide 55 hours
Azithromycin 2-4 days[$]	Fluconazole 30 hours[$]	Procainamide 2.5-4.75 hours[$]
Chloroquine 1-2 months[$]	Haloperidol 15 – 27 hours[$]	Quinidine 6 hours [$]
Citalopram 35 hours[$]	Ketoconazole 3 – 10 hours[$]	Sotalol 10 – 20 hours[$]
Clarithromycin 3-4 hours[$]	Methadone 25 – 55 hours[$]	Terfenadine 3.5 hours
Cocaine 0.6 – 1.3 hours[$]	Moxifloxacin 12 hours[$]	Thioridazine 21 – 24 hours[$]
Disopyramide 6.7 hours[$]	Ondansetron 3 hours[$]	Voriconazole 6 hours[$]
Droperidol 2 hours[$]		

[$] also TdP risk

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Concomitant treatment with CYP 3A4 substrates that have a narrow therapeutic window are specified in Table 5 below and must be discontinued before enrolment.

Table 5 Sensitive Cytochrome P450 3A4 Substrates With A Narrow Therapeutic Margin

IF IN USE, THESE MEDICATIONS SHOULD BE **DISCONTINUED** BEFORE ENROLMENT		
Alfentanyl 90-111 minutes	Dihydroergotamine & ergotamine 2 hours	Sirolimus 63 hours
Cisapride 12 hours	Fentanyl 8 – 10 hours	Tacrolimus (FK506) 12 hours
Cyclosporine 8.4 hours	Fluticasone[a] 3 – 8 hours	

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

There will be no recording of vitamins, but herbal supplements must be recorded due to their potential effect on cytochrome P450 (CYP) and QT interval (e.g. St John's Wort).

Treatment with antacids and histamine receptor 2 inhibitors should be avoided during the loading dose period of bemcentinib. Following the loading dose, they can be initiated, provided they are taken in the evening. For treatment with PPI, refer to section 6.5 for dose adjustments.

Following completion of investigational toxicology studies, it has been established that effects of steroids are not exacerbated by co-administration of bemcentinib. To date, no safety concern has been observed in patients treated with bemcentinib in clinical studies who have been given steroids to treat concomitant conditions. Systemic steroids as part of SoC for severe COVID is not regarded as a safety concern for co-administration of bemcentinib. Investigators are encouraged to follow their local guidelines for monitoring if a patient requires treatment with high dose steroids. Patients in the study will be assessed for any potential adverse events associated with high dose steroid use.

If it is not feasible to collect changes in all concomitant medication due to exhaustive medication lists, the priority should be to register start and discontinuation in concomitant medication that could interfere with safety or efficacy of the tested drug.

For bemcentinib, this should at least include medication related to QTc prolongation (not limited to the list of prohibited medication specified in the tables above), severe infection (antibiotics, antivirals, antifungals), immunosuppression (cytotoxic, immunomodulating and biological drugs), thromboembolism (anticoagulants), hepatotoxicity (including but not limited to antibiotics, antipsychotics, antiepileptics, statins, paracetamol), medications used to treat chronic comorbidities (including but not limited to ACE inhibitors and angiotensin AT2 inhibitors), or any other relevant drugs in the investigator's opinion.

For assessment of SAEs, always check all concomitant medication carefully and register changes.

Date on antiviral SARS-CoV2 therapy, dexamethasone, other immunomodulators and rescue medicine (see point 6.7.1for tocilizumab) will be explicitly asked for.

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6.7.1. Rescue Medicine

Patients will be treated according to best available standard of care, including any rescue medicine regarded medically needed. Tocilizumab or increased steroid dose as rescue therapy will be allowed in patients with clinical progression after inclusion if recommended by clinical guidelines and considered appropriate by the treating physician. In that case, this should be registered in the eCRF. If tocilizumab (or other rescue medication such as increased dose of steroids) is indicated, the investigational product should preferably be continued.

If treatment with JAK-inhibitor baricitinib is started, IMP should be discontinued due to potentially overlapping safety profile between baricitinib and bemcentinib. If, when rescue therapy is started, IMP is discontinued this should be registered as disease progression to the relevant WHO score and recorded in the eCRF. Of note, the investigator and team will be blinded to IMP allocation (*bemcentinib or placebo*) and the decision of adding rescue therapy will not be influenced by knowledge of the intervention.

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7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Treatment should be permanently discontinued in the following circumstances:

- Clinical disease progression which requires intubation and invasive ventilation, preventing the oral intake of study investigational product
- Absolute neutrophil count <500 cells/microliters in one sample
- Absolute lymphocyte count <200 cells/microliters in one sample
- QTcF prolongation > 60 ms from baseline or QTcF > 500 ms.
- Ventricular arrythmia
- eGFR below30 mL/min/1.73 m2
-
- Liver dysfunction defined as one of the following:
    - AST or ALT > 5 times ULN or
    - AST or ALT > 3 times ULN AND total bilirubin > 2 times ULN or INR > 1.5
- If the participant becomes pregnant during the study (refer to section 10.1 for pregnancy and contraception).
- If the participant develops systemic hypersensitivity reaction.
- Clinical necessity to commence therapy with any listed prohibited drug (see Exclusion Criteria SE-05, SE-06, SE-11 and Table 4 and Table 5).
- If the SARS CoV2 infection is resolved but the patient not discharged for other reasons. Such a patient should be recorded as WHO score 3.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or compliance reasons. For further details, refer to master protocol (section 7.2).

7.3. Lost to Follow up

Refer to master protocol.

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8. Study Assessments and Procedures

8.1. Schedule of Assessments (SoA)

Procedure	**Screening**	**Baseline**	**Assessments during hospitalisation**	**Core secondary endpoint**	**Secondary endpoint**	**Secondary endpoint**	**End of study**[12]
Day ± window		1	Day 3, 5, 8 (all ±1 day), then weekly (±3 d), or until discharge	15±3	29±3	61±7	91±14
Screening for eligibility[1]							
Demographics and medical history	X						
Vaccination history	X						
Review SARS-CoV-2 status (documented positive in the last 10 days)	X						
Informed consent	X						
Baseline procedures							
Randomization		X					
Standard of care (SoC)[2]		X					
Intervention (bemcentinib/placebo)		X	Note doses given				
Safety procedures							
Safety biochemistry[3]	X	(X)	D3, D5, D8	X[4]	X[4]	X[4]	X[4]
ECG[5]	X	(X)	D3, D8	X[4]			
Pregnancy test[6]		X[6]					X[6]
Study procedures							
Vital signs		X	D3, D5, D8	X[4]	X[4]	X[4]	X[4]
Oxygen therapy and SpO_2/FiO_2-ratio[7]		X	D3, D5, D8	X[4]	X[4]	X[4]	X[4]
Review WHO stage[8]		X	Daily until discharge up to D8	X[4]	X[4]	X[4]	X[4]
SARS-CoV2 serology		X[9]					
Concomitant medication[10]		X	Note changes daily until discharge up to D15, note on occurrence[10]	X[4]	X[4]	X[4]	X[4]
AE and SAE evaluation			On occurrence	X[4]	X[4]	X[4]	X[4]
PROM							X
Endpoints assessment							
Endpoint assessment[11]		X	D8	X	X	X	X
Biobanking (level II) [13]							
Serum, EDTA & Heparin plasma		X	D 3, D8	X[4]			
Naso/oropharyngeal swab/ Saliva		X	D 3, D8	X[4]			

A copy of this SoA table is also available in the Protocol summary (section 1.3). Modular data capture according to level of commitment (level I and level II will be implemented in this protocol). Assessments in level I are mandatory. Biobanking (level II) is necessary for virological and inflammatory end points, refer to section 8.2 and biobank manual for details.

1. Screening/baseline assessments should be performed prior to study drug administration. Time between screening and randomisation should be registered in the eCRF.
2. Standard of Care (SoC) details, including remdesivir (or other direct acting antivirals), anti-SARS-CoV2 monoclonal antibodies, dexamethasone (or other systemic steroids) and other COVID-specific medication.
3. The following laboratory results should be collected: Hb, leukocytes, lymphocytes, neutrophils, platelets, creatinine, glucose, total bilirubin, INR, ALT, AST, amylase, LDH, D-dimer, CRP, ferritin.
   - Repeat at baseline if >24 hours since screening. If not, enter laboratory results from screening.
   - If ferritin is not routinely gathered at a site for clinical follow-up, analyses should be prioritized at baseline, D8 and D15. The other laboratory parameters are considered necessary for safety assessment and should be performed according to time points in SoA table.
4. Register if still hospitalized. At discharge or early discontinuation, register SpO_2/FiO_2-ratio, WHO disease progression scale (Table 2), review concomitant medication and adverse events as detailed in section 8 (sub protocol and master protocol). AE and SAE should be collected after discharge as well.
5. ECG should be performed at screening or baseline (triplicate at baseline), after loading dose of IMP (D3), at D8, and at end of treatment (D15, if still hospitalized) for assessment of QTcF. In patients with significant QTcF prolongation from baseline, additional measurements could be indicated. ECG should be obtained pre-dose of IMP so that IMP can be stopped in case of significant QTc prolongations triggering discontinuation.

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6. Pregnancy test should be performed before randomization and at least 28 days after last dose of IMP (home based urine dip stick if discharged) and reviewed at end of study evaluation by phone, as detailed in section10.1.4.
7. If possible and patient is stable, record SpO_2/FiO_2-ratio while patient has been on room air for five minutes (on room air, FiO_2 equals 0.21). If oxygen is needed during measurement, specify oxygen therapy: a) Nasal prongs, b) Face mask, c) Face mask with reservoir, d) High flow oxygen e) Non-invasive ventilation (NIV) f) Mechanical ventilation/Extracorporeal membrane oxygenation (ECMO). Enter SpO_2, number of litres of O_2 provided or fraction of inspired O_2 (FiO_2), unless on ECMO. These measurements must be performed at the same time point to calculate SpO_2/FiO_2-ratio.
8. Review WHO daily stage including mode of oxygen therapy (disease state on WHO scale, table 2). Record the highest daily score within a 24-hour period (0000-2359). Note that daily scores may be entered retrospectively to the CRF by study staff, to cover the days when no other assessments are scheduled.
9. If available, SARS-CoV2 antibodies (total, anti S, anti N) should be measured at baseline. If all SARS-CoV2 antibodies are negative, patient is considered seronegative.
10. Register the start and discontinuation of concomitant medication. If it is not feasible to register all changes in concomitant medication, the priority should be to register start and discontinuation in concomitant medication that could interfere with safety or efficacy of the tested drug, as detailed in section 6.7. For bemcentinib, particular focus should be on drugs known to prolong QTc-interval., Changes in COVID-specific therapy, including tocilizumab, baricitinib or increased steroid dose as rescue therapy (see section 6.7.1), will be specifically asked for in eCRF.
11. If discharged, endpoint assessments including sustained recovery, will be conducted by telephone contact with the patient at end of study and/or by reviewing patient records and/or contacting primary caretaker and/or relatives.
12. End of study assessment will be performed by telephone contact at end of study (D91±14) to complete assessment of all end points (D8, D15, D29, D61, D91), safety, pregnancy status and that patient has completed patient related outcome measures (PROM).
13. Biobanking at D1, D3, D8 and D15, or following discharge. Note: PK sampling should be obtained before dosing of IMP, as detailed in section 8.2.

8.2. General considerations

Study procedures and their timing are summarized in the SoA above. Only level I and II (biobanking) commitment will be implemented in this sub protocol. Intervention-specific assessments are listed below:

Intervention-specific assessment

- Remember pregnancy test for women of childbearing potential, as pregnancy is an exclusion criterion.
- A pregnancy test must also be included approximately 30 days post intervention, by urine-based dipstick home test if the woman is discharged. For details on pregnancy and contraception, refer to section 10.1.

Biobanking

- Sample blood for safety laboratory tests as mentioned in SoA above and detailed in Appendix 2 of the master protocol.
- For level II participation, biobanking requirements will be specified in a separate standardized operating procedure (SOP) at D1, D3, D8 and D15 (as long as hospitalized or following discharge).
- For PK sampling (Li-Heparin plasma), it is important that sampling happens before dosing of IMP.
- For biobanking procedures, refer to section 10.2.2 in the master protocol for background information, and to SOP for details.
    - EDTA plasma (3-4 mL), Li-Heparin plasma (3-4mL), serum (3-4 mL) and naso/oropharyngeal swabs (on 2 ml virocult type medium, diluted with PBS or

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culture medium if necessary) and saliva will be collected for the biobank and stored at -70°C/or - 80°C (temporarily storage at -20°C for 1 month is possible).

- Planned analyses for this sub protocol include but are not restricted to:
  - EDTA plasma: cytokine panel including but not restricted to interleukin-6, interleukin-10,interferon- inducible protein-10 (IP-10),granulocyte-macrophage colony-stimulating factor. Soluble urokinase Plasminogen Activator Receptor (suPAR),
  - Li-Heparin plasma: bemcentinib pharmacokinetics
  - Serum: SARS-CoV2 specific antibodies, type I interferon antibodies.
  - Naso/oropharyngeal swabs and saliva: SARS-CoV2 viral RNA
  - In addition, ferritin, CRP, D-dimer, LDH and leukocyte subsets (neutrophils, lymphocytes) obtained from local biochemistry analyses and entered in eCRF will be included in the analyses of inflammatory markers

- Sponsor may store samples for up to 25 years after the end of the study to achieve study objectives, though national restrictions may apply. Additionally, with participants' consent, samples may be used for further research by sponsor or others such as universities or other companies to contribute to the understanding of SARS-CoV-2 or other diseases, the development of related or new treatments, or research methods. The biobank will be stored at Research Institute of Internal Medicine, Oslo University Hospital.

End of study evaluation

For end of study evaluation (including end points, safety evaluation and patient related outcomes), refer to SoA. In addition, confirmation and result of home based pregnancy test should be registered in the eCRF at the end of study evaulation at Day 90, as part of this sub protocol.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (section 8.1).

Careful monitoring of liver test and QT on ECG should be performed (see section 2.3.1), as well as monitoring of renal function if eGFR is comprised between 30 and 60 mL/min/1.73 m^2 (see section 6.5).

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The complete safety data circuit and safety working instructions is available in a standard operating procedure (SOP) related to the EU-SolidAct trial.

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The definitions of the EU Directive 2001/20/EC Article 2 based on the principles of GCP and EU guidance ENTR/CT 3 apply to this trial protocol. When required local requirements should also apply.

Table 8.11: Definitions of Adverse Events

TERM	DEFINITION
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant, which does not necessarily have a causal relationship with the research procedures or the investigational medicinal product (IMP).
Adverse Reaction (AR)	Any untoward and unintended responses to an IMP related to any dose administered.
Serious Adverse Event or Reaction (SAE/SAR)*	Any AE/AR that, at any dose, results in: - death; - a life-threatening AE; - hospitalization or prolongation of existing hospitalization; - a persistent or significant disability or incapacity; - a congenital anomaly/birth defect; - an "important medical event"
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An unexpected adverse reaction is an AR of which the nature, outcome, frequency or severity is not consistent with the applicable Reference Safety Information (RSI): Investigator's Brochure (IB).
New fact**	Any safety data that could modify significantly the evaluation of the benefit/risk ratio of the IMP or the clinical trial, likely to affect the safety of participants or that could modify the IMP administration, the trial documentation or the conduct of the trial, or to suspend, interrupt or modify the protocol or similar trials.

** EXCEPTIONS: the following events are not considered as SAE requiring immediate reporting to the sponsor:*

-the participant is formally admitted to a hospital for medical reasons with no seriousness criterion and does not require overnight hospitalization;
-elective or previously scheduled surgery or medical treatment(s);
-hospitalization for social or administrative reasons;
-pre-existing diseases or present conditions detected prior to start of study drug administration and which do not worsen.

***Example: a SAE which could be associated with the trial procedures, and which could modify the conduct of the trial, a significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease, recommendations of the data safety monitoring board, if any, where relevant for the safety of participants.*

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8.4.1. Time period and frequency for collecting AE and SAE information

- All AEs and SAEs will be collected from the signing of the informed consent form (ICF) until the follow-up visit at the time points specified in the SoA (section 8.1).
- 8.4.9All SAEs will be recorded and reported to the sponsor and the delegated designee, Inserm-ANRS Pharmacovigilance Office, immediately. Under no circumstance should the reporting period exceed 24 hours, as indicated in the trial Safety Management Plan (SMP). The investigator will submit any following updates to SAE data within 24 hours of it being available.
- Investigators are not obligated to actively seek information on 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 participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor and the delegated designee, Inserm-ANRS Pharmacovigilance Office.

8.4.2. 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 participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

- After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (AESI, as defined in section 8.4.108.4.10) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in section 7.3 of the Master Protocol.).

8.4.4. Assessment of AEs and SAEs

Complete procedure is described in the trial safety Working Instructions (WI).

Seriousness

For any adverse event, the investigator must determine whether the event meets one or more of the seriousness criteria described in table 8.1.

Severity (grading)

All AEs and SAEs will be assessed for severity, according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events, version 2.1 (July 2017), see section 10.11.

For AEs not included in the DAIDS scale, the following guidelines will be used to describe severity:

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Table 8.2 AE severity scale (not included in the DAIDS table)

Grade 1 (Mild)	Mild or transient discomfort, without limitation of normal daily activities; no medical intervention or corrective treatment required.
Grade 2 (Moderate)	Mild to moderate limitation of normal daily activities; minimal medical intervention or corrective treatment required.
Grade 3 (Severe)	Marked limitation of normal daily activities; medical intervention and corrective treatment required, possible hospitalization.
Grade 4 (Life-threatening)	Severe limitation of normal daily activities; medical intervention and corrective treatment required, almost always in a hospital setting.

Causality

The investigator must assess the causality of all AEs/SAEs in relation to IMP, research procedures, and concomitant medications, using the following guidelines:

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate aetiology has been established.

All AEs/SAEs for which the investigator or the sponsor considers a causal relationship to be a reasonable possibility are considered suspected SARs.

Assessment on expectedness is usually done by the sponsor.

8.4.5. Recording and reporting of AEs and SAEs

- All information on AEs (non-serious and serious) and pregnancies should be recorded on the appropriate eCRF (eCRF completion instructions are detailed in the eCRF user manual).
- Any AE that meets the definition of an SAE or AE of special interest (AESI, see section 8.4.108.4.10) must be notified immediately (within 24 hours of site awareness) on the corresponding SAE form.
- In case of eCRF unavailability, investigators should report all SAEs using the paper CRF form, dated and signed, and transmit it to the Sponsor and the delegated designee, Inserm-ANRS Pharmacovigilance Office, by fax or via a secured website for data transfer.

8.4.6. Regulatory reporting requirements for SAEs

- Complete procedure is described in the trial Safety Management Plan (SMP).

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- On behalf of the Sponsor, the Trial Safety Group (TSG), including Inserm-ANRS Pharmacovigilance Office staff, the medical officer (or an internal or external medically qualified delegate, mainly clinician) of Oslo University Hospital (OUH) and Clinical Trials Unit (CTU) representative, will review all SAE reports received.
- The role of the TSG will be detailed in the SMP.
- In case of lack of consensus within the TSG regarding the causality of the event, the final decision for the initial reporting to the applicable regulatory authorities will lay with the Inserm-ANRS Pharmacovigilance Office.
- The Inserm-ANRS Pharmacovigilance unit is responsible for assessing the causality and expectedness (using the applicable Reference Safety Information e.g., as given in the IB or SmPC) of all SAE reports received, in relation to the IMP, research procedures and concomitant medication (e.g., drug-drug interactions).
- All Suspected Unexpected Serious Adverse Reactions (SUSARs) must be reported, within the legal timeframe, by the Inserm-ANRS Pharmacovigilance unit to the European Medicine Agency (EudraVigilance, EMA), the National Competent Authority of the concerned Member State and concerned Ethics Committees according to local requirements.
- Fatal and life-threatening SUSARs must be reported within 7 days, other SUSARs within 15 days. If regulatory timeframes differ from the above timelines in participating countries, then local requirements should take precedence and be adhered to.
- The Inserm-ANRS Pharmacovigilance unit will immediately inform the National Competent Authorities of each member state and concerned Ethics Committees of safety data or safety issues that might alter the current benefit-risk assessment of the trial and may be relevant in terms of participant safety.
- Once a year, the Inserm-ANRS Pharmacovigilance unit will submit to the National Competent Authority and the Ethic Committee if applicable of each Member State a Development Safety Update Report (DSUR), according to applicable laws and regulations.

8.4.7. Pregnancy

- Pregnancy during hospitalisation is highly unlikely, and no specific procedures will be undertaken to discover pregnancies during hospitalisation except for the pregnancy test at screening.
- Depending on the IMP safety profile, pregnancy occurrence involving the participant's partner will be also recorded.
- Details of all pregnancies, including outcome, neonate information and any post-study pregnancy-related SAE, will be collected after the start of study intervention and as long as the patient is exposed to drug effects (detailed in the intervention-specific sub-protocol).
- Investigator will record pregnancy information on the appropriate form and submit it to the sponsor and the delegated designee, Inserm-ANRS Pharmacovigilance Office, within 24 hours of learning of the female participant pregnancy.

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- While pregnancy itself is not considered to be an AE, any pregnancy complication, abnormal outcome (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) or elective termination of a pregnancy for medical reasons will be reported with the same timeframe as an SAE.

- Further details are described in the trial Working Instructions.

8.4.8. Fatal Events

The sponsor or sponsor representative should be informed, immediately and without delay (and at the latest within 24 hours of the investigator being aware of the event) that a participant is dead using the corresponding eCRF death form. The cause of death should be recorded by the investigator in the eCRF, if known. In addition to the declaration of death, an SAE declaration should be recorded in the eCRF.

8.4.9. Disease-related Events (DREs) and/or Disease-related Outcomes not qualifying as AEs or SAEs

These events may refer to disease- or complication-related events that are common in Covid-19 patients and can be serious/life-threatening.

They are reported systematically on the eCRF in the pre-defined daily data sections. However, they will NOT be reported as SAE in the eCRF, even though the event may meet the definition of an SAE, unless the investigator considered that there is a reasonable possibility that the study intervention (blinded investigational agent/placebo or study-supplied SoC treatment) caused the event.

These events may occur during the initial hospitalization, lead to a re-admission, or occur in a later hospitalization during follow-up.

The DREs are given in Section 10.4 Appendix 4 of the master protocol.

8.4.10. Adverse Events of Special Interest (AESI)

Some adverse events of special interest (AESIs) are monitored for after administration of IMPs and require an immediate notification to sponsor. All participants enrolled in the study will be monitored for AESIs for the entire follow-up period. The occurrence of any of these adverse events has to be sent by the investigator to the sponsor immediately and no later than 24h after being aware of it using the SAE form.

The AESI in AXL-SolidAct include:

1. Bacterial pneumonia, including ventilator-associated pneumonia
2. Pulmonary embolism
3. Deep venous thrombosis
4. Arterial thrombosis
5. Liver dysfunction/hepatotoxicity (grade 3 and 4)
6. Reactivation of chronic infection including tuberculosis, herpes zoster and hepatitis B.
7. Invasive fungal infection, including invasive pulmonary aspergillosis
8. Serious cardiovascular events, including myocardial infarction and stroke.

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9. QTcF >500 ms or increase from baseline >60 ms, Torsade de Pointe, ventricular arrhythmias
10. Osteonecrosis of the jaw
11. Acute kidney injury defined as any of the following (KDIGO definition – Kidney Disease- Improving Global Outcomes):
    - Increase in serum creatinine (SCr) by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 hours
    - Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days
    - Urine volume ≤0.5 ml/kg/h for 6 hours (where monitored in patients on critical care).
12. Immune mediated hepatitis/pneumonitis
13. Generalized rash

Note that serious bacterial infections and thromboembolic events listed as DRE in the master protocol should be reported as AESI in this bemcentinib trial.

8.5. Pharmacokinetics

Pharmacokinetic parameters will be evaluated in this study, with sparse PK sampling approach based on venous blood samples collected according to the schedule of assessments (section 8.11.3) with time of sampling and time of prior dose recorded in the eCRF. 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 a validated method based on liquid chromatography with tandem mass spectrometry.

8.6. Genetics and/or Pharmacogenomics

Genetics are not evaluated in this study.

8.7. Biomarkers

Refer to master protocol.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

Not applicable.

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9. Statistical Considerations

9.1. Statistical Hypotheses

The primary null hypothesis to be tested in this trial is that there is no difference in disease state on the 11-point WHO progression state at Day 8 between patients receiving bemcentinib + SoC and patients receiving placebo + SoC.

Refer to master protocol for further considerations on the statistical hypotheses.

9.2. Sample Size Determination

The sample size calculation is based on showing superiority of bemcentinib + SoC vs placebo + SoC on the primary endpoint (disease state at Day 8 by the 11-point WHO ordinal clinical progression scale). The following background will inform the planned sample size:

1. We treat the primary endpoint as an ordinal variable
2. We base the null hypothesis test on the proportional odds ratio between the treatment groups
3. In previous trials with bemcentinib we observed an effect sizes (proportional odds ratio) of around 1.6
4. The power should be at least 80%
5. A single interim analysis for the primary endpoint, with stopping for safety and efficacy allowed, and stopping guideline determined using a Lan & DeMets alpha spending function approximating the O'Brien & Fleming boundary.
6. We use the sample size calculation according to Whitehead [12]

$$n_{tot} = \frac{12\left(z_{\alpha/2} + z_{\beta}\right)^2}{\theta^2\left(1 - \sum_{\{i=1\}}^{9} p_i^3\right)}$$

where $\theta$is the proportional odds ratio, p_i is the overall proportion of being in the ith category of the ordinal outcome, and $z_{\{\alpha/2\}}$ and $z_{\beta}$are the $1 - \alpha/2$ and βth quantiles of the standard normal distribution.

7. The overall proportion (combined over the two treatment groups) by disease state at day 8 is assumed distributed as

Score	Proportion	Score	Proportion
0	0.1	6	0.05
1	0.1	7	0.03
2	0.3	8	0.01
3	0.1	9	0
4	0.2	10	0.01
5	0.1		

based on previous bemcentinib trials and current information from the Bari-SolidAct trial (for the distribution between scores 0, 1, 2 and 3 gathered from discharge information).

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With these assumptions we get the following sample sizes with different proportional odds ratios and power:

Odds ratio	80%	90%
1.5	596	798
1.6	444	594
1.7	348	466

With an assumed proportional odds ratio of 1.6, randomisation of maximum 500 patients will provide at least 80% power even if approximately 10% of the information is lost, due to patients discontinuing study participation (444 evaluable patients required adjusting for the interim analysis). Note that this is expected to be a conservative calculation because of the gain in power by adjusting for the baseline WHO scale.

When analysed as a continuous variable, 500 patients will be enough to detect a mean difference of 0.4 and a standard deviation of 1.5 with at least 80% power given that the distribution over the disease states is similar to the Phase 2a study BGBC020. This sample size could also be sufficient to detect differences in the key secondary end point, occurrence of disease progression within 14 days. With an assumed treatment difference of 9% between the intervention arms, from 18% 14 days disease progression in the placebo arm to 9% in the bemcentinib arm, we need 450 evaluable participants in total to reach 80% power of detecting a treatment effect on the 5% two-sided significance level. The treatment difference for this calculation is similar to estimates from the Phase II study BGBC020 including individuals with baseline WHO severity 4 and 5 (on the 9- point WHO ordinal scale that preceded the 11-point WHO ordinal scale).

The sample size might be re-evaluated in a blinded manner if the underlying assumptions are clearly violated. Such violations could for example depend on the inclusion proportion and rate of respiratory dysfunction and disease progression in the total population and in important subgroups such as immunocompromised patients.

9.3. Statistical Analyses

The primary endpoint will be analysed using a proportional odds model, adjusted for baseline value and stratification factors at baseline. A sensitivity analyses will be performed treating the WHO clinical progression scale as a continuous measure to be analysed using an Analysis of Covariance (ANCOVA) model. We expect very few missing data for the primary endpoint. Any missing data will be handled by imputing the last known value. This method may be reconsidered after blinded review of the data.

In additional robustness analyses, the longitudinal measurements will be analysed using a mixed model repeated measures (MMRM) with fixed effects for treatment, time and treatment x time interaction. The analyses will be adjusted for stratification factors at baseline. The primary effect measure of this analysis will be the marginal mean treatment difference at day 8. Missing data will be considered missing at random and will be handled within the framework of the model.

Analyses of secondary endpoints are given in the master protocol. Further details and specifications will be given in a separate statistical analysis plan (SAP). This SAP will be prepared and finalised prior to unblinding. If needed, successive versions of the SAP will be

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made, with a clear description of the changes made after break blind. A blinded review of the data will be performed prior to breaking of the blind. In this review, methods for handling unused or spurious data will be specified, and the methods for handling missing data will be reassessed. We will report on all variables mentioned in the data collection section of the protocol. If there are serious doubts about the validity of collected data at a specific trial site raised by an independent data monitor, we will exclude such data from any analyses, and provide a full disclosure of the issue.

Heterogeneity will be handled by stratifying the randomization by center.

For the primary analysis, adjustment for the use of dexamethasone and other concomitant drugs (such as remdesivir and anti-SARS-CoV2 monoclonal antibodies) may be considered in sensitivity analyses.

Specific sub-group analyses to consider in addition to the ones specified in the master protocol is the use of dexamethasone (yes/no), remdesivir (yes/no), treatment with anti-SARS-CoV2 monoclonal antibodies (yes/no), seronegative at baseline (yes/no), lymphocyte count (normal/low), CRP-levels > 30 mg/L (yes/no), immunocompromised (yes/no), vaccination status (full, partial, none), age ≥65 years (yes/no), duration of symptoms ≥ 7 days (yes/no), type I interferon antibodies (yes/no).

9.4. Interim Analysis

In addition to the periodic reviews outlined in the DMC charter for the overall number of participants, DMC assessment for safety will be performed after a total of 25, 50, 100 and 200 patients (meaning roughly 50% in the active arm) have reached 14 days. An interim analysis to stop for efficacy is planned after 200 included evaluable participants. The stopping guideline will be according to a Lan & DeMets alpha spending function approximating the O'Brian & Fleming boundary. The precise p-value for stopping will be determined by the exact number of patients enrolled in the trial according to the Lan & DeMets alpha spending methodology. If the interim analysis happens at exactly 200 evaluable participants (out of 444 expected), the alpha threshold for stopping the trial for efficacy will be 0.00083. This would leave an alpha-level of 0.0247 for the one-sided significance test at the final analysis, given that the efficacy interim analysis was performed. Note that it will be up to the DMC to stop or continue the trial based on the totality of evidence at the interim analysis.

There may be reasons not to perform a formal efficacy interim analysis, e.g. if the accrual rate is very large. In this case, the reason for not performing the planned efficacy interim analysis will be given in the statistical analysis plan.

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10. Supporting Documentation and Operational Considerations

10.1. Pregnancy and contraception

10.1.1. Woman of childbearing potential

A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal, unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

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 post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

10.1.2. Contraception

Female patients of childbearing potential who are completely abstinent or in a same-sex relationship must agree to remain abstinent or in the same-sex relationship without sexual relationships with the opposite sex. Total abstinence is defined as refraining from intercourse during the entirety of the study and at least 28 days following the last dose of the investigational product. Periodic abstinence such as calendar, ovulation, symptothermal, post-ovulation, and withdrawal are not acceptable methods of contraception.

Women of childbearing potential must agree to refrain from intercourse or use highly effective contraception during the entire study and for at least 28 days following the last dose of the investigational product.

For men, unless permanently sterile by bilateral orchidectomy, they must agree to use contraception (i.e. condom) during the treatment period and for at least 28 days after the last dose of study treatment and refrain from donating sperm during this period.

10.1.3. Highly effective birth control methods

- Combined hormonal contraception (oestrogen and progestogen containing) associated with ovulation inhibition administered orally, intravaginally or transdermally
- Progestogen-only contraception associated with ovulation inhibition administered orally (continuous intake at the same time-point ± 2 hours every day), injectable or implantable
- Intrauterine device (IUD) / intrauterine hormone-releasing system (IUS) inserted no longer than 3 or 5 years (depending on brand) prior to inclusion in the study
- Male vasectomy (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)
- Bilateral tubal occlusion

10.1.4. Pregnancy

A pregnancy test must be included approximately 30 days after last dose of IMP. It is acceptable that the latter is performed using urine-based dipstick home test if the woman is

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discharged. In that case, confirmation and result of pregnancy test should be registered in the eCRF at the end of study evaulation by phone 90 days after inclusion.

Any female participant who becomes pregnant during the study will discontinue study intervention. The investigator will collect pregnancy information and follow the participant to determine the outcome of the pregnancy. Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

10.2. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the Protocol and the following:
  - 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 ICH Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, and all other applicable local regulations

10.3. Informed Consent Procedure

The informed consent procedures will be managed as described in the EU-SolidAct Recruitment and Informed Consent Procedure document. Briefly:

- Participants with moderate disease will be identified from within patients on the hospital ward.
- Screening may include the use of routine clinical testing to identify potential inclusion or exclusion criteria
- Participants will be contacted and informed directly by study staff. Information for the patients will be given in plain, understandable language, using the languages mandated in the country of inclusion.

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- Patients will be given full information about the trial and will have the freedom to choose whether they wish to be considered for inclusion or not. Patients wishing to take part will be asked to give their informed consent before baseline measurements, randomisation and drug administration. Patients will, at all times, have the right to withdraw consent.
- Patients for this arm of the EU-SolidAct platform trial will not be in critical condition and so are expected to be competent to give consent. Patients under the age of consent or incapacitated individuals will not be considered for this study.

10.4. Data protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant 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 participant who will be required to give consent for their data to be used as described in the informed consent

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

In case personal data needs to be sent for analysis outside the European Union (EU) or the European Economic Area (EEA), appropriate measures to guarantee the protection of the data will be taken. Such transfer will be in accordance with the informed consent form and will follow the measures of the General Data Protection Regulation (EU) 2016/679 (GDPR). Measures will include setting up standard contractual clauses for data transfers between EU/EEA and non-EU/EEA countries.

In case the data security has been breached for any of the participants, the sponsor must promptly but no later than 24 hours after becoming aware of the breach be notified. Prompt action to investigate the cause of the data breach must be made, and assistance to the sponsor in complying with Articles 32 to 36 of the GDPR.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

Personal data will be stored for 25 years after end of study to comply with the requirements in Regulation (EU) No 536/2014 (Clinical Trials Regulation).

10.5. Data quality assurance

- All participant data relating to the study will be recorded on electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data) via secure platform transfer or encrypted email. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of eCRFs will be provided in the Trial Master File.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

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- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- 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.

10.6. Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data 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, and its origin can be found in monitoring guidelines.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants 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.

10.7. Data Monitoring Committee

The independent Data Monitoring Committee is responsible for:
(i) Reviewing unblinded interim safety, efficacy and futility results according to the protocol.
(ii) Advising the Steering Committee if, in their view, the randomized data provide evidence that may warrant a change in the protocol (e.g., modification or cessation of one or more of the treatment arms).

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10.8. Study and site start and closure

10.8.1. First Act of Recruitment

- The study start date is the date when the clinical study will be open for recruitment of participants.
- The first act of recruitment is the informed consent and will be the study start date.

10.8.2. Study/Site Termination

- Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.
- The investigator may initiate study-site 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 site 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 IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
    - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
    - Total number of participants included earlier than expected
- Reasons for early study termination by the sponsor may include but are not limited to:
    - Discontinuation of further study intervention development
    - Occurrence of AEs unknown to date in respect of their nature, severity and duration
    - Medical or ethical reasons affecting the continued performance of the trial, including
        - external evidence indicating efficacy or harm of any of the study interventions
        - a general lack of eligible patients due to vaccination or other reasons

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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10.9. Country-specific Requirements

10.9.1. Norway

Addendum to section 8.2, replacing the paragraph “Additionally, with participants' consent, samples may be used for further research by sponsor or others such as universities or other companies to contribute to the understanding of SARS-CoV-2 or other diseases, the development of related or new treatments, or research methods.”:

- Samples may, on participant’s consent, be used to future research, but limited to research on COVID-19 or other diseases related to pandemics (using WHO’s definition of pandemic).
- Sponsor in Norway must store data for up to 15 years after end of study, or longer if required by Norwegian law.
- Handling and storage of personal data and biological samples must be finished by 29. March 2029. At this date, the biological samples in the study-specific research biobank "AXL-SolidAct" must be destroyed, or, if the participant has consented for secondary research, transferred to the general biobank "EU-SolidAct".
- Personal health data necessary for auditing the project will be stored for 25 years after end of study, according to EU Clinical Trials Regulation.

10.10. Protocol Amendment History

This is the third formal amendment of the protocol.

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

10.10.1. Previous amendment 2 protocol version 1.4 dated 10 July 2022

This amendment was considered to be non-substantial based on the criteria set forth in Article 2(2)(13) of The Clinical Trials Regulation (CTR).

Overall Rationale for the Amendment:

This amendment includes the following updates to address condition defined in the final Agency decision(s) following study assessment.

Section # and Name	Description of Change	Brief Rationale
Throughout	Updated version and date Minor typographical updates	For improved readability & version control
1.1 Synopsis	Amended secondary endpoint to include overall safety and tolerability and is not restricted to AESI	Addresses regulatory requirements (Decision – condition 3)
1.3 Schedule of assessments / 8.1 SoA	Amended review of SARS-CoV-2 status to align with updated GI-2 and SE-16 Included term ‘or following discharge’ for PK sampling	Addresses regulatory requirements (Decision – condition 1 & 6)

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Section # and Name	Description of Change	Brief Rationale
3 Objectives and Endpoints	Safety and tolerability secondary objective & endpoint updated	Addresses regulatory requirements (Decision – condition 3)
4.1 Overall Design	Additional detail of study design added from synopsis	Addresses regulatory requirements (Decision – condition 4)
5.1 Inclusion Criteria	GI4 updated to remove reference to 'legally authorized representative'	Not applicable to this study and addresses regulatory requirements (Decision – condition 8)
5.2 Exclusion Criteria	SE-19: updated to include 'known uncontrolled chronic viral infection	Addresses regulatory requirements (Decision – condition 7)
6.7. Concomitant Therapy	Revised to state herbal supplements will be recorded	Addresses regulatory requirements (Decision – condition 2)
8.2. General considerations	Included term 'or following discharge' for PK sampling Clarified that national restrictions may apply in relation to storage of biological samples	Addresses regulatory requirements (Decision – condition 6 & 9)
8.4. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting	Resolved typographical errors and references Removed surplus 'or' from list of AESI	Addresses regulatory requirements (Decision – condition 5 & 10)
10.3. Informed Consent Procedure	Removed reference to 'legally authorized representative'	Addresses regulatory requirements (Decision – condition 8)

10.10.2. Previous amendment 1 protocol version 1.3 dated 22 June 2022

This amendment was considered to be non-substantial based on the criteria set forth in Article 2(2)(13) of The Clinical Trials Regulation (CTR), specifically the change are being made prior to notification of a decision under the CTR. The summary of changes is maintained for clarity.

Overall Rationale for the Amendment:

The amendment included the following updates following Agency feedback during assessment.

Section # and Name	Description of Change	Brief Rationale
Throughout	Updates to minor typographical errors / inconsistencies have been made throughout. Section numbers updated.	Improved readability of the protocol. Section numbers account for new sub-headings
1.1 Synopsis	Protocol title and CTR numbers added. Primary and core secondary endpoints modified	Updated to meet regulatory requirements and regulatory request

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Section # and Name	Description of Change	Brief Rationale
1.2 Study outline	Additional secondary endpoint Trial population described Risk assessment description added Scheduled ECG updated in study design figure	Correction to schedule
1.3 Schedule of assessments	ECG Day 5 changed to Day 8 Pregnancy test schedule updated Reference to table with WHO disease progression scale updated	To bring in line with PK assessment Correction
2.1 Study rationale	Rationale update	Added to meet regulatory request
2.2 Background	Method of action in relation to Type 1 IFN / anti-viral response	Added to meet regulatory request
2.3 Benefit/Risk Assessment	Benefit/risk updates in support of inclusion of patients ≥ 65 years old	Added to meet regulatory request
3 Objectives and Endpoints	Added Diarrhoea as potential risk of clinical significance Haemoglobin removed as an analyte level that can lead to treatment discontinuation Primary and core secondary endpoints modified Additional secondary endpoint	Haemoglobin included in error Updated to meet regulatory request
4.1 Overall Design	Study design added	Updated to meet regulatory request
5.1 Inclusion Criteria	GI2 updated to confirm SARS-CoV-2 testing will be a documented PCR or antigen test in a specimen not more than 10 days old	Updated to meet regulatory request
5.2 Exclusion Criteria	SE-05 updated to clarify products with narrow therapeutic window to be discontinued or otherwise. SE-11: included planned TB treatment SE-14: clarified exclusion of patients with lactose intolerance SE-16: updated to COVID symptoms for 10 days SE-17, 18, 19: new exclusion criteria	To align with table 5 “Sensitive Cytochrome P450 3A4 Substrates With A Narrow Therapeutic Margin” as per regulatory request. Additional updates per regulatory request.
6.1. Study Intervention Administered (added to SoC)	IMP and placebo composition added	Meets regulatory request
6.5.2. Management of Laboratory Toxicity	Revised language for management of patients with renal impairment	Improved readability
6.6. Treatment of Overdose	Clarified study intervention should be interrupted or discontinued	Revised for consistency as dose modification not an option
6.7. Concomitant Therapy	Medications removed from Table 5, where already defined in Table 4. Confirmed herbal supplements will be recorded.	Alignment with SE-05 and to meet regulatory requests.

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Section # and Name	Description of Change	Brief Rationale
7.1. Discontinuation of Study Intervention	Addition of guidance for concomitant therapy with antiacids, histamine receptor 2 inhibitors and steroids. Added new stopping criterion if the infection is resolved but the patient not discharged for other reasons. Corrected stopping rules related cardiac events and liver enzymes.	New criterion added to meet regulatory request. Corrected criteria align with overall protocol.
8.1. Schedule of Assessments (SoA)	Inclusion of SoA in main body of the protocol. Duplicates SoA provided in Section 1.3.	Added to meet regulatory request
8.2. General considerations	New sub-heading. Updated to confirm timing of biobanking and PK sampling. Inclusion of additional planned analysis (Type 1 IFN antibodies)	Added to clarify PK sample timing & include Type 1 IFN antibody testing per regulatory request.
8.4. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting	Updated from section 8.2 to 8.4. Inclusion of definitions and reporting of AEs and SAEs from the master protocol.	Added to meet regulatory requirements and aligns with master protocol.
9.1. Statistical Hypotheses	Includes primary null hypothesis.	Added to meet regulatory requirements and aligns with master protocol.
9.2. Sample Size Determination	Update reflects the change to use the proportional odds model for sample size calculations.	Updated to meet regulatory request.
9.3. Statistical Analyses	Reflects a change to the proportional odds model, with ANCOVA model used for sensitivity analysis. Addition of procedures for handling unused and doubtful data. Defined additional sub-group analysis.	Updated to meet regulatory requirements and to define sub-group analysis for patients age ≥65 years, duration of symptoms ≥ 7 days & type I IFN antibodies.
10.1.2 Contraception	Deleted a conflicting paragraph	Both male and female participants must agree to use effective contraception for the entirety of the study and for at least 28 days following the last dose of the investigational product.
10.2. Regulatory and Ethical Considerations	New section added.	Added to meet regulatory requirements and aligns with master protocol.
10.3. Informed Consent Procedure	New section to briefly summarize informed consent procedure and confirm incapacitated individuals will not be considered	Added to meet regulatory requirements and aligns with supporting documentation with full details of informed consent.
10.4. Data protection	Updated from section 10.2 to 10.4. Includes duration personal information will be stored. Provided details of systems in place to protect against accidental or unlawful loss, alteration, or unauthorized disclosure or access, and measures that will be implemented in case of a data security breach.	Added in meet regulatory requirements and aligns with the master protocol.

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Section # and Name	Description of Change	Brief Rationale
10.5. Data quality assurance & 10.6. Source documents	Includes details regarding access to information by monitors and other responsible parties.	Added to meet regulatory requirements and aligns with the master protocol.
10.7. Data Monitoring Committee	Updated from section 10.3 to 10.7. Includes clarification that DMC will also review unblinded efficacy data.	Aligns with section 9.4 of the protocol.
10.8. Study and site start and closure	Added to include definition of clinical trial termination	Added to meet regulatory request and aligns with master protocol.
10.9. Country-specific Requirements	Updated from section 10.4 to 10.9. Includes country specific requirements for Norway.	Added to meet regulatory request and aligns with master protocol.
10.10. Protocol Amendment History	Updated from section 10.5 to 10.10 and to include brief details of amendment history (version 1.2 to v1.3)	Administrative update
10.11. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events	New section added to align with master protocol.	Added to meet regulatory requirements and aligns with master protocol for safety reporting.

10.11. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Corrected version 2.1 July 2017

Available from:

https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

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