Title Page

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

Master Protocol Number: 2.2 dated 23 February 2022

Amendment Number: 1.1

Brief Title: EU-SolidAct

EU-SolidAct is a multinational, European, Adaptive Platform Trial used for new clinical trials targeting SARS-CoV-2 in short-term and other emerging infectious diseases in the longer term.

This is a master protocol developed for COVID-19, detailing the general aspects of the trial. Investigational specific details will be provided as an appendix.

Study Phase: 2 and 3

Sponsor:

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Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 1.1, Protocol version 2.2	*23 February 2022*
Amendment 1, Protocol version 2.0	*1 November 2021*
Original Protocol v 1.1	*07 April 2021*

This is amendment 1.1 protocol version 2.2 - 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 Czech Republic, France, Germany and Norway	Making a consolidated protocol

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

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

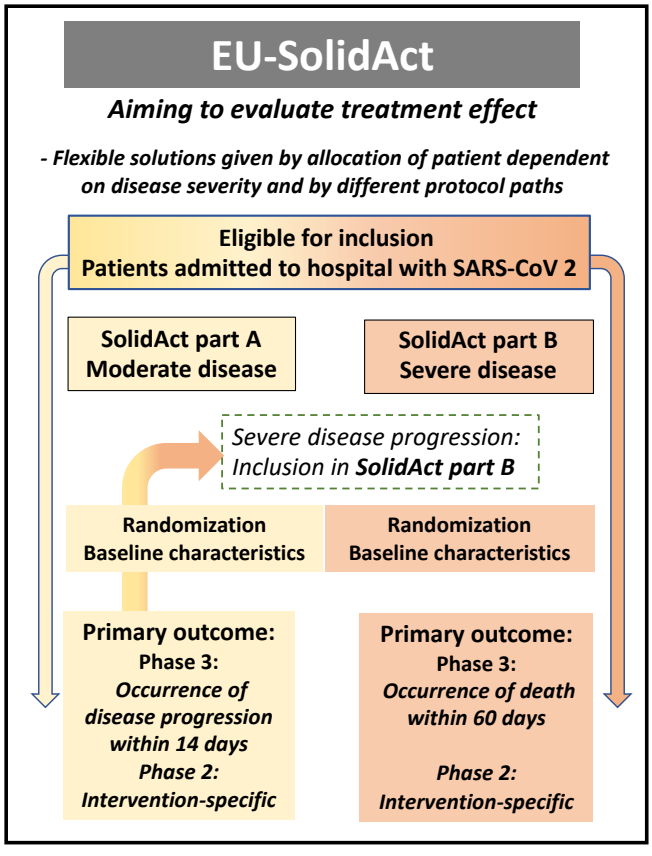
Brief Title:

EU-SolidAct

Rationale and Overall Design:

There is an urgent need for developing an adaptive pan-European research platform for rapid and coordinated investigation of new candidate drugs during ongoing pandemics. EU-SolidAct is an Adaptive Platform Trial master protocol developed for evaluating drug interventions in hospitalized patients with COVID-19. While this master protocol is developed for therapeutic interventions in hospitalized patients, it could also form the basis for trial protocols on other interventions and/or in non-hospitalized populations. The protocol is, additionally, developed to facilitate a joint European response to the challenge of evaluating interventions during future epidemics. The described disease states and endpoints may need to be adapted to the epidemic in question.

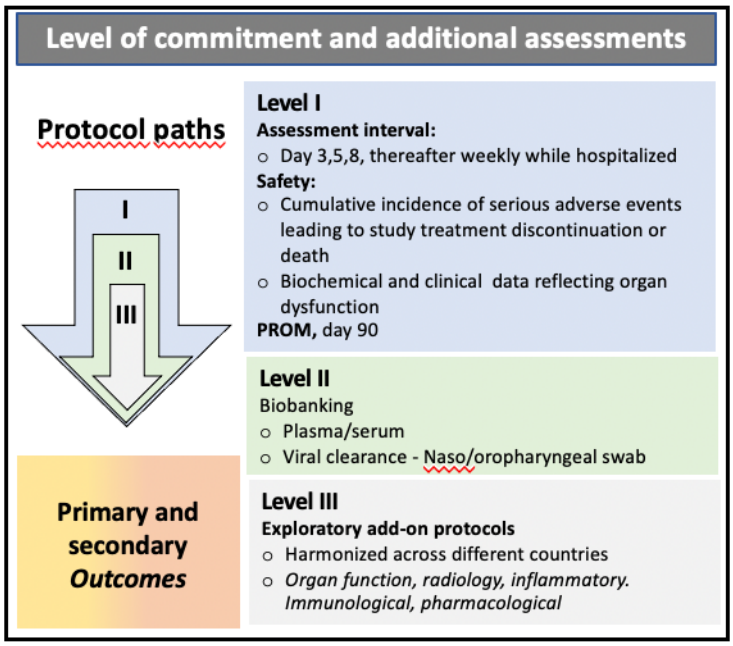
EU-SolidAct is a European, multicentre, randomized, parallel, phase 2 and 3 platform trial on drug interventions, both new and repurposed, single or in combination, in hospitalized adult patients with moderate or severe COVID-19, as defined by the WHO Working Group on the Clinical Characterisation and Management of COVID-19[1]. Participants with moderate disease (WHO score 4-5) will be eligible for EU-SolidAct Part A, whereas participants with severe/critical disease (WHO score 6-9) will be eligible for EU-SolidAct Part B. This might include participants progressing from Part A.



In Part A of phase 3 confirmatory trials, the primary objective is to determine the effect of *therapeutic interventions* on occurrence of disease progression, from moderate disease to severe/critical disease or death within 14 days. In Part B, the primary objective is to determine the effect of *therapeutic interventions* on occurrence of death within 60 days.

In phase 2 the default objective for both parts is to explore the effect of the therapeutic intervention on respiratory dysfunction at day 5. Other objectives, e.g. effect on virological outcomes may be considered based on the treatment mode of action.

In addition to single treatments, combination of treatments could also be assessed through factorial design. EU-SolidAct is designed to be adaptive and to enable inclusion of hospitals in Europe and beyond, regardless of epidemic waves and available resources. This requires the master protocol to be modular, ranging from a core set of outcomes to more advanced data capture. Hospitals will access the study on different pre-set levels, ranging from a core set of clinical endpoints and safety measures, to a more advanced level with biobanking and possibilities for add-on studies.



- Level I commitment is set as the minimum requirement for participation. This level includes a core set of clinical endpoints, safety measures and patient reported outcome measures (PROMs) to enable a maximum inclusion rate of eligible patients. These measures are developed in close dialogue with regulatory authorities to ensure that data collection is sufficient to allow for marketing authorization of drugs to be tested. The required data collection will depend on the drugs being tested.

- Level II commitment is strongly preferred and intended for hospitals with resources available for biobanking at time of inclusion. Biobanking is necessary to assess virological endpoints.

- Level III is intended for hospitals that can participate on a more advanced level. Level III participation enables further scientific questions to be explored, by including e.g. advanced biobanking, pharmacokinetics/dynamics, imaging, organ-related short and long-term outcomes and expanded collection of PROMs. Which outcomes to include would depend on the scientific interest of the participating hospitals, allowing for add-on studies in selected sites, with shared standardised protocols. An additional opportunity for Level III is to identify patient characteristics and biomarkers that aim to predict treatment responses and can lay the foundation for personalized treatment options. Follow-up may be extended beyond 90 days.

The level of complexity can be modulated depending on the scale of the pandemic at a given period, and a participating hospital can request to change between the levels during phases of the pandemic, as participation may depend on available resources.

Brief Summary:

The overall aim of EU-SolidAct is to evaluate the safety and efficacy of therapeutic agents in hospitalized patients diagnosed with SARS-CoV-2, to reduce overall mortality and morbidity, as well as burden of disease on the health systems.

General master study details include:

- The study duration will be up to 90 days (± 14 days) for each participant.
- The treatment duration will be defined in the investigational-specific subprotocols.
- The assessment frequency:
    - Participants will be screened, assessed for eligibility and enrolled as soon as possible after admission.
    - Baseline assessments and randomization at Day 1 as soon as possible after screening.
    - Day 3, 5, 8 (± 1 day) assessments during hospitalisation, then weekly visits until discharge (Day 15±3, Day 22±3, Day 29±3, etc.).
    - Assessments at Day 15 ±3, Day 29±3, Day 61±7 (end points) and Day 91±14 (end of study) will be done at hospital (if participants are still hospitalized); or in the outpatient setting or by phone (if participants are discharged from hospital).

- Number of enrolled Participants:
    - For phase 3 *superiority trials* approximately 1000 participants will be screened to achieve 950 randomly assigned to each arm in Part A and approximately 1000 participants will be screened to achieve 950 randomly assigned to each arm in Part B. For phase 3 *non-inferiority trials*, about 3000 in each arm is needed. *For phase 2 trials*, about 200 in each arm will be included.
    - Where combination therapies are assessed by factorial design, the main assumption will be that no interaction exists between the treatments and therefore no modification of the sample size will be planned. If synergies or effect modifications between treatments are of interest, the intervention-specific sub-protocols will define the sample size needed for detecting the interaction effect.

Note: *Enrolled* means a participant, or his/her legally authorised representative, has provided informed consent to participate and has been screened and found eligible for the trial. The participant will *not* be considered enrolled if the informed consent has been withdrawn prior to participating in any other study activity than screening.

- Intervention Groups and Duration:
    - Detailed in the intervention-specific sub protocols.

- Data Monitoring:
    - A data monitoring committee has been appointed for this study. The data monitoring committee is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of an intervention for harm or for futility. The composition of the committee is based on the scientific skills and knowledge required for monitoring the particular study. There will only be one data monitoring committee overseeing all trial arms.

1.2. Schedule of Assessments (SoA)

Procedure	**Screening**	**Baseline**	**Assessments during hospitalisation**	**Primary endpoint Part A**	**Core secondary end point**	**Primary endpoint Part B**	**End of study/Early withdrawal**
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]							
Review SARS-CoV-2 laboratory results	X						
Informed consent	X						
Allocation to EU-SolidAct Part A or B by WHO disease stage[2]	X						
Baseline procedures							
Demographics and medical history	X	X					
Randomization		X					
Standard of care (SoC)[3]		X					
Study intervention		X	Note doses given				
Safety laboratory							
Safety biochemistry[4]	X	(X)	X	X[5]	X[5]	X[5]	X[5]
Pregnancy test		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, Whole blood		X	Day 3, 8, 15, 22 (all ±1) or until discharge before D22				
Naso/oropharyngeal swab		X	Day 3, 8, 15 (all ±1) or until discharge before D15				
Add-on studies (level III)							
Biobanking, other material		X	Add-on sub protocols				
Radiology		X	Add-on sub protocols				
Organ function		X	Add-on sub protocols				
PROM		X	Add-on sub protocols				

Modular data capture according to level of commitment (level I, level II, level III). Assessments in level I are mandatory. Biobanking (level II) is necessary for virological end points. Add-on sub-studies (level III) will be developed in collaboration with participating sites, developing common standardised procedures for additional biobanking, radiology and organ function.

1. Refer to chapter 8 for details. Screening/baseline assessments should be performed prior to study drug administration.
2. See separate table 4.1 for WHO stage and allocation to EU-SolidAct Part A (moderate disease) or B (severe disease).
3. Standard of Care (SoC) details, including medication.
4. The following laboratory results should be collected: Hb, leukocytes, lymphocytes, neutrophils, platelets, sodium (Na), potassium (K), creatinine, glucose, total bilirubin, INR, ALT, AST, amylase, LDH, D-dimer, CRP, procalcitonin, ferritin. Repeat at baseline if >24 h 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.

5. If still hospitalized. At discharge or early discontinuation, register WHO disease progression scale, review concomitant medication and adverse events as detailed in section 8.
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 numbers 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 for end point assessment (progression on WHO scale)
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.

2. Introduction

2.1. Study Rationale and Background

The novel SARS-2 Coronavirus (SARS-CoV-2) was identified in December 2019 as a cause of severe pneumonia, acute respiratory distress syndrome (ARDS) and potential multiorgan failure in humans. The disease known as COVID-19 has since escalated into a pandemic affecting nearly all countries in the world where it has has caused widespread mortality and morbidity.

There is a pressing need for large scale testing of repurposed and novel agents to provide new treatment options for patients with COVID-19. This testing will be facilitated in an Adaptive Platform Trial master protocol. The protocol EU-SolidAct is developed in collaboration with relevant stakeholders including the European Medical Agency (EMA).

EU-SolidAct is a multicentre/multi-country trial aiming to include hospitalized patients at academic and non-academic centres in Europe and beyond, regardless of epidemic waves and available resources. This requires the master protocol to be modular, ranging from a core set of outcomes to advanced data capture described in the protocol as levels I, II and III. The sponsor is Oslo University Hospital (OUH) and the study is funded by the European Union`s Horizon 2020 research and innovation program.

The study will compare different investigational therapeutic agents plus standard of care (SoC) to SoC possibly in combination with matching placebo. There will be interim analyses to allow early withdrawal of therapeutic agents that show a suboptimal adverse event profile, and to allow for continuous monitoring of the futility of included drugs. While this master protocol is developed for drug interventions in hospitalized patients, it should be feasible to expand the protocol to other interventions and/or to non-hospitalized patients. Importantly, the protocol is developed so that it could form the basis of a joint European response to evaluating interventions in future epidemics.

2.2. Benefit/Risk Assessment

General risk/benefit assessment (excluding intervention-specific risk/benefit):

Participants in this study will be exposed to few general risks beyond being hospitalized. Through bio-banking, the participants will be subjected to additional blood sampling which should be of little inconvenience. Collection of other samples, like oropharyngeal or nasal swabs, can give some transient discomfort.

Participants' identities will be protected, and personal health information (PHI) held securely. No directly identifiable data will be stored in the clinical trial database, and the participant lists will be stored separately, secured, at the local study sites. The risk that unauthorized persons will see the participant's PHI will be kept at a minimum, and measures will be taken to keep PHI confidential and in accordance with the legal requirements.

Specific risk/benefit assessment:

Specific risk/benefit assessments are described in the intervention-specific sub-protocol in alignment with the Investigator's Brochure (IB) and Summary of Product Characteristics (SmPC) for the specific intervention. The severity of the disease (moderate/severe) will be decisive when the risk/benefit assessment is performed. Importantly, enrolled participants may develop critical illness and the implementation of a new drug in this situation may induce unknown effects that may aggravate organ dysfunction.

3. Objectives and Endpoints

3.1. Phase 3 Trial Objectives and Endpoints

In phase 3 confirmatory trials, the primary objectives and endpoints are described below. Secondary objectives and endpoints as listed below should be considered for all interventions studied within this platform. The final selection and any additional intervention-specific objectives or endpoints will be described in corresponding sub-protocols.

Table 3.1 Phase 3 objectives and corresponding endpoints

Objectives	Endpoints
Primary	
Part A, moderate disease	
The primary objective is to determine the effect of *therapeutic interventions* on occurrence of disease progression in hospitalized patients with moderate COVID-19	Occurrence of disease progression, defined as a progression of disease state from moderate (WHO score 4-5) to severe/critical (WHO score 6-9) or death (WHO score 10) within 14 days
Part B, severe disease	
The primary objective is to determine the effect of *therapeutic interventions* on occurrence of death in hospitalized patients with severe or critical COVID-19	Occurrence of death within 60 days
Secondary	
Secondary objectives are 1. to determine the effect of *therapeutic interventions* on other clinical endpoints	1.1 Occurrence of disease progression, defined as a progression of disease state from moderate (WHO score 4-5) to severe/critical/death (WHO score 6-10) or from severe/critical (WHO score 6-9) to death within 28 days 1.2 Time from randomization to sustained recovery, defined as being discharged from the index hospitalization, followed by being alive and at home for 14 consecutive days within 90 days

	1.3 Time from randomization to first hospital discharge within 90 days 1.4 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 1.5 Time from randomization to recovery defined as no need for oxygen 1.6 SpO_2/FiO_2-ratio at day 3, 5 and 8
2. to determine the effect of *therapeutic interventions* on viral clearance	2. Viral clearance as assessed by SARS-CoV-2 PCR in oropharyngeal specimens during hospitalization
3. to determine the effect of *therapeutic interventions* on biochemical parameters	3. Biochemical parameters including inflammatory markers (C-reactive protein, ferritin, lactate dehydrogenase, procalcitonin, D-dimer, leukocyte subsets and cytokine panels) during hospitalisation
4. to assess the safety impact of *therapeutic interventions* on major serious adverse events	4. Occurrence of serious adverse events leading to study treatment discontinuation or death
5. to determine the effect of *therapeutic interventions* on patient reported outcomes	5. The Oslo COVID-19 QLQ-PW80 subscale scores at Day 91

3.2. Phase 2 Trial Objectives and Endpoints

In phase 2 exploratory trials, the default primary objective for both part A and B is to explore the effect of the intervention on respiratory dysfunction, in line with the RECOVERY platform trial protocol. The same objectives and endpoints as for phase 3 trials should be considered, but the final selection, ranking and frequency of assessments will be given in the intervention-specific sub-protocols according to the intervention and the disease stage at inclusion. In addition, more specific end points should be specified according to the characteristics and mode of action of the IMP, and according to emerging variants of SARS CoV2.

Table 3.2 Phase 2 objectives and corresponding endpoints

Objectives	Endpoints
Primary	
The primary objective is to explore the effect of *therapeutic interventions* on respiratory dysfunction	SpO_2/FiO_2-ratio at day 5
Secondary	
Secondary objectives are selected from the objectives in **Table 3.1** as relevant for the IMP (based on the mode of action)	Corresponding endpoints are selected from **Table 3.1**, possibly with increased frequency of assessment

3.3. Further specification to endpoints

- Disease progression with scores refers to the WHO clinical progression scale as defined in Table 8.1
- Death is death by any cause.
- Home is defined as the level of residence or facility where the participant was residing prior to hospital admission leading to enrolment in this trial (the index hospitalization).
    - Residence or facility groupings to define home are:
        - Independent/community dwelling with or without help, including house, apartment, undomiciled/homeless, shelter, or hotel.
        - Residential care facility (e.g., assisted living facility, group home, other non-medical institutional setting).
        - Other healthcare facility (e.g., skilled nursing facility, acute rehab facility) and
        - Long-term acute care hospital (hospital aimed at providing intensive, longer term acute care services, often for more than 28 days).
        - Lower (less intensive) level of residence or facility will also be considered as home.
    - By definition, “home” cannot be a “short-term acute care” facility. Participants previously affiliated with a “long-term acute care” hospital recover when they return to the same or lower level of care.
    - Readmission from “home” may occur and if this occurs within 14 days of the first discharge to “home”, then sustained recovery will not be reached until such time as the participant has been at home for 14 consecutive days.

    - Participants residing in a facility solely for public health or quarantine purposes will be considered as residing in the lowest level of required residence had these public health measures not been instated.
- Hospital discharge is defined as a state without the need for hospitalization. If hospitalized for isolation reasons only, define as discharged.

4. Study Design

4.1. Overall Design

EU-SolidAct is a European, multi-centre, randomized, parallel group, platform trial, exploring and assessing the efficacy and safety of drug interventions, new or repurposed, single or in combination, in hospitalized participants with moderate or severe/critical COVID-19. In case combination treatment evaluations, a factorial design may be applied by adding a combination arm to the two separate single intervention arms. In phase 3 trials, both superiority and non-inferiority hypotheses may be evaluated. In phase 2 trials, only superiority hypotheses will be evaluated.

This master protocol describes the framework for the general study population and the common study elements of the platform trial. The accompanying sub-protocols will present the intervention-specific information, including any intervention-specific objectives and endpoints, details of administration and dose, additional inclusion and exclusion criteria and study procedures. The decision to include a new sub-protocol will be taken in the Trial Steering Committee based on the recommendations from a separate drug evaluation committee.

As available evidence suggests that different drugs may have different efficacy depending on the stage of the disease, EU-SolidAct will be divided into two parts according to disease stage at inclusion:

- EU-SolidAct Part A will include patients with moderate COVID-19 defined as hospitalised patients without oxygen therapy or oxygen by mask or nasal prongs needed (similar to WHO score[1] 4-5)
- EU-SolidAct Part B will include patients with severe/critical COVID-19 (corresponding to WHO score[1] 6-9 and WHO treatment guidelines for dexamethasone[2]) defined as hospitalised patients fulfilling at least one of the following criteria:

    1. SpO2 < 90% on room air, or
    2. SpO2 90-94% with a downward 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).

Control treatment:

- The control treatment for superiority trials will be the SoC at the local hospital defined as the best available treatment according to local hospital guidelines. The SoC might change as new treatment evidence emerges. Use of new treatment as part of SoC will be captured in the trial database.
- Placebo plus SoC might be considered as control treatment if available, otherwise open-label SoC will be given against open-label intervention. This will be detailed in the intervention-specific protocol.
- If components of SoC are contraindicated with the study intervention(s), we might consider head-to-head comparisons between the study intervention(s) and the SoC component, either to assess or confirm superiority or non-inferiority. This will be detailed in the intervention-specific protocol.
- Current SoC should include the use of dexamethasone 6 mg/day for 10 days in severe or critically ill patients (Part B). Duration and dose could change according to emerging evidence. Other doses or frequencies might be used at the discretion of the treating physician based on clinical judgement.

4.1.1. Randomization:

Participants in EU-SolidAct will randomly be assigned in an equal ratio between the comparator treatment arm(s) and the available active treatment(s) for which the participant is eligible. Over time, it is expected that SoC will evolve. Thus, randomization will be aligned with the current clinical situation and the incremental effects of the study treatment(s) will be appropriately assessed. The randomization will be stratified as described in section 6.3.

In the case of both open-label and blinded investigations in the same part, participants are still randomly assigned in an equal ratio between the arms they are eligible for. In the example figure below with a participant eligible for all five arms in Part B, first the participant is allocated to either investigation B1 or B2 in a 2:3 ratio, and then to either Active 1 or Placebo 1 in a 1:1 ratio or to Active 2, Active 3 or open-label SoC in a 1:1:1 ratio.

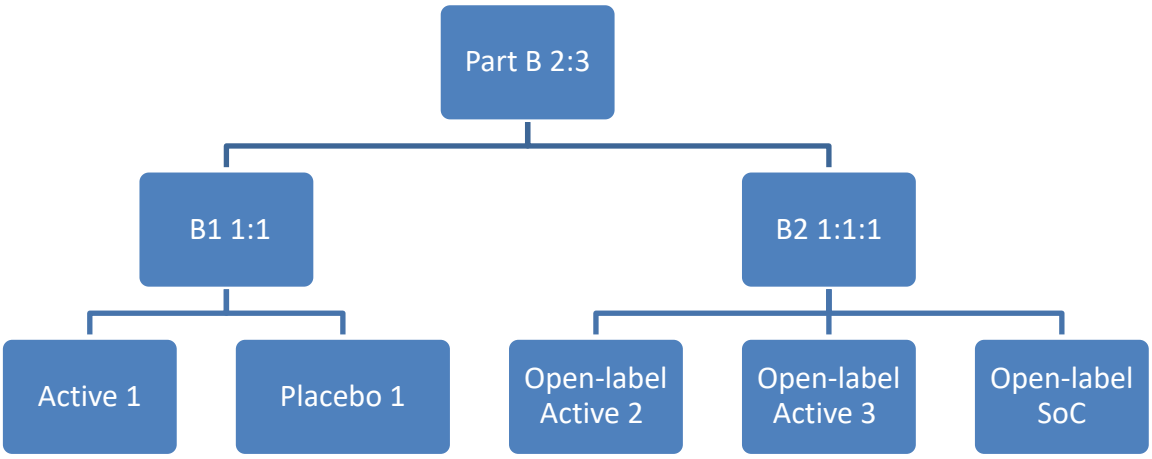


Figure 4.1 Randomisation illustration

4.1.2. Comparison(s):

Each study intervention arm will be compared to their concurrent comparator arm. Concurrent comparator arm encompasses participants that were randomized to the comparator arm when the study intervention was available and eligible for randomization. Thus, the same participant can act as comparator for more than one study intervention arm, dependent on hypothesis to be tested. Specifications on appropriate comparator(s) will be given in the intervention-specific sub-protocol. For blinded investigations the comparator will primarily be the matching placebo arm, while for open-label trials the arm with no treatment will be the comparator arm for all interventions. In the case of non-inferiority trials, the comparator will be the active treatment which the intervention will be compared to.

4.2. Scientific Rationale for Study Design

- Due to the high research focus on COVID-19, there are a multitude of treatment hypotheses being generated and in need of being tested in rigorous randomized controlled trials. Platform trials and the set-up of master protocols provide efficient and consistent paths to test new treatments through a common and concurrent control treatment arm, common eligibility criteria and outcome measures.
- While avoiding imminent death is the ultimate goal in hospitalised patients with a potential lethal disease, the incidence is usually much lower in patients with moderate

disease compared to patients with severe or critical disease. Therefore, the EU-SolidAct trial will evaluate interventions separately for moderate and severe/critical disease stages, with separate endpoints, assuming it will be easier to see an effect on disease progression compared to death in moderate disease.

- The master protocol includes a broad range of hospitalised patients, aiming for a wide generalisability of the results.
- The master platform accommodates both exploratory (phase 2) and confirmatory (phase 3) trials, thus encompassing two important phases of drug development in a new indication.
- The concept of combining treatments to optimize clinical effect is not new in infectious diseases.

4.3. Justification for Dose

Justification of dose of each intervention and combination, if applicable, will be given in the intervention-specific sub-protocol.

4.4. End of Study Definition

Participant Completion

A participant is considered having completed the study if he/she has completed all periods of the study including the last scheduled procedure at Day 91 shown in the Schedule of Assessments (SoA, section 1.2). The expected total trial duration for each participant will be approximately 90 days. If longer or shorter duration is warranted to meet the objectives of specific investigations, this will be stated in the corresponding sub-protocol.

Intervention-Specific Completion

The study of a specific intervention is considered completed when the last participant in the intervention cohort has completed all periods of the study including the last scheduled procedure shown in the SoA.

Platform Study Completion

The platform is considered completed when the last intervention-specific study has been completed.

5. Study Population

All participants must satisfy all the inclusion and exclusion criteria in this master protocol to be enrolled in the platform trial. Any additional intervention-specific criteria will be described in the applicable sub-protocol. The eligibility criteria will be considered by the principal investigator or delegated clinical site personnel.

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

The eligibility criteria listed below are quite general and is suited for phase 3 confirmatory trials. In phase 2 exploratory trials, more restrictive criteria might be necessary to accommodate the increased uncertainty and potential risk of the treatment.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following general inclusion (GI) criteria apply:

GI1. $\geq$ 18 years of age

GI2. Laboratory-confirmed SARS-CoV-2 infection (new infection or reinfection) as determined by PCR not more than 14 days old.

GI3. Admitted to hospital

GI4. Informed consent by the participant or legally authorized representative

GI5A: Moderate disease state defined as hospitalised patients without oxygen therapy or oxygen by mask or nasal prongs needed, or

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.

Additional inclusion criteria are given in the intervention-specific sub-protocols.

5.2. Exclusion Criteria

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

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

Additional exclusion criteria, including prohibited medication, confounding trials and details on contraception and pregnancy are given in the intervention-specific sub-protocols

5.3. Lifestyle Considerations

Included in intervention-specific sub-protocols if applicable.

5.4. Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is subsequently not entered in the study. A minimum set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failures) may not be rescreened.

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

If there are internal or external signs or evidence of harm by any of the study interventions, the randomization to the corresponding treatment arm could be temporarily delayed until further investigations or data analyses resolve the issue. This would be done by continuing the randomization or by permanently removing the intervention from the randomization. The sponsor is ultimately responsible for this decision, but it could be guided by an assessment in the data monitoring committee.

6. Study Interventions and Concomitant Therapy

Study intervention is defined as any investigational interventions, marketed products, or placebo, intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Details are provided in the intervention-specific sub-protocol(s).

6.2. Preparation, Handling, Storage, and Accountability

Instructions for the preparation of study intervention(s) are provided (e.g., reconstitution, mixing) in the applicable intervention-specific sub-protocol(s).

6.3. Measures to Minimize Bias: Randomization and Blinding

In addition to receiving SoC, all participants will be centrally assigned to randomized study interventions in the eCRF. When the participant has been deemed eligible for randomization, baseline information will be entered and then the participant will be randomised. Participants will be randomly assigned in an equal ratio between the intervention or comparator arms they are eligible for. Randomization will be computer-generated in permuted random-sized blocks with stratification. The stratification factors are shown in the table below. Randomization will be done at the baseline visit (day of study treatment initiation). For placebo-controlled interventions, the arm will not be revealed. Further details will be given in the intervention-specific protocol.

Table 6.3: Stratification factors of EU-SolidAct

EU-SolidAct Part A Moderate disease	EU-SolidAct Part B Severe disease
- Centre - Need for oxygen at baseline (yes/no)	- Centre - Previous entry in Part A (yes/no) - High flow oxygen or NIV vs mechanical ventilation/ECMO at baseline

Stratification by emerging treatment in SoC should be considered when these arise. Participants in EU-SolidAct Part A may undergo a second randomization at any point after being first randomized if they deteriorate and switch from moderate to severe/critical disease (EU-SolidAct Part B).

The second randomization will proceed as follow:

1. The informed consent form will cover both Part A and B. Thus, there will be no separate consent for the second randomization.

2. When a participant in Part A progresses and is eligible for Part B, the participant is screened against all intervention-specific protocols eligibility criteria. If the participant is eligible for at least one of the Part B interventions, the participant is randomised to one of the available interventions plus SoC or SoC alone.
3. The allocated treatment in Part A is continued unless instructed otherwise in the corresponding intervention-specific protocol, or by the discretion of the treating physician.

If one or more of the active drug treatments are not available at the hospital, opted out by the hospital or contraindicated for a specific participant, then this fact will be recorded via the web-based form prior to randomization; random allocation will then be between the remaining arms. If no treatments are available and suitable, the participant cannot be randomized and must be withdrawn from the trial.

This study could include both open-label and placebo-controlled interventions. In the case of open-label interventions, all investigators, site pharmacists, study nurses, sponsor safety staff and participants will be unmasked and aware of the treatment allocation throughout the study. However, they will be unaware of aggregate outcomes during the course of the study.

6.4. Study Intervention Compliance

This study is being conducted in hospitals. Treatment is administered at site and 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. Deviation(s) from the prescribed dosage regimen should be recorded via the web-based form. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

Further details are given in the intervention-specific sub-protocols.

6.5. Dose Modification

There are generally little clinical safety or pharmacokinetic data available for emerging diseases allowing modification in the recommended and approved dose of the study treatments for human.

Further details will be given in the intervention-specific sub-protocols.

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

Details given in the intervention-specific sub-protocol if applicable.

6.7. Treatment of Overdose

Details given in the intervention-specific sub-protocol if applicable.

6.8. Concomitant Therapy

Any medication or vaccine (including over the counter or prescription medicines and/or recreational drugs) at the time of enrolment or received during the study must be recorded along with:

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

The national Coordinating Investigator should be contacted if there are any questions regarding concomitant or prior therapy.

If it is not feasible to collect all concomitant medication due to exhaustive medication lists, the priority should be to register at least changes in concomitant medication that could interfere with safety or efficacy of the tested drug, as specified in the intervention-specific sub-protocol.

Details on concomitant therapy including prohibited therapies, rescue medication, recording of vitamins and/or herbal supplements are given in the intervention-specific sub-protocol if applicable.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study are detailed in Appendix 1.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue the study intervention. If the study intervention is permanently discontinued, the participant will remain in the study to be evaluated at all follow-up visits scheduled for the study. See section 8 for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed. The date and reasons for stopping intervention will be clearly stated on the participant's electronic Case Report Form (eCRF) and source document.

Intervention-specific stopping criteria (e.g., liver biochemistry abnormalities, cardiac changes, pregnancy etc). are given in the intervention-specific sub-protocol if applicable.

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. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See section 8. for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued from the study intervention and the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the study site records.

There will be no replacements of withdrawn patients.

7.3. Lost to Follow-Up

Lost to follow-up should not occur during the hospitalization period. However, after discharge from the hospital, participants could be lost to follow-up.

A participant will be considered lost to follow-up if he/she is unreachable for the study site per telephone directly to the patient or relatives (for at least two days), or by written correspondence, after hospital discharge and until end of study.

8. Study Assessments and Procedures

General instructions

Study procedures and their timing are summarized in Schedule of Assessments (SoA, section 1.2). Protocol waivers or exemptions are not allowed.
Safety concerns should be discussed with the sponsor or sponsor representative immediately upon notice, to determine if the participant should continue or discontinue the study intervention.
Adherence to the study design requirements, including those specified in the SoA, is essential and required for good study conduct.

- All assessments in level I (blue background colour in SoA table) are mandatory.
- Level II assessments (green background colour) include biobanking (necessary for virological outcomes) and are encouraged whenever possible.
- Level III assessments (grey background colour) include add-on studies on extended biobanking, imaging organ function and PROM. The accurate and complete description of what is to be measured and monitored will be defined by the units that run level III. This level will form the basis of sub-studies and is optional but should be performed according to common standardised protocols and standard operating procedures.

Screening assessments:

Screening for inclusion should be performed as soon as possible after hospitalisation. For participants progressing in Part A, screening for Part B should be done as soon as possible after progression. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the informed consent form may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and are performed the same day as screening or within 24 hours for baseline.

The following assessments should be performed to determine eligibility requirements as specified in the inclusion and exclusion criteria:

- Register and review the positive SARS-CoV-2 test result
- Register and review SpO_2 measurement
- Register and review need for oxygen therapy, see section 8.1.2.
- Register and review prior and concomitant medication for allergies or contraindications to investigational medicinal products according to intervention-specific sub-protocol(s) eligibility criteria
- Register and review medical history for contraindications according to intervention-specific sub-protocol(s) eligibility criteria

- Register and review any other information according to intervention-specific sub-protocol(s) eligibility criteria

Once the patient is found to be eligible, go through the consent form with the patient and obtain informed consent.

Baseline procedures (Day 1):

After screening and obtaining informed consent, enter baseline data in the eCRF and randomize the patient (see section 6.3. for randomization procedure) as soon as possible after screening.

If participant is eligible for Part A include in Part A, if eligible for Part B include in Part B.

If not already collected as part of the intervention-specific sub-protocol assessment of eligibility criteria, collect the following information:

- Focused on medical history, including the following information:
  - Day of onset of COVID-19 symptoms
  - Day of hospitalization
  - History of chronic medical conditions and risk factors related to developing a severe COVID-19 disease: chronic pulmonary diseases (obstructive pulmonary disease, interstitial pulmonary disease, other), cardiovascular diseases (heart failure, coronary artery disease, other), kidney disease, liver disease, diabetes mellitus, hypertension, smoking, cancer, autoimmune diseases, immunodeficiency (HIV infection, primary immunodeficiency, other), neurological diseases
  - History of vaccination against COVID-19
  - History of prior infection
- Demographics (age, sex, country of birth)
- Register SoC details
- Register other concomitant medication than SoC if not already collected during screening. See details in section 6.8.
- Clinical Safety Laboratory Tests including pregnancy test for women of childbearing age, see section 8.3.5 and Appendix 2.
  - if more than 24 hours since screening, repeat blood samples for safety before first dose of study medication
  - If ferritin and procalcitonin are not routinely gathered at a site for clinical follow-up of the patient, these analyses should be prioritized at baseline, D8 and D15.
- Obtain vital signs including height in cm and weight in kg, see section 8.3.2.
- Collect data on oxygen therapy, see section 8.1.2.
- Register WHO COVID-19 disease progression scale (0-10), see section 8.1.1.
- Details of study treatment administration according to intervention-specific sub-protocol

Assessment until discharge:

Participants will be assessed daily for AE and SAE while hospitalized, see section 8.6.

- Note AE and SAE in the eCRF upon notice
- Safety concerns should be discussed with the sponsor to determine if the participant should continue or discontinue study intervention

The following clinical data will be noted in the eCRF obtained on Days 3, 5, 8 (± 1 day), and thereafter weekly (Day 15 ± 3, Day 22 ± 3, Day 29 ± 3, etc.)

- Obtain vital signs, see section 8.3.2.
- Collect data on oxygen therapy, see section 8.1.2.
- Register WHO COVID-19 disease progression scale (0-10), see section 8.1.1.
- Review concomitant medication and note changes in the eCRF
- Draw and register blood samples for clinical safety laboratory tests (see section 8.3.5.)
    - If ferritin and procalcitonin are not routinely gathered at a site for clinical follow-up of the patient, these analyses should be prioritized at baseline, D8 and D15.

Details of study treatment adherence and administration will be given in the intervention-specific sub-protocol.

For level II of commitment:

Blood samples and naso/oropharyngeal swabs should be obtained at baseline (D1) before drug intervention starts. In addition, blood samples will be obtained on Days 3, 8, 15 and 22 (all ± 1 day), and naso/oropharyngeal swabs on Days 3, 8, 15 (all ± 1 day), as long as the patient is hospitalized.

Day 15 ± 3, 29 ± 3, 61 ± 7:

If the patient has been discharged, the following information is gathered by phone or by reviewing the patient records:

- Alive or dead

If alive, recovery status

- Readmitted to hospital
- If readmitted, date of readmission and reason for readmission. Report as SAE.
- Review concomitant medication
- Adverse events by open-ended and non-leading verbal questioning of the participant

Follow-up assessment at Day 91 ± 14:

A follow-up assessment by phone will be performed on Day 91 (± 14 days):

- Alive or dead

If alive, recovery status

- Readmitted to hospital
- If readmitted, date of readmission and reason for readmission. Report as SAE.
- Review concomitant medication
- Adverse events by open-ended and non-leading verbal questioning of the participant
- Check that patient has answered online patient reported outcome measure (the Oslo COVID-19 QLQ-PW80)

Discharge visit/Early discontinuation visit

- Register WHO COVID-19 disease progression scale (0-10), see section 8.1.1.
- Review concomitant medication and adverse events
- If discharged, register whether the patient is discharged to home, home care facilities, other hospitals or other institutions or locations
- If early discontinuation, register reason for early discontinuation
- Participant withdrew consent to further participation
- Participant withdrawn by the investigator for safety, behavioural or compliance reasons including lost to follow-up
- Death
- For early discontinuation, answer online patient reported outcome measure (the Oslo COVID-19 QLQ-PW80).

8.1. Core Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (section 1.2). Details of the efficacy assessments are provided below.

8.1.1. WHO COVID-19 disease progression scale

Table 8.1 Modified WHO clinical progression scale

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* Hospitalised; need of oxygen by mask or nasal prongs	4 5
Hospitalised: Severe disease	Need of oxygen by NIV or high flow, re-breather mask or SpO2<90% on room air or 90-94% with a downwards trend and/or signs of respiratory distress**	6
Hospitalised: Critical disease	Intubation and mechanical ventilation, $pO_2/ FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$ Mechanical ventilation $pO_2/FIO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO	7 8 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[1] 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[2]. 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[3] 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.

8.1.2. Oxygen therapy

For all patients included in the study, oxygen saturation (%) shall be measured according to the hospital's regular routines and respiratory rate (RR) shall be counted and registered.

- Patients not receiving oxygen (WHO score 4):
  - Oxygen saturation and RR shall be registered.
- Patients receiving oxygen by nasal prongs and face mask (WHO score 5):
  - Oxygen saturation, RR and numbers of litres of oxygen provided (l/min) and method of oxygen delivery, shall be registered.
- Patients receiving high flow oxygen, NIV or face mask with reservoir (WHO score 6):
  - Oxygen saturation, numbers of litres of oxygen provided (l/min), RR and fraction of inspired oxygen (FiO_2) shall be registered
- Patients that are intubated and on mechanical ventilation (WHO score 7-9):
  - Oxygen saturation and fraction of inspired oxygen shall be registered unless on ECMO.
- Patients on ECMO (WHO score 9):
  - No further information on oxygen therapy will be given.

The SpO_2/FiO_2-ratio will be calculated from registrations of SpO_2 and FiO_2 in patients receiving high flow oxygen, NIV or mechanical ventilation. For other patients, the FiO_2 will be approximated from supplementation of oxygen as described in the table below.

Table 8.2 Estimated FiO_2 % by supplementation of oxygen

Method	O_2 flow, l/min	Estimated FiO_2, %
Nasal Cannula	1	24
	2	28
	3	32
	4	36
	5	40
	6	44

Face mask	1*	24
	2*	28
	3*	32
	4*	36
	5	40
	6	50
	7	55
	>7	55
Face mask with reservoir	4	40
	5	50
	6	60
	7	70
	8	80
	>8	85

8.2. Modular Efficacy Assessments

8.2.1. Viral clearance

Viral load decay will be assessed from oropharyngeal swabs included in the biobank according to a standard operating procedure (level II), as detailed in section 8.4.

8.2.2. Biochemical parameters

Biochemical parameters for safety and inflammatory outcomes are detailed in the SoA (section 1.2) and Appendix 2. In addition, plasma, serum and full blood samples will be biobanked (level II and III) for analysis of SARS-CoV-2 antibodies and exploratory markers as detailed in section 8.4.

8.2.3. Patient reported outcome measures (PROMs)

The Oslo COVID-19 Quality of Life Questionnaire Provisional Weekly 80 item version (The Oslo COVID-19 QLQ-PW80 ®) will be used to collect the patient's reported outcome (PRO) at Day 91. The responses will be collected using a web-based form.

This COVID-19 specific questionnaire has been developed since March 2020 according to international guidelines[4] based on literature review, and interviews with health care professionals and patients in seven countries. It covers the perspectives of patients with COVID-19 disease related to their symptoms, functioning, concerns and general health status.

Most items have a 4-point verbal rating scale (not at all, a little, quite a bit and very much), while items 79 and 80, have a 7-point modified visual analogue rating scale (ranging from very poor to excellent). The recall timeframe is 7 days, and it takes 15-20 minutes to fill in the questionnaire. A daily version is available. This provisional version of the questionnaire will be psychometrically tested in an international validation study (NCT04740372) involving more than 10 countries, and the scoring manual and description of subscales will be available in spring 2021.

All patients will be asked to fill in the questionnaire at Day 91 (± 14 days). In addition, institutions on level III may be asked to participate in an extended PROM-protocol, involving assessments at day 1 and at discharge. Health care professionals may read the questions for the patient, but the patient should respond themselves.

8.3. Safety Assessments

8.3.1. Physical examination

Physical examination will be performed according to local procedures. Any new findings will be recorded as medical history if found before randomization or as adverse events if discovered after randomization.

8.3.2. Vital signs

Vital signs collection will be performed according to local procedures

- Body temperature (ºC)
- Pulse rate (beats/min), regular/not regular
- Blood pressure (mmHg), diastolic and systolic pressure
- Respiratory rate (breath/min)
- Oxygen saturation (%)

8.3.3. Electrocardiograms

Electrocardiograms (ECGs) will be performed according to local procedures. If registered, the following will be registered from ECG machine reading:

- Heart rate
- PR
- QRS
- QT
- QTc

8.3.4. Other clinical assessments

The use of vasopressors, dialysis, continuous renal replacement therapy, prone positioning (hours/day) and exact recording of pO_2- and FiO_2-values will be registered at the assessment timepoints when indicated.

8.3.5. Clinical safety laboratory tests

See SoA table (section 1.2) as well as Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the medical records.
Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition. Abnormal laboratory findings associated with adverse events of special interest (AESI) as detailed in the intervention-specific sub-protocols should be considered clinically significant unless judged otherwise by the investigator.
All laboratory tests with values considered clinically significantly abnormal during participation in the study or within five half-lives after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified, and the sponsor notified.
- All protocol-required laboratory tests, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (section 1.2).
- If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically relevant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.3.6. Pregnancy testing

Pregnancy test by human chorionic gonadotropin (HCG) levels in blood or urine should be performed at screening or baseline before receiving first dose of investigational medicinal product.

8.3.7. Suicidal ideation and behaviour risk monitoring

Detailed in the intervention-specific sub-protocol if applicable.

8.4. Biomarkers

Biobanking will be performed according to procedures described in Appendix 2 (level II and III), and samples taken at baseline (D1), Day 3, 8, 15 and 22 (all ±1). Depending on research questions, the following volumes of blood will be obtained, as further detailed in the IMP specific protocol and standard operating procedure (SOP):.

- Serum: 1.5-2 mL (3-4 mL blood)
- EDTA Plasma: 1.5–2 mL (3-4 mL blood)
- Citrate Plasma: 1-2 mL (2-3 mL blood)
- Whole blood: 2 mL

Naso/oropharyngeal swab will be taken at baseline, Day 3, 8 and 15 (all ±1).

Sponsor may store samples for up to 25 years after the end of the study. 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.

8.5. Imaging

Details of imaging protocols will be developed for add-on sub-studies (level III).

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

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

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

Table 8.3: Definitions of Adverse Events

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

New fact**	Any safety data that could modify significantly the evaluation of the benefit/risk ratio of the IMP or the clinical trial, likely to affect the safety of participants or that could modify the IMP administration, the trial documentation or the conduct of the trial, or to suspend, interrupt or modify the protocol or similar trials.

** EXCEPTIONS: the following events are not considered as SAE requiring immediate reporting to the sponsor:*
-the participant is formally admitted to a hospital for medical reasons with no seriousness criterion and does not require overnight hospitalization
-elective or previously scheduled surgery or medical treatment;
-hospitalization for social or administrative reasons;
-pre-existing diseases or present conditions detected prior to start of study drug administration and which do not worsen.

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

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

- All AEs and SAEs will be collected from the signing of the informed consent form (ICF) until the follow-up visit at the time points specified in the SoA (section 1.2.).
- Except disease-related events as defined in section 8.6.9. and exceptions mentioned above, all SAEs will be recorded and reported to the sponsor and the delegated designee, Inserm-ANRS Pharmacovigilance Office, immediately and under no circumstance should this exceed 24 hours, as indicated in the trial Safety Management Plan (SMP). The investigator will submit any updated SAE data within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor and the delegated designee, Inserm-ANRS Pharmacovigilance Office.

8.6.2. Method of detecting AEs and SAEs

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

8.6.3. Follow-up of AEs and SAEs

- After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (AESI, as defined in section 8.6.11) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in section 7.3.).
- Follow-up period duration after the last dose administered will be determined based on IMP's half-life and toxicity profile.

8.6.4. Assessment of AEs and SAEs

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

Seriousness

For any adverse event, the investigator must determine whether the event meets one or more of the seriousness criteria described in Table 8.3.

Severity (grading)

All AEs and SAEs will be assessed for severity, according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events, version 2.1 (July 2017), see Appendix 9.

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

Table 8.4 AE severity scale (not included in the DAIDS table)

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

Causality

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

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship

between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate aetiology has been established.

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

Assessment on expectedness is usually done by the sponsor.

8.6.5. Recording and reporting of AEs and SAEs

- All information on AEs (non-serious and serious) and pregnancies should be recorded on the appropriate eCRF (eCRF completion will be detailed into eCRF user manual).
- Any AE that meets the definition of an SAE or AE of special interest (AESI, see section 8.6.11) must be notified immediately (within 24 hours of site awareness) on the corresponding SAE form.
- In case of eCRF unavailability, investigators should report all SAEs using the paper CRF form, dated and signed, and transmit it to the Sponsor and the delegated designee, Inserm-ANRS Pharmacovigilance Office, by fax or via a secured website for data transfer.

8.6.6. Regulatory reporting requirements for SAEs

- Complete procedure is described in the trial Safety Management Plan (SMP).
- On behalf of the Sponsor, the Trial Safety Group (TSG), including Inserm-ANRS Pharmacovigilance Office staff, the medical officer (or an internal or external medically qualified delegate, mainly clinician) of Oslo University Hospital (OUH) and Clinical Trials Unit (CTU) representative, will review all SAE reports received.
- The role of the TSG will be detailed in the SMP.
- In case of lack of consensus within the TSG regarding the causality of the event, the final decision for the initial reporting to the applicable regulatory authorities will lay with the Inserm-ANRS Pharmacovigilance Office.
- The Inserm-ANRS Pharmacovigilance unit is responsible for assessing the causality and expectedness (using the applicable Reference Safety Information e.g., as given in the IB or SmPC) of all SAE reports received, in relation to the IMP, research procedures and concomitant medication (e.g., drug-drug interactions).
- All Suspected Unexpected Adverse Reactions (SUSARs) must be reported, within the legal timeframe, by the Inserm-ANRS Pharmacovigilance unit to the European

Medicine Agency (EudraVigilance, EMA), the National Competent Authority of the concerned Member State and concerned Ethics Committees according to local requirements.

- Fatal and life-threatening SUSARs must be reported within 7 days, other SUSARs within 15 days. If regulatory timeframes differ from the above timelines in participating countries, then local requirements should take precedence and be adhered to.
- The Inserm-ANRS Pharmacovigilance unit will immediately inform the National Competent Authorities of each member state and concerned Ethics Committees of safety data or safety issues that might alter the current benefit-risk assessment of the trial and may be relevant in terms of participant safety.
- Once a year, the Inserm-ANRS Pharmacovigilance unit will submit to the National Competent Authority and the Ethic Committee of each Member State a Development Safety Update Report (DSUR), according to applicable laws and regulations.

8.6.7. Pregnancy

- Pregnancy during hospitalisation is highly unlikely, and no specific procedures will be undertaken to discover pregnancies during hospitalisation except for the pregnancy test at screening.
- Depending on the IMP safety profile, pregnancy occurrence involving the participant's partner will be also recorded.
- Details of all pregnancies, including outcome, neonate information and any post-study pregnancy-related SAE, will be collected after the start of study intervention and as long as the patient is exposed to drug effects (detailed in the intervention-specific sub-protocol).
- Investigator will record pregnancy information on the appropriate form and submit it to the sponsor and the delegated designee, Inserm-ANRS Pharmacovigilance Office, within 24 hours of learning of the female participant pregnancy.
- While pregnancy itself is not considered to be an AE, any pregnancy complication, abnormal outcome (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) or elective termination of a pregnancy for medical reasons will be reported with the same timeframe as an SAE.
- Further details are described in the trial Working Instructions.

8.6.8. Cardiovascular and Death Events

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

investigator in the eCRF if known. In addition to the declaration of death, an SAE declaration should be recorded in the eCRF.

Handling of cardiovascular events will be detailed in the intervention-specific sub-protocol

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

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

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

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

The DREs are given in Section 10.4 Appendix 4.

Some of these events can be recorded as AESI, depending on the IMP profile.

8.6.10. Solicited and unsolicited AEs (applicable for injectable IMPs)

- Injectable drugs are associated with a number of well-characterized reactions referred to as ‘solicited adverse events’ (see Appendix 3), including local and systemic manifestations.
- By opposition, unsolicited AE represents signs and symptoms outside the pre-defined checklist reported by the participant/participant’s legally authorized representative.
- Further details on handling of solicited and unsolicited AEs will be given in investigator-specific subprotocol.

8.6.11. Adverse Events of Special Interest (AESI)

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

Details will be given in the intervention-specific sub-protocol if applicable.

8.6.12. Potentially relevant risks of the research procedures and IMP, and management guidelines in case of Adverse Event

Part to be updated based on information provided by marketing authorization holders regarding the safety language of AE management, for the guidelines that cannot be captured in the specific risk/benefit assessments of the intervention-specific sub-protocol and 6.5 sections.

8.7. Pharmacokinetics

Details will be given in the specific sub-protocols if applicable.

8.8. Genetics

Genetic analyses are not planned in the core platform. If genetic analyses are relevant and indicated for a particular IMP, details on sample collection, storage and analyses will be detailed in the IMP-specific sub-protocol, and in that case, this will be specified in the informed consent form.

8.9. Immunogenicity Assessments

Immunogenicity is not evaluated in this study but could be included in IMP-specific sub protocols if indicated.

8.10. Medical Resource Utilization and Health Economics Parameters

Medical resource utilization and health economic parameters are not evaluated in this study.

9. Statistical Considerations

The statistical analysis plan will be finalized prior to database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1. Statistical Hypotheses

This master protocol opens for testing a wide range of hypotheses, including superiority and non-inferiority. The primary phase 3 trial objective includes demonstrating that study intervention is superior or non-inferior to concurrent comparator in achieving disease progression-free at day 15 for EU-SolidAct Part A, death at day 61 for EU-SolidAct Part B.

For phase 2 trials the primary objective includes exploring if the study intervention is superior to concurrent control on respiratory dysfunction as measured by the SF-ratio at day 5.

Non-inferiority hypotheses will generally not be tested because most explorative trials will want to focus on superiority at least as the primary hypothesis.

In the case of non-inferiority testing, we set the default non-inferiority margin at 3% risk difference both for Part A (occurrence of disease progression) and B (occurrence of death). The argument for this is that a relative risk reduction of 0.8 (lower bound of the confidence interval) is in the Solidarity trial[5] enough to claim no clinically relevant effect of remdesivir and lopinavir on mortality. With an assumed overall rate of 15%, a 0.8 relative risk reduction corresponds to 3% absolute risk reduction. The final margin will be specified in the intervention-specific sub-protocol in case a non-inferiority hypothesis is tested.

EU-SolidAct Part A (Phase 3)	EU-SolidAct Part B (Phase 3)	EU-SolidAct (Phase 2)
Null superiority hypothesis: Intervention is not different from concurrent control on occurrence of disease progression at day 14.	Null superiority hypothesis: Intervention is not different from concurrent control on occurrence of death at day 60.	Null superiority hypothesis: Intervention is not different from concurrent control on respiratory dysfunction as measured by the SF-ratio at day 5.
Null non-inferiority hypothesis: The difference in occurrence of disease progression at day 14 is at least 3% in favour of concurrent control.	Null non-inferiority hypothesis: The difference in occurrence of disease progression at day 14 is at least 3% in favour of concurrent control.	NA

Superiority

H0: $\pi_A = \pi_B$ against Ha: $\pi_A \neq \pi_B$

where π_A and π_B are the probability of primary endpoint occurrence when treated with the intervention therapy (A) or concurrent control (B).

Operationally the hypotheses will be evaluated by 2-sided tests.

Non-inferiority

H0: $\pi_A - \pi_B \geq 0.03$ against Ha: $\pi_A - \pi_B < 0.03$

Operationally the hypothesis will be evaluated by the two-sided 95% confidence interval with non-inferiority claimed if the interval excludes a 3% difference in favour of the concurrent control treatment.

9.1.1. Multiplicity adjustment for multiple arms

The present study is a multi-arm study with multiple experimental treatment arms and a single control arm. As experimental arms are put together in a single study, because of logistical reasons, no multiplicity adjustment is required.

9.2. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	**Description**
Full analysis set	• All randomized participants. Participants will be included in the analyses according to the planned randomized intervention.
Safety analysis set	• All participants who are exposed to a study intervention. Participants will be analysed according to the intervention they actually received.

The full analysis set is used to analyse endpoints related to the efficacy objectives and the safety analysis set is used to analyse the endpoints and assessments related to safety.

The following data points sets are defined:

Defined Data Points Sets	**Description**
DPS1	• All observed data will be included in the analysis set.

Defined Data Points Sets	Description
DPS2	• For participants who discontinue study intervention and/or receive rescue therapy, post-discontinuation or post-rescue observations will not be included.

Full analysis set and DPS1 are used to estimate the primary endpoints and the secondary endpoints for secondary core objective.

Full analysis set and DPS2 are used to for sensitivity analyses.

Safety analysis set and DPS1 are used to present safety data.

9.3. Statistical Analyses

9.3.1. General considerations

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation (SD), 1st quartile, median, 3rd quartile, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical variables.

The number of participants and the flowchart of the study will be presented. The period of enrolment and the total number of participants screened to be included in the study will be presented. The number of ineligible participants and the total number of randomized participants will be presented. The number of participants who never receive the study intervention will also be presented by treatment group and those who were included in the full analysis set and the safety analysis set will be presented.

Baseline is considered as the day 1 visit and the baseline data is data collected just before intervention at day 1.

For all outcomes, comparisons will be made between each study intervention group and the control group. The comparisons between each study intervention and the control group will be tested using Fisher's exact test or Pearson chi-square test for categorical variables and Man-Whitney test for continuous variables. All p-values are two-sided with a significant level set at 0.05.

9.3.2. Primary endpoint(s) analysis

The primary endpoint for Part A is the occurrence of disease progression, defined as a progression of disease state from moderate (WHO scores 4-5) to severe/critical (WHO score 6-9) or death within 14 days, and the primary endpoint for Part B is the occurrence of death within 60 days. The Kaplan-Meier estimate will be used to estimate the disease progression rates. Kaplan-Meier curves will be plotted for the primary endpoints. We will calculate the Cochran-Mantel-Haenszel treatment difference and the 95% associated confidence interval in

the percentage of participants with disease progression (i.e., study intervention group response rate minus control group response rate) adjusted for the stratification factors of the randomization. The analyses may also be adjusted for other prognostic factors as sensitivity analyses. If the primary analysis adjusted for centre becomes unstable or non-identifiable due to small strata, adjustment by country will be done instead. The effect of study intervention will also be assessed using a time-to-event regression model with treatment group and adjustments for stratification factors.

The validity of the proportionality assumption will be evaluated and tested. Efforts to minimize lost to follow-up will be considerable. However, small amounts of missing data may occur. In such cases, participants without final outcome data will be censored at the date of last information. Sensitivity analyses will be conducted assuming all participants lost to follow-up progressed in both arms at time of censoring (worst case imputation), or none progressed and did not meet the primary endpoint (best case imputation). These sensitivity analyses will be fully defined in the statistical analysis plan (SAP).

9.3.3. Secondary endpoint(s) analysis

The occurrence of disease progression, defined as a progression of disease state from moderate (WHO score 4-5) to severe/death (WHO score 6-10) or from severe (WHO score 6-9) to death within 28 days will be estimated using Kaplan-Meier estimates. The same methodology will be used for these endpoints than the one described in section 9.3.2.

The median 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 will be estimated using the Kaplan-Meier method. The log-rank test will be used to compare each study intervention and the control survival functions. Participants will be censored at the date of lost to follow-up or at the 90^{th} day after randomization when the participant has not achieved the event before. The effect of study intervention on the time to sustained recovery will also be assessed using Cox regression model with treatment group and adjustments for stratification factors.

The median time from randomization to first hospital discharge within 90 days will be analysed with the methodology described above.

Continuous endpoints will be analysed using analyses of covariance adjusted by stratification factors in the randomization and baseline value if applicable, or appropriate (generalised) linear mixed model with random intercept and possibly slope for repeated measures.

For the analysis of disease state on a 5-point scale a proportional odds model will be used. The hypothesis test will be based on a test of whether the common odds ratio for treatment is equal to one. Model fit will be evaluated using a goodness-of-fit likelihood ratio test. The distribution of severity results will be summarized by treatment arm as percentages. The validity of the proportionality assumption will be evaluated and tested.

9.3.4. Exploratory/subgroup analysis

Subgroup analyses for the primary endpoints will be conducted to assess consistency of the intervention effect across the following subgroups:

- Participating country
- Immediate entry in the severe group: yes vs no (only EU-SolidAct Part B)
- Age group: < 65 vs ≥ 65 years
- Sex: female vs male
- Duration of symptoms prior to enrolment (≤ 7 days, 8-14 days, >14 days)
- Prior vaccination for COVID-19: yes vs no
- Mechanically ventilated/on ECMO vs not at baseline

In addition, subgroup analyses on use of certain therapeutic drug components of the standard of care will be considered, especially if the standard of care changes during the trial.

If the number of participants is too small (less than 10%) within a subgroup, then the subgroup categories may be redefined before locking the database. Further details on the statistical analysis or additional subgroup analyses will be provided in the SAP.

9.3.5. Safety analyses

Safety endpoints include serious adverse events (SAEs) leading to study treatment discontinuation and death. SAEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). SAEs leading to study treatment discontinuation and death will be summarized with number and proportion. More details on the statistical analysis will be provided in the SAP.

9.3.6. Other analyses

All outcomes relative to the modular secondary objective will be summarized with the appropriate descriptive statistic. Outcomes will be compared between each study intervention group and the control using the appropriate statistical test. More details on the statistical analysis will be provided in the SAP.

9.4. Interim Analysis

No formal interim analysis for efficacy will be done. However, an independent data monitoring committee (DMC) consisting of independent scientists not otherwise involved in the trial has been appointed and will review the data regularly during the study for safety and scientific integrity and will make recommendations to the sponsor regarding the stopping of an intervention for harm or for futility. The frequency of the committee data review meetings and other aspects such as stopping rules will be detailed in a separate charter and possibly in the statistical analysis plan depending on the safety profile of the study intervention(s). There will only be one DMC overseeing all trial arms, and this committee will communicate with the DMCs of other corresponding platform trials to exchange information. The level of monitoring will depend on the safety profile of the intervention.

9.5. Sample Size Determination

9.5.1. Phase 3 General Considerations

In the DisCoVeRy (NCT04315948) and Nor-Solidarity (NCT04321616) trials, the proportion of patients with moderate disease at inclusion in achieving disease progression at day 14 and those with severe disease in achieving death at day 60 are shown in

Table *9.1* below.

Table 9.1 Event rate on SoC patient in Discovery and Nor-Solidarity trials

	Discovery	**Nor- Solidarity**	**Nor-Solidarity**
	(included: July-October 2020)	(included before 1st July 2020)	(included after 1st July 2020)
14-day rate of progression in moderate patients	13.1% [7.5-22.4]	13.5% [9.8-22.8]	20.5% [7.6-31.5]
28-day mortality in severe patients	9.7% [3.7-24.3]	5.1% [1.4-8.8]	9.1% [0.2-17.2]

According to numbers published by Santé publique France on December 29, 2020 there were 770 deaths out of 4411 (17.5%) patients admitted in ICU in France, suggesting a slightly higher rate compared to the autumn numbers in Discovery and Nor-Solidarity.

Based on these data, we assumed a cumulative probability of disease progression of 15% at 14 days in the SoC group for Part A (moderate disease) and mortality at 15% at 60 days for Part B (severe disease).

The sample size and power calculations were made using the statistical software package nQuery Advanced, using the two sample Log-Rank test module (Version 8.6.1.0), based on the primary efficacy estimand and its endpoint. The results are presented in Table 9.2 and Table 9.3 below.

Assuming a 15% progression for the SoC group in Part A and a 2-sided type-1 error rate of 5% and using the Log-Rank test, the study will have over 90% power under a sample size of 924, 521 and 378 per arm to detect a treatment difference of 5%, 6.5% and 7.5% respectively. We hypothesize that a treatment difference in progression rates at day 14 of 5% seems achievable. Therefore, we plan to enrol 950 participants per arm, considering potential dropouts before the assessment of the primary endpoint at day 14.

Table 9.2: Sample size calculation for EU-SolidAct Part A superiority trial

	Scenario 1	**Scenario 2**	**Scenario 3**
Outcome (Disease progression at day 14)			
Hypothesized event rate with SoC	15%	15%	15%
Expected event rate with intervention	**10%**	**8.5%**	**7.5%**
Type I error (two-sided)	0.05	0.05	0.05
Power	90%	90%	90%
Hazard ratio (HR)	0.648	0.547	0.48
N per group	**924**	**521**	**378**
Total number of events required	**224**	**115**	**78**

Similarly, assuming a 15% mortality for the SoC group in Part B and a 2-sided type-1 error rate of 5% and using the Log-Rank test, the study will have over 90% power with a sample size of 924, 521 and 378 per arm to detect a treatment difference of 5%, 6.5% and 7.5% respectively. We hypothesize that a treatment difference in mortality rates at day 61 of 5% seems achievable. Therefore, we plan to enrol 950 participants per arm, considering potential drop-outs before the assessment of the primary endpoint at day 61

Table 9.3: Sample size calculation in EU-SolidAct Part B superiority trial

	Scenario 1	**Scenario 2**	**Scenario 3**
Outcome (Death at day 61)			
Hypothesized event rate with SoC	15%	15%	15%
Expected event rate with intervention	**10%**	**8.5%**	**7.5%**
Type I error (two-sided)	0.05	0.05	0.05
Power	90%	90%	90%
Hazard ratio (HR)	0.648	0.547	0.48
N per group	**924**	**521**	**378**
Total number of events required	**224**	**115**	**78**

In case combination therapies are assessed by factorial design, the main assumption will be that no interaction exists between the treatments and therefore no modification of the sample size will be necessary. If synergies or effect modifications between treatments are of interest, the intervention-specific sub-protocols will define the sample size needed for detecting the interaction effect.

For a non-inferiority trial, assuming a 15% primary endpoint rate (progression in Part A and mortality in part B) in the active comparator arm, a non-inferiority margin of 3%, a 95%

confidence interval of the effect size and a 90% power, we need to enrol 3000 participants per arm

9.5.2. Phase 2 General Considerations

Based on unpublished data from 8500 patients with COVID-19 as described in the RECOVERY protocol (https://www.recoverytrial.net/files/recovery-protocol-v14-0-2021-02-15.pdf), assuming a mean (standard deviation) SF-ratio of 3.3 (1.7) at day 5, and a correlation between an individual's baseline and day 5 SF-ratio of 0.5, randomization of 400 participants will provide 90% power at a two-sided 5% significance level to detect a difference in SF-ratio ratio of 0.5 (the chosen minimum clinically meaningful difference [which is similar to the difference in 1 point on the WHO ordinal scale]), even if 10% of participants discontinue study treatment before day 5.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
    - Applicable ICH Good Clinical Practice (GCP) guidelines
    - Applicable laws and regulations

The protocol, protocol amendments, ICF, investigator's brochure and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant, their legally authorized representative (LAR) or relative and answer all questions regarding the study.

If the patient is unable to give consent due to the severity of their medical condition (e.g., acute respiratory failure or need for immediate ventilation) or prior disease, then consent may be obtained from a close relative acting as the participant's designated representative or, if a suitable relative is not immediately available, an independent doctor. Further consent will then be sought with the participants if they recover sufficiently or with the designated representative at the earliest opportunity (continuation consent).

If the patient is unable to give consent due to the severity of their medical condition or if hospital visiting rules or parental infection mean a relative or legally authorized representative cannot be physically present, witnessed consent may be obtained over the telephone or web video link.

Participants must be informed that their participation is voluntary. Participants, their LAR or their designated representative (relative) will be required to give a statement of informed consent that meets the requirements, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that informed consent was obtained before the participant was enrolled in the study, the nature of consent (participant, LAR, designed representative or independent doctor), and the date the consent was obtained. The authorized person obtaining the informed consent must also sign the ICF. In case of urgent oral consent is obtained it should be written in medical record. This refers to countries in which according to their national drug law oral consent under such circumstances are allowed to be given.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study if relevant.

A copy of the ICF must be provided to the participant, their legally authorized representative or their designated representative. The ICF (including patient information and data protection statement) will be translated into the languages of the participating countries in this trial.

Participants who are rescreened are required to provide a new informed consent.

The ICF will contain a separate section that addresses the use of remaining samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be informed that they are free to refuse participation and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow remaining specimens to be used for exploratory research. Participants who decline to participate in this additional research will not provide this separate signature.

10.1.4. Data protection

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

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

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

10.1.5. Committees structure

Trial Steering Committee

The Trial Steering Committee is responsible for:
(i) Agreement of the final Protocol and the Data Analysis Plans;
(ii) Reviewing progress of the study and, if necessary, deciding on Protocol changes;
(iii) Review and approval of study publications and sub-study proposals;
(iv) Reviewing new studies that may be of relevance.

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).

Central Coordinating Office (CCO)

The CCO is responsible for the overall coordination of the study, including:
(i) Study planning and organisation of Steering Committee meetings;
(ii) Ensuring necessary regulatory and ethics committee approvals;
(iii) Development of Standard Operating Procedures and computer systems;
(iv) Monitoring overall progress of the study;
(v) Provision of study materials to regional or local coordinating centres (RCCs/LCCs);
(vi) Monitoring and reporting safety information in line with the protocol and regulatory requirements;
(vii) Dealing with technical, medical and administrative queries from LCCs.

Regional/Country specific Coordinating Centre (RCC)

The RCCs are responsible for:
(i) Ensuring necessary regulatory and ethics committee approvals;
(ii) Provision of study materials to LCCs;
(iii) Dealing with technical, medical and administrative queries from LCCs.

Local Clinical Centres (LCC)
The LCC lead investigator and LCC clinic staff are responsible for:
(i) Obtaining all relevant local permissions (assisted by the CCO);
(ii) All trial activities at the LCC, including appropriate training and supervision for clinical staff;
(iii) Conducting trial procedures at the LCC in line with all relevant local policies and procedures;
(iv) Dealing with enquiries from participants and others.

10.1.6. Data quality assurance

- All participant data relating to the study will be recorded on electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data) via secure platform transfer or encrypted email. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of eCRFs will be provided in the Trial Master File.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data, and its origin can be found in monitoring guidelines.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8. Study and site start and closure

First Act of Recruitment

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

Study/Site Termination

- Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.
- The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:
    - Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
    - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
    - Total number of participants included earlier than expected
- Reasons for early study termination by the sponsor may include but are not limited to:
    - Discontinuation of further study intervention development
    - Occurrence of AEs unknown to date in respect of their nature, severity and duration

- Medical or ethical reasons affecting the continued performance of the trial, including
  - external evidence indicating efficacy or harm of any of the study interventions
  - a general lack of eligible patients due to vaccination or other reasons

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

10.1.9. Publication policy

The study will be registered in a public register, in which trial results will be posted. The results of this study will be published in a suitable publication irrespective of findings. Results will also be presented at scientific meetings.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Conflicts of interests will be disclosed. The contribution of ECRIN and its national partners will be fairly described in the acknowledgement section or as co-author, depending on the contribution in the trial design, planning and publication.

Individual patient-level data will be made as public as possible while maintaining the integrity and privacy of the trial participants. Anonymized data will be made publicly available using a data repository, including any programming code used to produce the trial results. De-identified data will be made available upon request and evaluation of the requestee's ability and willingness to maintain the integrity and privacy of the trial participants. Further details of data sharing will be given in a separate data sharing plan.

10.2. Appendix 2: Clinical Laboratory Tests and Biobanking

10.2.1. Clinical Laboratory Tests

The tests detailed in table 10.2.1 will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in section 5. of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10.2.1: Protocol-required Safety Laboratory Tests

Laboratory Tests	**Parameters**
Haematology	
	Haemoglobin (g/dL)
	Platelet count (x 10^9/L)
	White blood cell count (x 10^9/L)
	Neutrophils (x 10^9/L)
	Lymphocytes (x 10^9/L)
Clinical chemistry	
	K, Potassium (mmol/L)
	Na, Sodium (mmol/L)
	Creatinine (µmol/L)
	Total bilirubin (µmol/L)
	INR, International normalized ratio
	ALT, Alanine aminotransferase or SGOT, serum glutamic-oxaloacetic transaminase (U/L)
	AST, Aspartate aminotransferase or SGPT, Serum glutamic-pyruvic transaminase (U/L)
	Glucose (mmol/L)
	D-dimer (mg/L FEU)
	Ferritin (µg/L)
	LDH, Lactate dehydrogenase (U/L)
	Amylase (U/L)
	Procalcitonin (ng/mL)

	CRP, C-reactive protein (mg/L)
Pregnancy testing	
	Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)

NOTES: Details of liver chemistry stopping criteria and required actions and follow-up are given in section [7.1.1. Liver Chemistry Stopping Criteria] and Appendix [5: Liver Safety: Suggested Actions and Follow-up Assessments [and Study Intervention Rechallenge Guidelines]]. All events of ALT [or AST] ≥ 3 × upper limit of normal (ULN) and total bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT [or AST] ≥ 3 × ULN and international normalized ratio (INR) > 1.5 (if INR measured), which may indicate severe liver injury (possible Hy's law), must be reported to [sponsor] in an expedited manner (excluding studies of hepatic impairment or cirrhosis).

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.

10.2.2. Biobanking

Blood samples

Samples will be processed and centrifuged within 1 hour and stored at -80°C before analysed collectively at future decided research labs within the EU-SolidAct consortium. Freeze at -70°C/or -80°C as soon as possible and latest within 12 hours.

We recognize that -80°C storage is not available at all sites. In this case it will be possible to store the samples temporarily at -20°C for 1 month before transfer to -80°C storage.

Depending on research questions, the following volumes of blood will be obtained and processed, as further detailed in the IMP specific protocol, SOP and biobank manual:

EDTA-plasma (3-4 mL blood): Collect EDTA-blood into two tubes. Immediately after sampling, mix blood by inverting the tube 8-10 times without shaking. Centrifuge as soon as possible (within 30 minutes, latest within 60 minutes) at 3000g for 15 minutes. Isolate plasma (leave the 0.5 cm closest to the cell layer) into two cryotubes.

Citrate-plasma (2-3 mL blood): Collect citrate-blood into one tube. Immediately post sampling, mix blood by inverting the tubes 8-10 times without shaking. Place the tubes in room temperature and centrifuge as soon as possible (within 30 minutes) at 3000*g* for 15 minutes. Isolate plasma into two cryotubes (but leave approximately 0.5 cm of the plasma closest to the cell layer).

Serum (3-4 mL blood): Collect the blood in a serum separator tube with clot activator. Leave it undisturbed at the bench, approximately 30 minutes until coagulation. Then centrifuge at 2000g for 10 minutes. Isolate serum (leave the 0.5 cm closest to the cell layer) into two cryotubes.

EDTA whole blood (2mL blood): Collect blood into one EDTA tube. Immediately post sampling, mix blood by inverting the tubes three times before transfer into two cryotubes.

Labelling: Will be specified in the biobank manual for the respective study arm.

Naso/oropharyngeal swabs

- Use a flocked swab for nasopharyngeal samples. Gently insert the swab along the nasal septum, just above the floor of the nasal passage, to the nasopharynx, until resistance is felt. Rotate the swab for 5-10 seconds to obtain cellular material.

- If nasopharyngeal sample is not possible, an oropharyngeal sample is an alternative. Again rotate the swab for 5-10 seconds. The same procedure should be followed at all time points for the same patient for reproducibility.

- The swab should be stirred and placed in a transport medium (virocult type). Number and volume of aliquots will be specified in SOP and biobank manual, depending on whether centralized PCR or local PCR if indicated in the sub protocol.

-Labelling: Will be specified in the biobank manual for the respective study arm.

10.3. Appendix 3: Solicited AEs (applicable for injectable IMPs)

TYPE	EVENT	
Local AEs (injection or infusion site)	Discomfort Itching Redness Swelling (soft) Induration (hard) Blisters	
Systemic Clinical AEs following injections/infusions	Temperature Chills/night sweats Myalgia/flu-like general muscle aches Arthralgia Malaise (excess fatigue) Headache Nausea Vomiting Nasopharyngitis/Upper respiratory tract infection/cough/sinusitis Generalised rash Generalised itching	
Systemic Laboratory AEs	Creatinine ALT Alkaline phosphatase Total bilirubin INR Glucose Sodium Chloride	Haemoglobin Total White Cell Count Neutrophils Lymphocytes Platelets

10.4. Appendix 4: Disease-related Events (DREs)

- Hyper/Hypoglycaemia
- Anaemia
- Coagulation disorder
- Acute renal failure
- Pancreatitis
- Cardiac disorders: cardiac arrhythmia (cardiac flutter, cardiac fibrillation), cardiac ischemia, cardiac arrest, congestive heart failure
- Endocarditis / bacteraemia
- Myocarditis / pericarditis
- Severe Acute Respiratory Distress Syndrome (severe ARDS)
- Pneumothorax
- Pleural effusion
- Pulmonary embolism
- Arterial thrombosis
- Deep venous thrombosis
- Meningitis / Encephalitis
- Stroke / Cerebrovascular accident
- Liver dysfunction
- Bacterial pneumonia, including ventilator-associated pneumonia
- Coma / Confusion
- Gastrointestinal haemorrhage

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

To be detailed in the intervention-specific sub-protocol(s).

10.6. Appendix 6: Country-specific Requirements

10.6.1. Czech Republic

The National Czech Amendment includes the following specifications to the master protocol:

1. 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.

2. 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."

10.6.2. France

The following general exclusion criteria have been added in France

fr-E1. Les personnes mineures.

fr-E2. Patients majeurs sous un régime de protection juridique.

10.6.2.1. Germany

Country specific general 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.

10.6.3. Norway

The following text is regarded as a national-specific protocol addendum to the EU-SolidAct master protocol version 1.1 dated 07 April 2021, and thereby to all following protocol versions unless specifically removed.

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.

10.7. Appendix 7: Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	alanine aminotransferase
ANRS	Agence nationale de recherches sur la sida et les hépatites
AR	Adverse Reaction
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
BIPAP	Bi-level Positive Airway Pressure
CCO	Central Coordinating Office
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus-induced disease first described in 2019
CPAP	Continuous Positive Airway Pressure
CRF	case report file
CRP	C-reactive protein
CTU	Clinical Trials Unit

DAIDS	Division of AIDS
DPS	Data Point Set
DRE	Disease-related event
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
e.g.	example given
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report file
EDTA	ethylene diamine tetraacetic acid
EMA	European Medicines Agency
FiO2	fraction of inspired oxygen
GCP	Good Clinical Practice
GE	General exclusion criterion
GI	General inclusion criterion
Hb	haemoglobin
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
IB	Investigator Brochure
ICF	informed consent form
ICH	International Council for Harmonization
ICU	intensive care unit
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	international normalized ratio
IRB	Institutional Review Board
IWRS	interactive web response system
K	potassium
LAR	Legally Authorized Representative
LCC	local coordinating centre
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
Na	sodium
NIV	non-invasive ventilation
O2	oxygen
OUH	Oslo University Hospital
PHI	personal health information
PI	principal investigator
pO2	partial pressure of oxygen
PRO	Patient Reported Outcome
PROM	Patient Reported Outcome Measure
RCC	regional coordinating centre
RNA	ribonucleic acid

RR	respiratory rate
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	statistical analysis plan
SAR	Serious Adverse Reaction
SARS-CoV-2	SARS-coronavirus-2
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SMP	Safety Management Plan
SmPC	Summary of Product Characteristics
SoA	Schedule of Assessments
SoC	Standard of Care
SOP	standard operation procedure
SpO2	oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse reaction
The Oslo COVID-19 QLQ-PW80	The Oslo COVID-19 Quality of Life Questionnaire Provisional Weekly 80 item version
TOC	table of contents
TSG	Trial Safety Group
ULN	upper limit of normal
WHO	World Health Organisation
WI	Working Instructions

10.8. Synopsis of intervention-specific sub-protocols

10.8.1. 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 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.

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.

10.9. Appendix 8: 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:

Adjustments to the overall sampling frequency of assessments to lessen the burdens of the study personnel without loosing scientific value or compromising the safety and well-being of the patient.

Section # and Name	Description of Change	Brief Rationale
1.2 SoA	Reducing the sampling duration of serology and naso/oropharygial swabs	Less burden on the study personnel without losing scientific value or safety assessment.
	Added a note on which ferritin and procalcitonin samples to prioritize	Some sites do not gather these samples routinely, this note specify which time points to prioritize
5.1 Eligibility	Change General Inclusion Criteria GI2; confirmed SARS-Cov-2 infection confirmed by PCR from 9 to 14 days prior	Clinical experience that many patients are hospitalized within this timeframe
6.8 Concomitant Therapy	Specification on which concomitant medication to register	The current registration was exhaustive, need to prioritize the registration according to IMP in question.

Section # and Name	**Description of Change**	**Brief Rationale**
8. Study Assessments and Procedures	Reducing the sampling duration of serology and naso/oropharyngeal swabs	Less burden on the study personnel without losing scientific value or safety assessment.
	Added a note on which ferritin and procalcitonin samples to prioritize	Some sites do not gather these samples routinely, this note specify which time points to prioritize
10.2.2 Biobanking	Further specification on biobanking logistics	More details were required
Appendix 9	Included Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events	Added for reference

10.10. Appendix 9: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Corrected version 2.1 July 2017

Available from:

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

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