Intervention Specific Appendix Title:

Efficacy and safety of baricitinib for the treatment of severe COVID-19

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

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Refers to EU-SolidAct Master Protocol Number: 1.1 dated 07 April 2021

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Compound: baricitinib

Brief Title: Bari-SolidAct

Study Phase: 3

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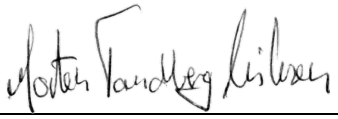
Sponsor Signatory:  12-Apr-2021

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1. Protocol Summary

1.1. Synopsis

Protocol Title: Efficacy and safety of Baricitinib for the treatment of severe COVID-19

A double bind, multicentre, randomized, placebo-controlled, phase 3 trial to investigate the safety and efficacy of baricitinib + standard of care (SoC) compared with placebo + SoC on the occurrence of death in male and female participants aged ≥ 18 years with severe COVID-19.

Brief Title: Bari-SolidAct

Rationale: COVID-19 severity has been shown to be due in part to a dysregulated inflammatory response. By inhibiting Janus kinase 1 and 2 (JAK 1 and 2), baricitinib inhibits the intracellular signalling pathway of pro-inflammatory cytokines including interleukin-2, interleukin-6, interleukin-10, interferon-γ, and granulocyte-macrophage colony-stimulating factor. Baricitinib can also prevent the cellular entry and infectivity of SARS-CoV-2 through the impairment of AP2-associated protein kinase 1. Studies are currently evaluating the efficacy of baricitinib in non-ventilated COVID-19 patients as part of a combination treatment with remdesivir. However, no studies have so far evaluated the efficacy of baricitinib as the sole agent added to SoC in the subpopulation of severe and critical COVID-19 patients, including those on mechanical ventilation. There is a rationale for investigating the effect of baricitinib, without the addition of remdesivir, on mortality, safety and other outcomes in severe COVID-19.

Objectives and Endpoints:
The primary objective is to determine the effect of baricitinib vs placebo added to SoC on the occurrence of death within 60 days in severe COVID-19.

Primary endpoint: Death within 60 days.

Secondary end points:

- Disease progression on WHO scale within 28 days
- Time from randomization to sustained recovery
- Time from randomization to first hospital discharge within 90 days
- Modified WHO score at day 15 and 29
- Occurrence of serious adverse events leading to study treatment discontinuation or death
- Viral clearance (SARS-CoV-2 PCR)
- Systemic inflammation during hospitalization

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

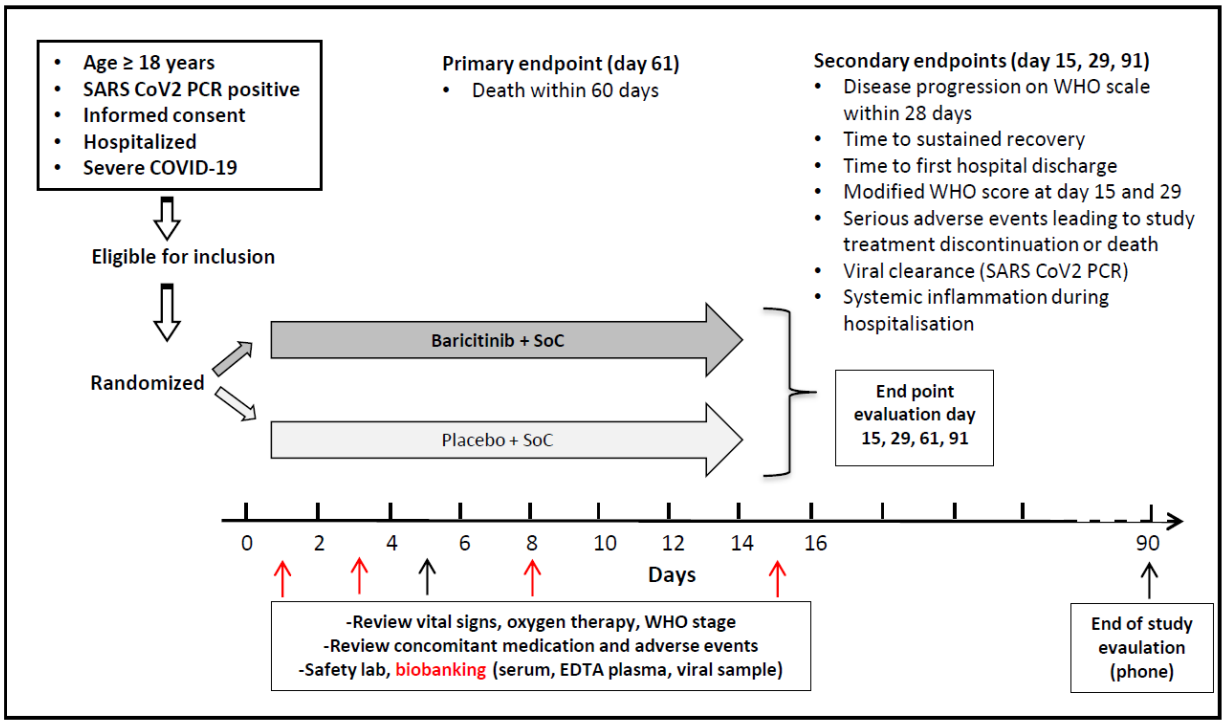
Number of Participants enrolled:
Approximately 2000 participants will be screened to achieve 1900 randomly assigned to baricitinib or placebo to end up with 1848 evaluable participants (924 per arm).

Intervention Groups and Duration:

- 4mg Baricitinib up to 14 days + SoC
- Matching placebo up to 14 days + SoC

The study duration will be up to 90 days (± 14 days) for each participant. Baricitinib and placebo will be provided for up to 14 days, as long as the patient is hospitalized.

1.2. Study outline



1.3. Schedule of Assessments (SoA)

Procedure	**Screening**	**Baseline**	**Assessments during hospitalisation**	**Secondary end point**	**Secondary end point**	**Primary endpoint**	**End of study**[9]
Day ± window		1	Day 3, 5, 8 (±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						
Review SARS-CoV-2 PCR (positive within last 9 days)	X						
Informed consent	X						
Baseline procedures							
Randomization		X					
Standard of care (SoC)[2]		X					
Intervention (baricitinib/placebo)		X	Note doses given				
Safety laboratory							
Safety biochemistry[3]	X	(X)	X	X[5]	X[5]	X[5]	X[5]
Pregnancy test[4]		X			X		
Study procedures							
Vital signs including SpO_2		X	X	X[5]	X[5]	X[5]	X[5]
Review oxygen therapy[6]		X	X	X[5]	X[5]	X[5]	X[5]
Review WHO stage[7]		X	X	X[5]	X[5]	X[5]	X[5]
Concomitant medication		X	Note changes daily until discharge, note on occurrence	X[5]	X[5]	X[5]	X[5]
AE and SAE evaluation				X[5]	X[5]	X[5]	X[5]
PROM							X
Endpoints assessment							
Endpoint assessment[8]		X	X	X	X	X	X
Biobanking (level II)							
Serum, EDTA Plasma		X	Day 3, 8 (±1), weekly				
Naso/oropharyngeal swab		X	Day 3, 8 (±1), weekly				

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 chapter 8 and SOP for details.

1. Screening/baseline assessments should be performed prior to study drug administration.
2. Standard of Care (SoC) details, including remdesivir, dexamethasone 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, procalcitonin, ferritin. Repeat at baseline if >24 hours since screening. If not, enter laboratory results from screening.
4. Pregnancy test should be performed before randomization and repeated approximately 30 days post intervention (home based urine dip stick if discharged) and reviewed at end of study evaluation, as detailed in section 10.1.
5. Register if still hospitalized. At discharge or early discontinuation, register WHO disease progression scale (table 3.1), review concomitant medication and adverse events as detailed in section 8 (sub protocol and master protocol).
6. 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 number of litres of O_2 provided or fraction of inspired O_2 (FiO_2), unless on ECMO.
7. Review WHO stage including mode of oxygen therapy and need for rescue therapy for end point assessment (progression on WHO scale, table 3.1)
8. If discharged, endpoint assessments including sustained recovery, will be conducted by telephone contact with the patient and/or by reviewing patient records and/or contacting primary caretaker and/or relatives.
9. End of study assessment will be performed by telephone contact to assess end points, safety, home based pregnancy test and that patient has completed patient related outcome measures (PROM).

2. Introduction

The Intervention Specific Appendix (ISA) Protocol, "Bari-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

COVID-19 severity has been shown to be linked, in part, to a dysregulated inflammatory response. By inhibiting Janus kinase 1 and 2 (JAK 1 and 2), baricitinib inhibits the intracellular signalling pathways of pro-inflammatory cytokines. Baricitinib can also prevent the cellular entry and infectivity of SARS-CoV-2 through the impairment of AP2-associated protein kinase. Whilst studies are currently evaluating the efficacy of baricitinib in non-ventilated COVID-19 patients as part of a combination treatment with remdesivir, no studies have assessed the effect of baricitinib added to standard of care (SoC) on mortality, and no studies have focused particularly on the subpopulation of severe and critical COVID-19 patients including those on mechanical ventilation. There is a rationale for investigating the effect of baricitinib, without addition of remdesivir, on mortality, safety and other outcomes in severe COVID-19.

2.2. Background

In a recent systematic review, the JAK inhibitor baricitinib was identified as the most promising candidate for immunomodulation beyond systemic steroids for severe COVID-19.[1] Baricitinib has been identified to have dual action, including broad inhibition of cytokine release by blocking the subtypes JAK1 and JAK2, and through its high affinity for AP2-associated protein kinase 1 (AAK1), inhibiting viral cell entry.

The ACTT2 trial recently reported one-day reduction in median recovery time for the overall patient population (moderate + severe COVID-19) treated with baricitinib in combination with remdesivir versus those treated with remdesivir alone, in addition to background SoC permitted per local guidelines. The study also met a key secondary endpoint comparing patient outcomes at Day 15 using an ordinal 8-point scale ranging from fully recovered to death. The largest effect on sustained recovery seemed to be in patients requiring high flow oxygen or non-invasive ventilation (WHO stage 6).[2]

The ongoing ACTT4 trial (NCT04640168) investigates remdesivir + baricitinib vs remdesivir + dexamethasone on a combined progression endpoint in patients with moderate/severe COVID-19 but excluding patients on mechanical ventilation.

COV-BARRIER (NCT04421027) investigates baricitinib vs placebo added to SoC on a combined progression endpoint in moderate/severe COVID-19 but excluding patients on mechanical ventilation. From the ongoing studies, the question will remain how baricitinib performs without the addition of remdesivir, and whether or not baricitinib reduces mortality in severe COVID-19 despite the use of dexamethasone.

Although no class effect of JAK inhibition on viral entry is to be expected, this cannot be ruled out. However, the dual effects on cytokine release and viral entry have only been reported for baricitinib and is hence part of the rationale for selecting baricitinib for the present trial, along with promising data from the ACTT2 trial.

2.3. Benefit/Risk Assessment

Detailed information about known and expected benefits, risks and reasonably expected adverse events of baricitinib, including malignancy, elevated cholesterol levels, elevated transaminase levels and diverticulitis that are associated with prolonged therapy, can be found in the Investigator's Brochure (IB).

For dose adjustments 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.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Mitigation Strategy
1. Increased risk of serious infections, including bacteraemia, sepsis, bacterial pneumonia, disseminated/systemic fungal infections as well as reactivation of tuberculosis and chronic viral disease (i.e. herpes simplex, herpes zoster, hepatitis B). 2. Increased risk of venous thromboembolism (DVT/PE). 3. Increased risk of hematologic toxicity including anaemia, neutropenia and lymphopenia. 4. Hepatotoxicity. 5. Exacerbation of pre-existing diverticular disease.	1. Investigators and patients will be informed about this risk, so that pre-emptive measures will be started. Baricitinib/placebo intervention will be interrupted if serious infection not responding to standard therapy and/or reactivation of chronic infection is identified/suspected. 2. Thromboprophylaxis with low molecular heparin as per clinical guidelines will be used if not contraindicated. 3. Continuous monitoring of haemoglobin, neutrophil and lymphocyte parameters will ensure prompt interruption of intervention should the parameters have the following values: a. Absolute neutrophil count <1000 cells/microliters b. Absolute lymphocyte count <200 cells/microliters c. Hemoglobin (Hb) < 8.0 g/dL. 4. Continuous monitoring of Alanine aminotransferase (ALT) or aspartate aminotransferase (AST). Baricitinib/placebo will be interrupted if AST and/or ALT levels increase to >5 times upper limit of normal (ULN). 5. Exacerbation of pre-existing diverticular disease is not expected but treatment with baricitinib/placebo will be stopped if this occurs.

2.3.2. Benefit Assessment

Participation in this trial may have benefits for the individual patients, as baricitinib may improve prognosis for severe COVID-19. Potential benefits also include contributing to the process of developing new therapies for severe COVID-19, which is an area of unmet need.

2.3.3. Overall Benefit: Risk Conclusion

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

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• The primary objective is to determine the effect of baricitinib vs. placebo added to SoC on occurrence of death in hospitalized patients with severe or critical COVID-19	• Occurrence of death within 60 days
Secondary	
• Secondary objectives are -to compare the efficacy of baricitinib vs. placebo on disease progression, time to sustained recovery and time to first hospital discharge -to compare baricitinib vs. placebo on major serious adverse events -to compare baricitinib vs. placebo on patient reported outcomes -to compare the efficacy of baricitinib vs. placebo on viral clearance -to compare the efficacy of baricitinib vs. placebo on markers of systemic inflammation	• Occurrence of disease progression, defined as a progression from severe (WHO score 6) to critical/death (WHO score 7-10) or from critical (WHO score 7-9) to death within 28 days • Time from randomization to sustained recovery, with sustained recovery defined as being discharged from the index hospitalization, followed by being alive and home for 14 consecutive days within 90 days • Time from randomization to first hospital discharge within 90 days • Disease state on a 5-point scale defined as 1. Mild (WHO score 1-3) or better, 2. Moderate (WHO score 4-5), 3. Severe (WHO score 6), 4. Critical (WHO score 7-9) or 5. Death at Day 15 and 29 • Occurrence of serious adverse events leading to study treatment discontinuation or death • Viral clearance as assessed by SARS-CoV-2 PCR in oropharyngeal specimens during hospitalization • Inflammatory markers (C-reactive protein, ferritin, lactate dehydrogenase, procalcitonin, D-dimer, leukocyte subsets and cytokine panels) during hospitalisation

Table 3.1 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.
**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[3] 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 guidelines[4]. 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[5] 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.

4. Study Design

4.1. Overall Design

Double blind, multicentre, **r**andomized, placebo-**c**ontrolled **t**rial.

Refer to master protocol for further details.

4.2. Scientific Rationale for Study Design

Refer to master protocol.

4.3. Justification for Dose

The study dose (4 mg once daily) and treatment duration (up to 14 days, as long as patient is hospitalized) is based on dosing studied in ACTT2 and recommended dosing in the U.S. Food and Drug Administration (FDA) approved fact sheet for healthcare providers emergency use authorization (EUA) of baricitinib. The potential benefit of the 4 mg-dose in reducing the hyperinflammatory state in COVID-19, and the short duration of treatment with this dose with a well-established safety profile, 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 in elderly COVID-19 patients. For dose adjustments due to drug interactions and decreased renal function, see section 6.5.

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 1.3). End of study is defined as last visit for the last patient.

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 according to the master protocol inclusion criteria (SolidAct Part B). Only the general inclusion criteria (GI) for severe/critical COVID-19 are applicable:

GI1. ≥ 18 years of age

GI2. Laboratory-confirmed SARS-CoV-2 infection (new infection or reinfection) as determined by PCR in any specimen not more than 9 days old

GI3. Admitted to hospital

GI4. Informed consent by the participant or legally authorized representative.

GI5B: Severe/critical disease state defined as fulfilling at least one of the following criteria:

1. SpO2<90% on room air, or
2. SpO2 90-94% with a downwards trend and/or signs of respiratory distress*****, or
3. Need of oxygen by NIV (CPAP, BIPAP), high flow or non-rebreather mask, or
4. Need of mechanical ventilation/ECMO

*****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).

NIV=non-invasive ventilation. CPAP= Continuous Positive Airway Pressure, BPAP= Bi-level Positive Airway Pressure, ECMO = extracorporeal membrane oxygenation.

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 intervention cohort if any of the additional specific exclusion (SE) criteria below apply:

- SE-01. Receiving cytotoxic or biologic treatments (such as tumour necrosis factor [TNF] inhibitors, anti-interleukin-1 [IL-1, e.g. anakinra], anti-IL-6 [e.g. tocilizumab or sarilumab],

T-cell or B-cell targeted therapies (e.g. rituximab), interferon, or Janus kinase (JAK) inhibitors (including baricitinib) for any indication at study entry.
    - Note: A washout period is required prior to screening:
    - B-cell targeted therapies: a washout period of 24 weeks or 5 half-lives (whichever is longer)
    - TNF inhibitors: a washout period of 2 weeks or 5 half-lives (whichever is longer)
    - JAK inhibitor: a washout period of 1 week or 5 half-lives (whichever is longer).
    - IL-6 inhibitor: a washout period of 6 weeks or 5 half-lives (whichever is longer).
  - Note: Although the biological treatments listed above are prohibited at study entry without a required wash-out period, tocilizumab as rescue therapy will be allowed in patients with clinical progression after inclusion, see section 6.8 concomitant medication.
- SE-02. Have received high dose corticosteroids at doses >20 mg prednisone (or prednisone equivalent) per day administered for ≥14 consecutive days in the month prior to study entry.
- SE-03. Have received dexamethasone 6 mg once daily for more than 4 days prior to screening as part of SoC for severe/critical COVID-19
- SE-04. Had COVID-related symptoms > 14 days or hospitalized > 7 days.
  - Note: If hospitalized early in the disease and then progressing after >7 days of hospitalization, the patient could still be included if COVID-related symptoms had a duration < 14 days.
- SE-05. Strong inhibitors of organic anion transporter 3 [OAT3], (e.g., probenecid) that cannot be discontinued at study entry.
- SE-06. Have received neutralizing antibodies for COVID-19, except if receiving such treatment as part of EU SolidAct part A after disease progression.
- SE-07. Have received any live vaccine within 4 weeks before screening, or intend to receive a live vaccine during the study (until day 90 (+/- 14 days)).
  - Note: Use of non-live (inactivated) vaccinations, including COVID-19 vaccinations, is allowed for all participants.
- SE-08. Are using or will use extracorporeal blood purification (EBP) device to remove proinflammatory cytokines from the blood such as a cytokine absorption or filtering device, for example, CytoSorb®.
- SE-09. Have diagnosis of current active tuberculosis (TB) or, if known, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines (by history only, no screening tests required).
- SE-10. Suspected serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking investigational product.
  - Note: Immunocompromised patients, patients with a chronic medical condition, or those taking a medication that cannot be discontinued at enrolment, who, in the judgment of the investigator, are at increased risk for serious infections or other safety concerns should be excluded. However, well treated HIV infection with normal CD4+ T cell count and undetectable HIV-RNA is not an exclusion criterion per se.
- SE-11. Current diagnosis of active malignancy that, in the opinion of the investigator, could constitute a risk when taking investigational product.

    - Note: although this risk is established from long term use of baricitinib, and probably does not pose the same risk in short term use for COVID-19, particular attention should be paid, as reflected in the list of adverse events of special interest
- SE-12. Have a history of venous thromboembolism (VTE) (deep vein thrombosis [DVT] and/or pulmonary embolism [PE]) within 12 weeks prior to randomization or have a history of recurrent (>1) VTE (DVT/PE).
- SE-13. Neutropenia (absolute neutrophil count <1000 cells/microliters).
- SE-14. Lymphopenia (absolute lymphocyte count <200 cells/microliters).
- SE-15. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 times ULN.
- SE-16. Subjects with estimated glomerular filtration rate (eGFR) (Modification of Diet in Renal Disease [MDRD]) <15 millilitre/minute/1.73 meters squared are excluded.
    - Note: Subjects with eGFR 15-30 are excluded unless in the opinion of the PI, the potential benefit of participation outweighs the potential risk of study participation.
- SE-17. Known hypersensitivity to baricitinib or any of its excipients.
- SE-18. Are pregnant or breastfeeding, or intend to become pregnant or breastfeed during the study.
    - Note: Women of child bearing 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.
- SE-19 Participation in any therapeutic clinical trials investigating immunomodulators for COVID-19

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 baricitinib negatively, pausing enrolment to the baricitinib trial should be initiated, and the sub protocol discontinued if necessary. Refer to master protocol for general criteria and procedures.

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)

ARM Name	BARICITINIB	PLACEBO
Intervention Name	Baricitinib (Olumiant®) plus SoC	Placebo plus SoC
Type	Drug	Placebo for baricitinib
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	2 mg tablets	2 mg tablets
Dosage Level(s)	4 mg (2x2 mg tablets) once daily while hospitalised but not more than 14 days For dose adjustments due to drug interaction and decreased renal function, refer to section 6.5.	4 mg (2x2 mg tablets) once daily while hospitalised but not more than 14 days For dose adjustments due to drug interaction and decreased renal function, refer to section 6.5.
Route of Administration	Oral For alternate administration, refer to section 6.2.	Oral For alternate administration, refer to section 6.2.
Use	Experimental	Placebo comparator
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the manufacturer.	Provided centrally by the manufacturer.
Packaging and Labeling	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)]	Olumiant®	Placebo for baricitinib

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee will confirm that appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies will be reported 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: baricitinib tablets are given orally once daily with or without food.

   For patients who are unable to swallow whole tablets or for intubated patients, alternate administration may be considered:

   Oral dispersion

   Gastrostomy tube (G tube)

   Nasogastric tube (NG tube)

   Preparation for Alternate Administration:

   Oral administration of dispersed tablets in water: for patients who are unable to swallow whole tablets, 2 x 2-mg baricitinib tablets may be placed in a container with approximately 10 mL (5 mL minimum) of room temperature water, dispersed by gently swirling the tablet(s) and immediately taken orally. The container should be rinsed with an additional 10 mL (5 mL minimum) of room temperature water and the entire contents swallowed by the patient.

   Administration via gastrostomy feeding tube: for patients with a gastrostomy feeding tube 2 x 2-mg baricitinib tablets may be placed in a container with approximately 15 mL (10 mL minimum) of room temperature water and dispersed with gentle swirling. Ensure the tablet(s) are sufficiently dispersed to allow free passage through the tip of the syringe. Withdraw entire contents from the container into an appropriate syringe and immediately administer through the gastric feeding tube. Rinse container with approximately 15 mL (10 mL minimum) of room temperature water, withdraw the contents into the syringe, and administer through the tube.

Administration via nasogastric feeding tube: for patients with an enteral feeding tube, 2 x 2-mg baricitinib tablets may be placed into a container with approximately 30 mL of room temperature water and dispersed with gentle swirling. Ensure the tablet(s) are sufficiently dispersed to allow free passage through the tip of the syringe. Withdraw the entire contents from the container into an appropriate syringe and immediately administer through the enteral feeding tube. To avoid clogging of small diameter tubes (smaller than 12 Fr), the syringe can be held horizontally and shaken during administration. Rinse container with a sufficient amount (minimum of 15 mL) of room temperature water, withdraw the contents into the syringe, and administer through the tube.

Intact tablets are not hazardous. Tablets may be crushed to facilitate dispersion. It is not known if powder from the crushed tablets may constitute a reproductive hazard to the preparer. Use appropriate precautions if exposure to contents occurs. Dispersed tablets are stable in water for up to 4 hours.

Administration via	Dispersion Volume	Container Rinse Volume
Oral dispersion	10 mL	10 mL
Gastrostomy tube (G tube)	15 mL	15 mL
Nasogastric tube (NG tube)	30 mL	15 mL

The intervention and placebo will be administered to the patients by the treating nurses. The treating nurses will also be responsible for the extemporaneous handling of tablets that will need to be given in liquid form. At sites where a resident pharmacist is available, such extemporaneous handling will be undertaken by her/him.

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 baricitinib 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 10. The allocation list and kit list will be aligned in the eCRF system to provide the patient with the allocated treatment.

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

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

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

- 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.
- Dosage adjustments in patients with renal impairment:
    - eGFR ≥30 to <60 mL/min/1.73 m2: 2 mg once daily*
    - eGFR ≥15 to <30 mL/min/1.73 m2: withdraw treatment or 2 mg every other day**
    - eGFR <15 mL/min/1.73 m2: withdraw treatment

  *Patients with eGFR 30-60 mL/min/1.73 m2 at screening should remain with the decreased dose of 2 mg once daily during the entire study. Patients with normal renal function at screening who decrease to eGFR 30-60 mL/min/1.73 m2 should decrease dose to 2 mg once daily until eGFR returns to >60 mL/min/1.73 m2.

  ** In subjects with eGFR 15-30 mL/min/1.73 m2, treatment should be withdrawn, unless in the opinion of the PI, the potential benefit of participation outweighs the potential risk of study participation. In that case, the patient should remain with the decreased dose of 2 mg every other day during the entire study.

- Dosage adjustments due to drug interactions are recommended. Baricitinib dosage should be reduced to 2mg once daily when benzylpenicillin (penicillin-G) or probenecid is used simultaneously due to an expected reduction in renal clearance of 50%.

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

Not relevant.

6.7. Treatment of Overdose

For this study, any dose of baricitinib greater than 4 mg within a 24-hour time period 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 whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until baricitinib can no longer be detected systemically (at least 2 days). Any case of overdose will be collected in the eCRF + notified immediately to the pharmacovigilance team even without 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.

6.8. Concomitant Therapy

Prohibited medication is described under exclusion criteria (section 5.2). These include cytotoxic or biologic treatments (washout period specified under section 5.2), with the exception of tocilizumab as rescue therapy.

There will be no recording of vitamins and/or herbal supplements.

6.8.1. Rescue Medicine

Patients will be treated according to best available standard of care, including any rescue medicine regarded medically needed. Tocilizumab 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 treating physician should make a risk/benefit assessment of the individual patient whether or not the investigational product should be discontinued. Of note, the investigator will be blinded, and decision of adding rescue therapy will not be influenced by knowledge of the intervention *(baricitinib or placebo).*

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Refer to section 2.3.1 for levels of neutrophils, lymphocytes, haemoglobin, ALT and AST leading to interruption and mitigation strategies.

Treatment should be temporarily discontinued in the following circumstances:

-Absolute neutrophil count <500 cells/microliters in one sample

-Absolute lymphocyte count <200 cells/microliters in one sample

-AST or ALT > 5 times ULN

Treatment should be permanently discontinued in the following circumstances:

-The participant experiences any 1 of the following events on 2 consecutive samples taken 48 hours to 7 days apart:

-Total white blood cell count < 1000 cells/ microliters

-Absolute neutrophil count <500 cells/microliters

-Absolute lymphocyte count <200 cells/microliters

-The participant develops liver dysfunction defined as one of the following:

-AST or ALT > 8 times ULN or

- AST or ALT > 3 times ULN AND total bilirubin > 2 times ULN or INR > 1.5

-If prohibited medication as noted under exclusion criteria (section 5.2) is started, with the exception of tocilizumab as rescue therapy (decision to continue or discontinue study treatment at treating physician's discretion).

-If the participant becomes pregnant during the study (refer to section 10.1 for pregnancy and contraception).

-If the participant develops systemic hypersensitivity reaction.

-If the participant develops any of the following:

-New malignancy

-HIV infection (detectable HIV-RNA and/or AIDS)

-Tuberculosis (active or latent)

-Active hepatitis B (HBV-DNA) or hepatitis C (HCV-RNA) infection

-VTE (DVT/PE)

-Serious infection not responding to standard therapy

-Diverticulitis (including exacerbation of pre-existing diverticular disease)

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.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA. 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 (section 1.3) 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).
- 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), serum (3-4 mL) and naso/oropharyngeal swabs (on 2 ml virocult type medium, diluted with PBS or culture medium if necessary) will be collected for the biobank and stored at -70°C/or - 80°C (temporarily storage at -20°C for 1 month is possible).
        - EDTA whole blood and citrate plasma are not planned for this sub protocol.
    - Planned analyses for this sub protocol are as follows:
        - EDTA plasma: cytokine panel including but not restricted to interleukin-6, interleukin-10, interferon- inducible protein-10 (IP-10) and granulocyte-macrophage colony-stimulating factor.
        - Serum: SARS-CoV2 specific antibodies
        - Naso/oropharyngeal swabs: SARS-CoV2 viral RNA
        - In addition, ferritin, CRP, D-dimer, LDH, procalcitonin 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. 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.

8.1. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

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

Refer to master protocol for definitions and reporting of AEs and SAEs.

8.2.1. Disease-Related Events (DRE) and/or AEs of special interest (AESI)

For complete list of DREs in COVID-19, refer to master protocol.

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

1. Endocarditis / bacteraemia
2. Meningitis / Encephalitis
3. Bacterial pneumonia, including ventilator-associated pneumonia
4. Pulmonary embolism
5. Deep venous thrombosis
6. Arterial thrombosis
7. Liver dysfunction/hepatotoxicity
8. Reactivation of chronic infection including tuberculosis, herpes simplex, herpes zoster and hepatitis B.

In addition, the following AEs (normally associated with long term use) should be reported as AESI in this trial:

1. Gastrointestinal bleeding

2. Diverticulitis (including exacerbation of pre-existing diverticular disease)
3. Gastrointestinal perforation

8.3. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study. Pharmacodynamic parameters are not evaluated in this study.

8.4. Genetics and/or Pharmacogenomics

Genetics are not evaluated in this study.

8.5. Biomarkers

Refer to master protocol.

8.6. Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

8.7. Health Economics OR Medical Resource Utilization and Health Economics

Not applicable.

9. Statistical Considerations

9.1. Statistical Hypotheses

Refer to master protocol.

9.2. Sample Size Determination

The same sample size assumptions and motivation as presented in the master protocol will be used in this sub-protocol: With an assumed treatment difference of 5% between the intervention arms, from 15% 60 days mortality in the placebo arm to 10% in the baricitinib arm, we need 924 evaluable participants in each arm to reach 90% power of detecting a treatment effect on the 5% two-sided significance level. We plan to randomise 950 participants per arm to account for some drop-out.

To ensure enough participants receiving mechanical ventilation at baseline, at least 200 participants will be included in this subgroup.

9.3. Statistical Analyses

Refer to master protocol.

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) 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).

9.4. Interim Analysis

Refer to master protocol.

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 one week 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.

Female patients of childbearing potential must agree to use 1 highly effective form of contraception (< 1 % failure rate per year when used consistently and correctly) for the entirety of the study and for at least 1 week following the last dose of the investigational product.

Women of childbearing potential must agree to refrain from intercourse or use highly effective contraception during the entire study and for at least 1 week following the last dose of investigational product. For men, there are no contraception requirements.

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 post intervention. It is acceptable that the latter is performed using urine-based dipstick home test if the woman is 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. 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.

10.3. Data Monitoring Committee

The independent Data Monitoring Committee is responsible for:
(i) Reviewing unblinded interim 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).

11. References

1. Cantini F, Goletti D, Petrone L, et al (2020). Immune therapy, or Antiviral Therapy, or Both for COVID-19: A systematic Review. Drugs 80, 1929-46.
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