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.

Intervention Specific Appendix Protocol Number: 2.3 dated 23 February 2022

Refers to EU-SolidAct Master Protocol Number: 2.2 dated 23 February 2022

Amendment Number: 1.1

Compound: baricitinib

Brief Title: Bari-SolidAct

Study Phase: 3

Sponsor Name: Oslo University Hospital

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Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 1.1 protocol version 2.3	*23 February 2022*
Substantial Amendment 1 protocol version 2.0	*1 November 2021*
Original Protocol v 1.1	*07 April 2021*

This is amendment 1.1 protocol version 2.3 - 23 February 2022

Overall Rationale for the Amendment:

This minor amendment adds a section on Country-specific protocol requirements requested by national competent authorities and ethics committees. This has been done to consolidate the protocol for the transfer to the Clinical Trial Regulation No 536/2014.

Section # and Name	**Description of Change**	**Brief Rationale**
10.4	Added country-specific requirements for Austria, Czech Republic, France, Germany and Norway	Required change for the transferal

Table of Contents

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. The COV-BARRIER trial recently reported survival benefit of baricitinib compared to placebo added to standard of care, although the primary end point of preventing disease progression was not met. There is a rationale to investigate whether these results are confirmed in an independent placebo-controlled trial with mortality as the primary end point. A limitation of published and ongoing COVID-trials of baricitinib and other immunomodulators is that immunocompromised patients are largely excluded. As immunocompromised patients often have signs of hyperinflammation in the setting of severe COVID-19, there is also a rationale to include this patient group in the ongoing trial provided close follow-up of safety is performed. Immunocompromised patients have impaired response to COVID-19 vaccines, therefore it is likely that this population would be overrepresented among hospitalized patients with COVID-19 in the coming months.

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)

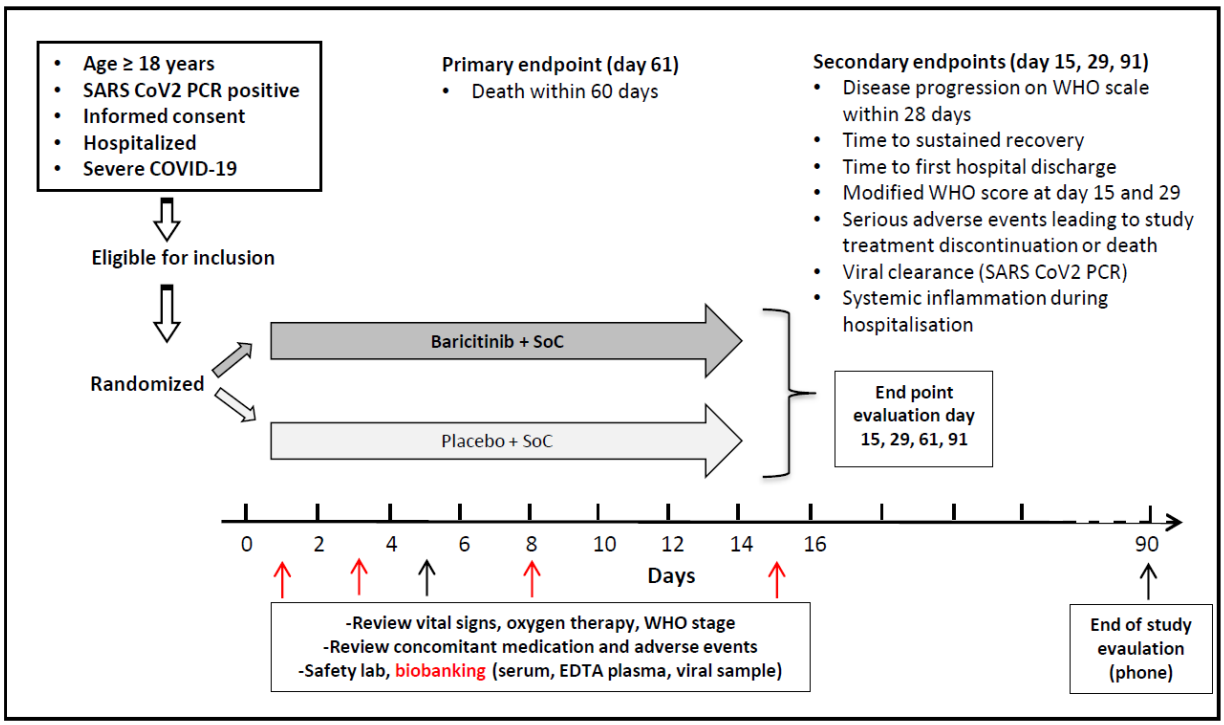
Number of Participants enrolled:
Approximately 2000 participants will be screened to achieve 1900 randomly assigned to baricitinib or placebo to end up with 1848 evaluable participants (924 per arm).

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**[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						
Review SARS-CoV-2 PCR (positive within last 14 days)	X						
Informed consent	X						
Baseline procedures							
Randomization		X					
Standard of care (SoC)[2]		X					
Intervention (baricitinib/placebo)		X	Note doses given				
Safety procedures							
Safety biochemistry[3]	X	(X)	X	X[5]	X[5]	X[5]	X[5]
Evaluation for secondary infection with microbiological work-up [4]			D3, D5, D8, then twice weekly	X[5]	X[5]	X[5]	X[5]
Pregnancy test[6]		X			X		
Study procedures							
Vital signs including SpO_2		X	X	X[5]	X[5]	X[5]	X[5]
Review oxygen therapy[7]		X	X	X[5]	X[5]	X[5]	X[5]
Review WHO stage[8]		X	X	X[5]	X[5]	X[5]	X[5]
IgG and SARS-CoV2 serology		X[9]					
Concomitant medication[10]		X	Note changes daily until discharge, note on occurrence[10]	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[11]		X	X	X	X	X	X
Biobanking (level II)							
Serum, EDTA Plasma		X	D 3, 8, 15, 22 (all ±1)				
Naso/oropharyngeal swab		X	D 3, 8 , 15 (all ±1)				

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, anti-SARS-CoV2 monoclonal antibodies, 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.
    - If ferritin and procalcitonin are not routinely gathered at a site for clinical follow-up, these 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. Patients will be followed twice weekly with clinical evaluation of potential secondary infectious diseases. If clinically indicated, microbiological sampling of airway specimens for bacterial and fungal infection and blood cultures should be obtained. If available and clinically indicated, blood samples for viral PCR (cytomegalovirus, herpes simplex) and serum galactomannan should be obtained. In mechanically ventilated patients, sampling of tracheal aspiration or bronchial lavage for bacterial and fungal culture should be obtained twice weekly. See chapter 8 for details.
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. 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.
7. 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.
8. Review WHO stage including mode of oxygen therapy and need for rescue therapy for end point assessment (progression on WHO scale, table 3.1)
9. Serum levels of IgG should be obtained at baseline. If available, also SARS-CoV2 antibodies should be measured.

10. If it is not feasible to register all changes in concomitant medication, the priority should be to register changes in concomitant medication that could interfere with safety of efficacy of the tested drug, as detailed in chapter 6.8.
11. 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.
12. 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. The COV-BARRIER study recently reported survival benefit of baricitinib compared to placebo added to standard of care, although the primary end point of preventing disease progression was not met. There is therefore a rationale to investigate whether these results are confirmed in an independent placebo controlled trial with mortality as the primary end point. A limitation of published and ongoing COVID-trials of baricitinib and other immunomodulators is that immunocompromised patients are largely excluded. Immunocompromised have impaired response to COVID-19 vaccines, therefore it is likely that this population of patients would be overrepresented among hospitalized patients with COVID-19 in the following months. As immunocompromised patients often have signs of hyperinflammation in the setting of severe COVID-19, there is a clear rationale to include such patients in the ongoing trial, with particular focus on safety in this pre-specified sub-group.

2.2. Background

In a 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 ACTT4 trial (NCT04640168) investigated remdesivir + baricitinib vs remdesivir + dexamethasone on a combined progression endpoint in patients with moderate/severe COVID-19, but was stopped for futility as it was unlikely that either treatment arm would be significantly superior to the other.

The recently published COV-BARRIER trial (NCT04421027) investigated baricitinib vs placebo added to SoC on a combined progression endpoint in moderate/severe COVID-19. Although the primary endpoint was not met, there was a significant survival benefit, in particular in patients with severe disease[3].

Bari-SolidAct is currently the only placebo controlled trial investigating baricitinib with mortality as a predefined end point. Compared to other trials, including the ongoing RECOVERY trial, patients are followed longer, with primary end point assessment performed 60 days after randomisation and with a key secondary end point of patient related outcomes assessment (PROM) performed remotely after 90 days.

A limitation of all the above mentioned trials, including the original version of Bari-SolidAct, is that immunocompromised patients are largely excluded. This is a patient group that is expected to increase in proportion with increasing vaccine coverage in the general population, and a patient group with high mortality risk and unmet therapeutic needs. Although patients with cancer, solid organ transplants or haematopoietic transplants often have increased inflammatory markers in the setting of COVID-19[4], it is not clear if immunosuppressive therapy beyond steroids is beneficial or potentially harmful due to increased risk of severe secondary infections. Of note, a large multicentre trial of organ transplanted individuals reported that age and comorbidities, rather than intensity of immunosuppression were the major drivers of mortality[5]. Furthermore, the COV-BARRIER trial reported no increased risk of serious infections in patients treated with baricitinib compared to placebo, even when added to steroid treatment[3]. Compared to tocilizumab, baricitinib with its short half-life, oral administration and balanced immunomodulating effects could be a good candidate drug for immunocompromised COVID-19 patients with disease progression and signs of inflammation. There is therefore a clear rationale to open the Bari-SolidAct trial also for inclusion of immunocompromised patients. If baricitinib should receive marketing authorisation and become standard of care for severe COVID-19 during the course of the trial, inclusion may continue in patient groups where the risk benefit assessment is still not clarified, including immunocompromised patients.

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.

Patients will be followed by bi-weekly clinical evaluation and appropriate microbiological work-up as described in the Risk Assessment table 2.3.1 and the SoA, table 1.3, and further detailed in chapter 8.

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 (including ventilator associated pneumonia), disseminated/systemic fungal infections as well as reactivation of tuberculosis and chronic viral disease (i.e. herpes simplex, cytomegalovirus, herpes zoster, hepatitis B). 2. Increased risk of venous thromboembolism (DVT/PE). 3. Increased risk of hematologic toxicity including anaemia, neutropenia and lymphopenia.	1. Investigators and patients will be informed about this risk, so that pre-emptive measures will be started. Bi-weekly clinical evaluation and appropriate microbiological work-up for bacterial infection, invasive fungal infection and reactivation of chronic viral disease will be scheduled. Baricitinib/placebo intervention will be interrupted if serious infection 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. Monitoring of haemoglobin, neutrophil and lymphocyte parameters will ensure prompt discontinuation (temporarily or permanent, refer to

4. Hepatotoxicity. 5. Exacerbation of pre-existing diverticular disease.	section 7.1) of intervention should the parameters have the following values: a. Absolute leukocyte count <1000 cells/microliters b. Absolute neutrophil count <500 cells/microliters c. Absolute lymphocyte count <200 cells/microliters d. Hemoglobin (Hb) < 8.0 g/dL. 4. 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 patients, including immunocompromised individuals, which is a patient group with unmet needs.

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 bi-weekly clinical evaluation and appropriate microbiological diagnostics for secondary infections, 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[6] 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[7]. 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[8] 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 14 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.

Note: these are based on the same criteria as in the WHO living guidelines recommending corticosteroid treatment for severe and critical COVID-19[5].

In addition, the following specific inclusion criterion applies to immunocompromised patients:

SI-01. Immunocompromised patients are eligible only if they have elevation of 2 or more inflammatory markers above the following cutoffs:
-Ferritin ≥ 700 ug/l
-LDH ≥ 400 U/L
-CRP ≥75 mg/dL

Immunocompromised patients are defined as the presence of at least one of the following conditions[9]:

1. Hematological malignancy or pre-malignancy, except acute leukemia or history of lymphoma

2. Organ transplant recipients, except recipients of bone marrow or solid organ transplant last 6 months, or with transplant rejection last 6 months

3. HIV positive with CD4 count < 350 cells and on stable antiretroviral therapy

4. Primary immunodeficiency

5. Rheumatoid arthritis, lupus, vasculitis, inflammatory bowel disease or other autoimmune disorder for which a patient is being treated with systemic immunosuppressive medication

6. Other specified cause, such as history of cancer, cancer treatment or other condition that in the opinion of the investigator could cause impaired host immunity

Note: Carefully check exclusion criteria SE-01, SE-20 and SE-21 (immunosuppressive therapy), SE-22 (medical condition), SE-13 (neutropenia) and SE-14 (lymphopenia) for eligibility criteria.
Immunocompromised patients should receive appropriate SoC, including anti-SARS-CoV2 monoclonal antibodies or emerging antiviral treatment, if available and indicated by current treatment guidelines at time of inclusion.

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. Patients receiving Janus kinase (JAK) inhibitors (including baricitinib) for any indication at screening.
- SE-20. Have received tocilizumab or sarilumab for any indication 4 weeks prior to screening.

  Note: Tocilizumab as rescue therapy will be allowed in patients with clinical progression after inclusion, see section 6.8 concomitant medication. If tocilizumab or other immunosuppressive rescue therapy is started, IMP should be discontinued.
- SE-21. Patients with recent changes in immunosuppressive therapy that could interfere with the potential effect of baricitinib.

  Note: An assessment of the total level of immunosuppression, hematological parameters (SE-13 and SE-14), drug half-lives, drug-drug interactions, and underlying medical conditions (SE-22) must be performed as part of the risk/benefit evaluation.

  - Recipients of bone marrow transplant or solid organ transplant last 6 months, or with transplant rejection last 6 months, should not be included.
  - Organ transplant recipients receiving triple immunosuppression can only be included if the anti-metabolite (mycophenolic acid or mTOR inhibitor) has been temporarily discontinued per clinical practice[10]. IMP should be discontinued once triple immunosuppression is restarted.
- SE-22. Any medical condition that in the opinion of the investigator poses an inacceptable risk of serious infection or aggravation of the medical condition by participating in the trial.

Note: Patients with acute leukemia or history of lymphoma should not be included. Cancer patients under active treatment, HIV positive individuals with detectable HIV-RNA, or other patient group associated with high risk of serious infection or aggravation of the medical condition should only be included if, in the judgement of the investigator, the potential benefit outweighs the potential risk.

- SE-03. Have received dexamethasone 6 mg daily (or alternative regimens with equivalent of corticosteroids) for more than 4 days prior to screening as part of SoC for severe/critical COVID-19
- SE-04. Had COVID-related symptoms > 21 days or hospitalized > 7 days.
- SE-05. Strong inhibitors of organic anion transporter 3 [OAT3] (e.g., probenecid) that cannot be discontinued at study entry.
- 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.
- 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).

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

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

For baricitinib, this should at least include medication related to severe infection (antibiotics, antivirals, antifungals), immunosuppression (cytotoxic, immunomodulating and biological drugs), thromboembolism (anticoagulants), hepatotoxicity (including but not limited to antibiotics, antipsychotics, antiepileptics, statins, paracetamol), gastrointestinal bleeding/perforation (antacids, platelet inhibitors, NSAIDs), medications used to treat chronic comorbidities (including but not limited to ACE inhibitors and 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 6.8.1 for tocilizumab) will be explicitly asked for.

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 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 CMV, HSV, hepatitis B (HBV-DNA) or hepatitis C (HCV-RNA) infection

-Invasive fungal infection, including invasive pulmonary aspergillosis

-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.

Immunocompromised patients should be followed twice weekly with clinical evaluation of potential secondary infections.

If clinically indicated, microbiological sampling of airway specimens for bacterial and fungal infection and blood cultures should be obtained. If available and clinically indicated, blood samples for viral PCR (cytomegalovirus, herpes simplex) and serum galactomannan should be obtained.

In mechanically ventilated patients, sampling of tracheal aspiration or bronchial lavage for bacterial and fungal culture should be obtained.

These measures are primarily for clinical management of the individual patients. IMP should be permanently stopped and appropriate treatment started if severe infection is detected. If pathogens detected are regarded as not relevant (colonization) the IMP should be continued. Serious infections should be reported as AESI/SAE as appropriate.

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 AESI 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 (grade 3 and 4)
8. Reactivation of chronic infection including tuberculosis, herpes simplex, cytomegalovirus, herpes zoster and hepatitis B.

9. Invasive fungal infection, including invasive pulmonary aspergillosis
10. Serious cardiovascular events, including myocardial infarction and stroke.

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, even with the inclusion of immunocompromised patients: 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.

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 mortality of immunocompromised patients.

9.3. Statistical Analyses

Refer to master protocol.

Heterogeneity will be handled by stratifying the randomization by center.

In addition to stratification factors used in the randomisation, the primary and secondary analyses will be adjusted for immunocompromised status (yes/no) as defined in inclusion criterion SI-01.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), anti-SARS-CoV2 monoclonal antibodies (yes/no), seronegative at baseline (yes/no), IgG levels (normal/low), lymphocyte count (normal/low), hyperinflammation with elevation of a least two inflammatory markers as defined in SI-01 (yes/no), immunocompromised as defined in SI-01 (yes/no).

9.4. Interim Analysis

In addition to the periodic reviews outlined in the DMC charter for the overall number of participants, DMC safety assessment will also be conducted after 25, 50, 100, 200 and 400 immunocompromised participants have reached 60 days.

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).

10.4. Country-specific Requirements

10.4.1. Austria

„Addendum (Österreich) Nr. 01 vom 08.09.2021

zum Baricitinib-spezifischen Protokoll (Version 1.1 vom 07.04.2021)

Information an die Prüfärzte: Einschlusskriterien

Participants are included in the study if any of the following general inclusion criteria (GE) apply:

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

Participants unable to give their personal consent can be included into the trial without the consultation of the legal representative following the description in §43a of the Austrian pharmaceutical act (AMG).

Since the patients included in this trial are seriously ill it is necessary to also include patients, who are intubated, sedated, and mechanically ventilated. Due to that circumstance, it is to expect that some of the patients may not be able to give informed consent prior to randomization. However, adequate measures will be taken to protect this vulnerable population in accordance to local laws. Accordingly, we would like to point out here and by announcement in front of our department ("black board") that this study at the Department of Internal Medicine, Division of Intensive Care and Emergency Medicine of the Medical University Innsbruck is also carried out within § 43a of the Austrian pharmaceutical act (AMG). This means that this facility is a centre where clinical trials are carried out in emergency situations on patients who are unable to give informed consent. Therefore, the following must be considered:

I. If a clinical trial of a type that can only be carried out in emergency situations, in which the consent of the legally acceptable representative can not be obtained within a reasonable time, it is possible to include this patient into the study although she/ he is unable to give informed consent if:

a) there is no evidence that the patient has declined or would refuse the clinical trial,
b) there is no other research possibility to gain valid data during clinical trials from patients who can give informed consent or other research methods, and therefore only a study carried out in emergency situations is appropriate,
c) the medicinal product being tested is intended to detect, cure, alleviate or prevent disease in an emergency situation,
d) the use of the medicinal product being tested is indicated by medical research to detect, cure or alleviate an illness or to prevent from further diseases in an emergency patient and by being included in the clinical trial the benefit outweighs the risk for the patient,
e) the conduct of the clinical trial and the clinical investigation plan was approved, especially for patients who are not capable to give informed consent, by an ethics committee with knowledge of the disease under investigation, the emergency situation and the patient population concerned or seeked clinical and ethical advice about the field of the disease in question concerning emergency situations and the population of patients concerned, and

f) in doubt, the interests of the patient are always above the public interest and the interests of science.

II. If the patient regains the ability to give informed consent, she/ he must be informed without delay that she/ he was included into a clinical trial in an emergency situation which has been or will be carried out on her/ him. She/ he must be informed within the meaning of §§ 38 and 39 AMG. Continued participation in the clinical trial of the patient is only permitted if informed consent is obtained. Further processing of the personal data collected until then requires explicit data protection consent.

III. As soon as the consent of the legally acceptable representative can be obtained, a continuation of the clinical trial is only permitted under the conditions of § 42 or § 43 AMG.

IV. If the patient dies before the in section II. and III. stated time points, the data processed so far may be used for the purposes of this clinical trial."

10.4.2. Czech Republic

"Public health emergency EU-SolidAct

National Czech Amendment

European DisCoVeRy for Solidarity: An Adaptive Pandemic and Emerging Infection Platform Trial

EUDRACT NUMBER: 2021-000541-41

NATIONAL AMENDMENT VERSION: 1.0

NATIONAL AMENDMENT DATE: 2021-04-19

1. SUMMARY OF THE TRIAL DESIGN

EU-SolidAct is multi-center, randomised, double blind, platform clinical trial with two parallel treatment arms. Control arm uses the standard of care (defined in Chapter 2 of this amendment) plus placebo, the other consist of investigated anti-SARS-CoV-2 medication – baricitinib plus standard of care. Randomisation ratio is 1 : 1 with additional stratification parameters:

– Part A (moderate disease): Centre and Need for oxygen at baseline (yes/no)

– Part B (severe disease): Centre, Previous entry in Part A (yes/no) and High flow oxygen or NIV vs mechanical ventilation/ECMO at baseline

Primary and secondary outcomes of the trial are defined in the Master protocol and Intervention Specific protocol. National Czech Amendment provides only supplement and specifying information to the Master protocol of EU-SolidAct clinical trial. According to the Intervention Specific protocol (version 1.1), patients will be randomized only into Part B.

2. DEFINITION OF THE STANDARD OF CARE

Standard of care is the symptomatic treatment according to the patient's current condition and physician's decision which includes:

• Nutrition, hydration, electrolytes, and glucose administration

• Oxygenation, if needed invasive or non-invasive ventilation, or extracorporeal membrane oxygenation (ECMO)

• Inhaled bronchodilators

• Antipyretics (i.e. paracetamol, metamizole)

• Antibiotics (i.e. cefotaxime)

• Mucolytics/expectorants/antitussives

• Nonsteroidal anti-inflammatory drugs

• Corticosteroids (i.e. dexamethasone)

• Anticoagulants

• Remdesivir

Standard of care will be noted in source documentation and eCRF.

3. INFORMED CONSENT PROCEDURE

This chapter replaces described process of obtaining informed consent in the Master protocol chapter 10.1.3. as the text is not in accordance with Paragraph 52, Article 9 of Act No. 378/2007 Coll., the Act on Pharmaceuticals.

The investigator assesses patient´s ability to decide and extent of potential consciousness impairment based on GCS and other appropriate clinical measures (at discretion of the trial centre).

a) Fully conscious and oriented patients (GCS 15)
Patient with decision-making capacity will go through the standard procedure (informative interview with the investigator, written information for the patients, the possibility to ask questions, and adequate time to discuss with family and decide). If the patient wishes to participate, he/she will be provided with a written informed consent. If the patient is under legal protection, their legal representative will decide about the patient's participation.

b) Patients with limited ability to decide (GCS 14 or 13)
Some patients may be limited in their decisional capacity due to their acute health status, or medication. Generally, if a patient understands simplified information and can communicate verbally, the simplified procedure of obtaining informed consent will be applied. The shortened (one-page) information sheet and consent form for signature will be used.

As soon as the patient regains full decisional capacity, he/she will be approached to provide consent with the continuation of his/her participation in the trial. Patients will be informed about the option to withdraw from the trial. Patients who decide to terminate their involvement

can permit the sponsor to use the data collected, or they can ask for deleting all data collected. Both options will be presented to them.
If the patient does not regain a decisional capacity, the initial consent will remain valid.

c) Patients lacking capacity to decide (GCS 12 of less)
It is expected that a proportion of screened patients will lack the capacity to provide informed consent due to altered consciousness, severe respiratory distress, or sedation necessary to facilitate mechanical ventilation. In this situation, the deferred consent policy will be applied. Such a patient will be enrolled after an independent physician witnesses (in writing) that the patient cannot give his/her consent and will be able to give an input on the eligibility criteria (as well as the benefice/risk ratio). This independent physician will not be linked to the site's principal investigator.

Patient's close person (spouse/partner, close relative, caregiver) will be informed about the patient's enrolment and the nature of the study. If possible and compliant with the epidemiological restrictions by the government, patient's close person will meet the investigator for an informative interview and obtain the information leaflet.

As soon as the patient regains decisional capacity, he/she will be approached to provide consent with the continuation of his/her participation in the trial. Patients will be informed about the option to withdraw from the trial. Patients who decide to terminate their involvement can permit the sponsor to use the data collected, or they can ask for deleting all data collected. Both options will be presented to them.

If the patient does not regain a decisional capacity, the initial consent by an independent physician will remain valid."

10.4.3. France

"TITRE : «Efficacité et sécurité du baricitinib dans le traitement du COVID-19 sévère»

Addendum au protocole spécifique pour la France, version 1.0

Date : 22.04.2021

Les critères de non inclusion suivants ont été ajoutés:

- Les personnes mineures.
- Patients majeurs sous un régime de protection juridique.

Suite à la demande du CPP datant du 22.04.2021, les critères de non-inclusion seront bien appliqués en France.

Le protocole Bari SolidAct étant promu par un organisme étranger, ces modifications ne peuvent être ajoutées au protocole. Mais celles-ci ont bien été mentionnées dans le synopsis en français (cf. synopsis version 1.1 du 22.04.2021)."

Amendment 2, Bari-SolidAct protocol v2.1 dated 5 January 2022

Overall Rationale for the Amendment:

The background for this amendment was an updated Investigator's Brochure (IB) from the marketing-authorisation holder Eli Lilly dated 22 September 2021. A review from our pharmacovigilance team concluded that patients with eGFR less than 30 millilitre/minute/1.73 meters squared should be excluded. This was implemented in all member states as an Urgent Safety Measure awaiting a protocol amendment after transition to the new Clinical Trials Regulation. The French Authorities requested this to be applied to the competent authorities as a national-specific amendment.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Changed the threshold for estimated glomerular filtration rate from 15 to 30 in exclusion criterion SE-16	Updated Investigator's Brochure

10.4.4. Germany

Addendum (DE) Nr. 04 vom 16.11.2021

zum Baricitinib-spezifischen Protokoll (Version 2.0 vom 01.11.2021)

Voraberklärung (ergänzt am 16.11.2021):

Addendum (DE) Nr. 01 wird durch den Investigator-Letter-de02 vom 08. JUL 2021 (Erklärung über das Vorgehen bei Nicht-Einwilligungsfähigkeit) ersetzt und ist somit nicht mehr gültig.

Addendum (DE) Nr. 02 wird durch Addendum (Deutschland) Nr. 03 (Präzisierung der Ausschlusskriterien) ersetzt und ist somit nicht mehr gültig.

Addendum (Deutschland) Nr. 03 wird durch Addendum (DE) Nr. 04 (Ergänzung der Ausschlusskriterien des Protokolls Version 2.0) ersetzt und ist somit nicht mehr gültig.

Im Vergleich zum Addendum (Deutschland) Nr. 03 basierend auf Bari-SolidAct Protokoll Version 1.2 wurden folgende Ausschlusskriterien modifiziert: SE-01, SE-03, SE-04, SE-10;

folgende Ausschlusskriterien gestrichen: SE-02, SE-06, SE-11;
folgendeAusschlusskriterienhinzugefügt: SE-20,SE-21,SE-22,de-E2.

Information to the investigator: Exclusion criteria

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

Country specific exclusion criteria (de-E):

• de-E1. In Germany, according to German drug legislation (AMG §41(3)), a person who is incapable of comprehending the nature, significance and implications of the clinical trial and of determining his/her will in the light of these facts and who is suffering from a disease in the treatment of which the investigational medicinal product is to be used will be excluded from the participation in the study.

• de-E2. Subjects with estimated glomerular filtration rate (eGFR) (Modification of Diet in Renal Disease [MDRD]) < 30 mL/min/1.73 m2 are excluded (instead of < 15 mL/min/1.73 m2).

o Note: This exclusion criterion replaces the exclusion criterion SE-16 based on available information on baricitinib's safety profile (impairment of renal function significantly impacting baricitinib exposure) which was not modified in the current amendment.

General exclusion criteria (GE) – referring to the Master protocol:

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

Specific exclusion criteria (SE) – referring to the Baricitinib-specific protocol:

• SE-01. Patients receiving Janus kinase (JAK) inhibitors (including baricitinib) for any indication at screening.

• SE-20. Have received tocilizumab or sarilumab for any indication 4 weeks prior to screening. o Note: Tocilizumab as rescue therapy will be allowed in patients with clinical progression after inclusion. See section 6.8. Concomitant Therapy

• SE-21. Patients with recent changes in immunosuppressive therapy that could interfere with the potential effect of baricitinib.

o Note: An assessment of the total level of immunosuppression, hematological parameters (SE-13 and SE-14), drug half-lives, drug-drug interactions, and underlying medical conditions (SE-22) must be performed as part of the risk/benefit evaluation.

- Recipients of bone marrow transplant or solid organ transplant last 6 months, or with transplant rejection last 6 months, should not be included.

- Organ transplant recipients receiving triple immunosuppression can only be included if the anti-metabolite (mycophenolic acid or mTOR inhibitor) has been temporarily discontinued per clinical practice10. IMP should be discontinued once triple immunosuppression is restarted.

• SE-22. Any medical condition that in the opinion of the investigator poses an inacceptable risk of serious infection or aggravation of the medical condition by participating in the trial.

o Note: Patients with acute leukemia or history of lymphoma should not be included. Cancer patients under active treatment, HIV positive individuals with detectable HIV- RNA, or other patient group associated with high risk of serious infection or aggravation of the medical condition should only be included if, in the judgement of the investigator, the potential benefit outweighs the potential risk.

• SE-03. Have received dexamethasone 6 mg daily (or alternative regimens with equivalent of corticosteroids) for more than 4 days prior to screening as part of SoC for severe/critical COVID-19.

• SE-04. Had COVID-related symptoms > 21 days or hospitalized > 7 days.

• SE-05. Strong inhibitors of organic anion transporter 3 [OAT3] (e.g., probenecid) that cannot be discontinued at study entry.

• 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)).

o 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.

• 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.

o 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.

o Note: Excipients of the baricitinib and the placebo tablets are as follows:

(source: SmPC Olumiant from 15-DEC-2020, IMPD LY3009104 from FEB-2020)

- Tablet cores: microcrystalline cellulose, croscarmellose sodium, magnesium stearate, mannitol, lactose monohydrate (placebo only)

- Film coating: iron oxide red (E172), lecithin (soya) (E322), macrogol, polyethylene glycol 3350 (vinyl alcohol), talc, titanium dioxide (E171)

• SE-18. Are pregnant or breastfeeding, or intend to become pregnant or breastfeed during the study.

o 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. Pregnancy and contraception.

• SE-19 Participation in any therapeutic clinical trials investigating immunomodulators for COVID-19.

10.4.5. Norway

Bari-SolidAct: Norwegian national specific protocol addendum to EU-SolidACT protocol version 1.1, dated 07 April 2021 and Bari-SolidAct Protocol version 1.1, dated 07 April 2021

Version 1.1, 11.05.2021

The following text is regarded as a national-specific protocol addendum to the EU-SolidAct master protocol version 1.1 dated 07 April 2021. The addendum is specific to Norwegian patients included in the EU-SolidAct trial.

1. Addendum to section 8.4, 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.

2. Addendum to section 8.0, under paragraph "Biobanking", new bullet point:

• Any rest materials after analysis will be destroyed, or transferred to and stored in the study specific biobank "Bari-SolidAct", located at Research Institute of Internal Medicine, Oslo University Hospital.

10.5. Protocol Amendment History

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

Amendment 1 protocol version 2.0 1 November 2021

Overall Rationale for the Amendment:

Expanding the eligibility criteria to include immunocompromised patients. These patients have impaired response to COVID-19 vaccines, therefore it is likely that this population would be overrepresented among hospitalized patients with COVID-19 in the coming months.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Updated rationale	Emerging evidence and inclusion of immunocompromised patients
1.2 SoA	To be consistent with the changes in the amendment	
2.1 Study rationale	Updated with emerging evidence and rationale for including immunocompromised patients	Gives reason for expanding the study population
2.2 Background	Updated with emerging evidence	Further background to the rationale for expansion of study population

Section # and Name	Description of Change	Brief Rationale
2.3 Risk/Benefit Assessment	Updated risk assessment, corresponding mitigation strategies and overall benefit to risk conclusion	With an expanded study population, the risk of this inclusion has to be weighed against the potential benefit.
5. Study population	Updated inclusion and exclusion criteria to safely include immunocompromised patients.	Immunocompromised patients are a wide and heterogeneous group. Care has to be taken to include the immunocompromised patients most probable to gain an effect of the intervention and to be able to tolerate the added immunomodulation.
	Removed exclusion criterion SE-06 Receipt of neutralizing antibodies for Covid-19	At the time of establishing the original protocol, neutralizing antibodies for Covid-19 was regarded as experimental treatment with unknown impact on patient outcome. During the last year, neutralizing antibodies for Covid-19 has proven to be efficient in certain subgroups of SARS-CoV2 infection and are now recommended treatment both for prehospital high-risk patients and for hospitalized seronegative patients with severe disease. There is no biological rationale for interaction between baricitinib and neutralizing antibodies.
6.8 Concomitant Therapy	Specification on which concomitant medication to register	The previous registration was exhaustive, need to prioritize the registration.
7.1.Discontinuation of Study Intervention	Added active CMV, HSV and invasive fungal infection as reasons to stop study intervention	Safety measures of particular importance in immunocompromised patients
8.1 Safety Assessments	Added more safety assessments such as more frequent clinical evaluation, microbial sampling if clinically indicated, and sampling of tracheal aspiration or bronchial lavage for bacterial and fungal	Safety measure

Section # and Name	Description of Change	Brief Rationale
	culture in mechanically ventilated patients.	
8.2. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting	Added adverse events of special interest	Safety measure
9.2 Sample Size Determination	Added a notion that a sample size re-evaluation might be necessary if the underlying assumptions are clearly violated.	It is highly uncertain how many immunocompromised patients will be included in the end, and what the mortality rate is among these patients. Therefore, we have added a note stating that the sample size might be re-evaluated in a blinded manner.
9.3 Statistical Analysis	Added immunocompromised status as adjustment factor in the primary analysis, and new pre-specified sub-group analyses.	Immunocompromised patients have a worse prognosis compared to non-immunocompromised. Further sub-group analyses are warranted based on emerging evidence.
9.4 Interim Analysis	Added DMC safety assessments based on included immunocompromised patients	Safety measure

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