**Charité coronavirus disease 2019 (COVID-19) trial**

Protocol according to the master protocol “A Multi-center, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Patients”

**Short title / Acronym**

TBA

**EudraCT-Number:**

TBA

**Protocol code:**

TBA

**Protocol**

**Version 1.0 / Date dd.mm.2020**

**Sponsor of the clinical study** [according to § 40 AMG]

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TBA

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**The following persons accept the content of this protocol and confirm to conduct this study in compliance with Good Clinical Practice and applicable regulatory requirements.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Sponsor/Representative** |  |  |  |  |
|  |  | name, title |  | place, date |
|  |  |  |  |  |
| **Principal Investigator** |  |  |  |  |
|  |  | name, title |  | place, date |

* Confidential -

The information contained in this protocol has to be kept strictly confidential. Therefore the protocol is only provided to Investigators in confidence for review, to study staff, Independent Ethics Committee/Institutional Review Board, regulatory authorities and CROs (or CTO) and for obtaining written informed consent from patients.

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# Abbreviations

AE Adverse Event

ALT Alanine Transaminase

AST Aspartate Transaminase

BP Blood Pressure

CFR Code of Federal Regulations

CI Confidence Interval

CLIA Clinical Laboratory Improvement Amendments

CMP Clinical Monitoring Plan

CMS Clinical Material Services

Cr Creatinine

CRF Case Report Form

CROMS Clinical Research Operations and Management Support

CSR Clinical Study Report

CQMP Clinical Quality Management Plan

DHHS Department of Health and Human Services

DMID Division of Microbiology and Infectious Diseases

DSMB Data Safety and Monitoring Board

EC Ethics Committee

FDA Food and Drug Administration

FWA Federal Wide Assurance

GCP Good Clinical Practice

GLP Good Laboratory Practices

Hgb Hemoglobin

HR Heart Rate

IB Investigator’s Brochure

ICD International Classification of Diseases

ICF Informed Consent Form

ICH International Council for Harmonisation

IND Investigational New Drug Application

IRB Institutional Review Board

ITT Intent to treat Population

IV Intravenous

MCG Microgram

MedDRA Medical Dictionary for Regulatory Activities

MERS Middle East Respiratory Syndrome

MOP Manual of Procedures

N Number (typically refers to subjects)

NDA New Drug Application

NIAID National Institute of Allergy and Infectious Diseases

NIH National Institutes of Health

OHRP Office for Human Research Protections

PHI Protected Health Information

PI Principal Investigator

PLT Platelet

PP Per Protocol

PPP Per protocol population

PT Prothrombin Time

SAE Serious Adverse Event

SAP Statistical Analysis Plan

SARS Severe Acute Respiratory Syndrome

SDCC Statistical and Data Coordinating Center

SDSP Study Data Standardization Plan

SMC Safety Monitoring Committee (= DSMB)

SNP Single Nucleotide Polymorphisms

SOA Schedule of Activities

SOC System Organ Class

SOP Standard Operating Procedure

SUSAR Suspected Unexpected Serious Adverse Reaction

T. Bili Total Bilirubin

UP Unanticipated Problem

US United States

WBC White Blood Cell

# Charité COVID-19 Master Trial Protocol Synopsis

|  |  |
| --- | --- |
| **Study title** | Charité coronavirus disease 2019 (COVID-19) trial |
| **EudraCT Number** | TBA |
| **Study design** | This study is an adaptive, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adult patients diagnosed with COVID-19. |
| **Study phase** | Phase 2 |
| **Medical Condition** | In December 2019, the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus RNA was quickly identified in some of these patients. This novel coronavirus has been designated SARS CoV-2, and the disease caused by this virus has been designated COVID-19. Currently there are no approved therapeutic agents available for coronaviruses. |
| **Sponsor** | Charité - Universitätsmedizin Berlin  Charitéplatz 1, D-10117 Berlin |
| **(Principal) Investigator** | TBA |
| **Representative of the Investigator** | TBA |
| **Hypotheses** | The study will compare different investigational therapeutic agents to a placebo. There will be interim monitoring to introduce new arms and allow early stopping for futility, efficacy, or safety. If one therapy proves to be efficacious, this treatment will then become the control arm for comparison(s) with new experimental treatment(s).  Because of the possibility that background standards of supportive care may evolve/improve over time as more is learned about successful management of COVID-19, comparisons of safety and efficacy will be based on data from concurrently randomized participants. |
| **Rationale** | In December 2019, the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus RNA was quickly identified in some of these patients. This novel coronavirus has been designated SARS CoV-2, and the disease caused by this virus has been designated COVID-19. Currently there are no approved therapeutic agents available for coronaviruses. |
| **Primary objective / endpoint** | **Primary objective**  The overall objective of the study is to evaluate the clinical efficacy of different investigational therapeutics relative to the control arm in patients hospitalized with COVID-19.   * The primary objective will be determined by a pilot study of the first defined subjects. * Subject clinical status (7-point ordinal scale) at Day 15 is the default primary endpoint.   **Primary endpoint**  Clinical status of subject at Day 15 (7-point ordinal scale):   1. Not hospitalized, no limitations on activities 2. Not hospitalized, limitation on activities; 3. Hospitalized, not requiring supplemental oxygen; 4. Hospitalized, requiring supplemental oxygen; 5. Hospitalized, on non-invasive ventilation or high flow oxygen devices; Hospitalized, on invasive mechanical ventilation or ECMO; 6. Death. |
| **Secondary objectives** | **Secondary objectives**  1. Evaluate the clinical efficacy of different  investigational therapeutics as compared to the  control arm as assessed by:  Clinical Severity   * Ordinal scale:   + Time to an improvement of one category from admission using an ordinal scale.   + Subject clinical status using ordinal scale at Days 3, 5, 8, 11, and 29.   + Mean change in the ordinal scale from baseline to Days 3, 5, 8, 11, 15 and 29 from * National Early Warning Score (NEWS):   + The time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.   + Change from baseline to Days 3, 5, 8, 11, 15, and 29 in NEWS * Oxygenation:   + Oxygenation free days in the first 28 days (to Day 29).   + Incidence and duration of new oxygen use during the study   + Mechanical Ventilation:     - § Ventilator free days in the first 28 days (to Day 29).     - § Incidence and duration of new mechanic * Hospitalization   + Duration of hospitalization (days). * Mortality   + 28-day mortality   2. Evaluate the safety of the intervention through 28 days of follow-up as compared to the control arm as assessed by:   * Cumulative incidence of serious adverse events (SAEs) through 29 days of follow-up. * Cumulative incidence of Grade 3 and 4 AEs. * Discontinuation temporary suspension of infusions (for any reason) * Changes in white cell count, haemoglobin, platelets, creatinine, glucose, total bilirubin, ALT and AST over time.   **Secondary endpoints**   * Ordinal outcome assessed daily while hospitalized and on Days 15 and 29. * NEWS assessed daily while hospitalized and on Days 15 and 29. * Duration of supplemental oxygen (if applicable). * Duration of mechanical ventilation (if applicable). * Duration of hospitalization. * Date and cause of death (if applicable). * Grade 3 and 4 adverse events * SAEs. * White cell count, haemoglobin, platelets, creatinine, glucose, total bilirubin, * ALT, and AST on Days 1; 3, 5, 8, 11 (while hospitalized); and Day 15 and 29 (if able to return to clinic or still hospitalized). |
| **Inclusion criteria** | In order to be eligible to participate in this study, a patient must meet all of the following  criteria:   1. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures. 2. Understands and agrees to comply with planned study procedures. 3. Agrees to the collection of OP swabs and venous blood per protocol. 4. Male or non-pregnant female adult ≥18 years of age at time of enrollment. 5. Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen < 72 hours prior to randomization. 6. Illness of any duration, and at least one of the following:  * Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR * Clinical assessment (evidence of rales/crackles on exam) AND SpO2 ≤ 94% on room air, OR * Requiring mechanical ventilation and/or supplemental oxygen.  1. No participation in other clinical trials according to AMG (x months before and after) at the time of this trial |
| **Exclusion criteria** | An individual who meets any of the following criteria will be excluded from participation  in this study:   1. ALT/AST > 5 times the upper limit of normal. 2. Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30) 3. Pregnancy or breast feeding. 4. Anticipated transfer to another hospital which is not a study site within 72 hours. 5. Allergy to any study medication 6. Patients unwilling to consent to saving and propagation of pseudonymized medical data for study reasons 7. Subjects who are legally detained in an official institution |
| **Study medication** | Subjects will be randomized to receive either active product or placebo. Initially, the trial will have several arms. |
| **Placebo/ Reference Medication** | TBA |
| **Visit and documentation schedule** | **Study Duration**  The study will last for up to 3 years.  **Participant Duration**  An individual subject will complete the study in about 29 days, from screening at Day -1 or 1 to follow-up on Day 29 ±3 days. |
| **Efficacy Assessment** | **Measures of clinical support**  At each study day while hospitalized, the following measure of clinical support should be assessed:   1. Hospitalization 2. Oxygen requirement 3. Non-invasive mechanical ventilation (via mask) 4. Mechanical ventilator requirement (via endotracheal tube or tracheostomy tube) 5. ECMO requirement   **Ordinal Scale**  The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. Each day, the worse score for the previous day will be recorded. i.e. on Day 3, Day 2 score is obtained and recorded as Day 2. The scale is as follows:   1. Not hospitalized, no limitations on activities 2. Not hospitalized, limitation on activities; 3. Hospitalized, not requiring supplemental oxygen; 4. Hospitalized, requiring supplemental oxygen; 5. Hospitalized, on non-invasive ventilation or high flow oxygen devices; 6. Hospitalized, on invasive mechanical ventilation or ECMO; 7. Death.   **NEW Score**  The NEW score has demonstrated an ability to discriminate patients at risk of poor outcomes. (Smith, 2016). This score is based on 7 clinical parameters. The NEW Score is being used as an efficacy measure. This should be evaluated at the first assessment of a given study day. These parameters can be obtained from the hospital chart using the last measurement prior to the time of assessment. This is recorded for the day obtained. i.e. on Day 3, Day 3 score is obtained and recorded as Day 3. |
| **Safety** **Assessment** | For this study, all Grade 3 and 4 AEs and all SAEs occurring from the time the informed consent is signed through the Day 29 (end of study) visit will be documented, recorded, and reported. |
| **Other assessments** | See protocol. |
| **Safety and**  **Discontinuation Criteria** | This study may be prematurely terminated for the patient or in total if there is sufficient reasonable cause, including but not limited to:   1. Determination of unexpected, significant, or unacceptable risk to subjects 2. Results of interim analysis 3. Insufficient compliance to protocol requirements 4. Data that are not sufficiently complete and/or not evaluable 5. Regulatory authorities |
| **Pharmacological-toxicological evaluation** | TBA |
| **Risks, adverse drug reactions, drug interactions, restrictions, contraindications, procedures in case of emergency** | TBA |
| **Risk-benefit analysis** | TBA |
| **Trial Duration** | The study will last for up to 3 years. |
| **Duration of Intervention per Patient** | An individual subject will complete the study in about 29 days, from screening at Day -1 or 1 to follow-up on Day 29 ±3 days. |
| **Follow- up per Patient** | Until Day 29 ±3 days |
| **Total number of patients** | *to be assessed for eligibility (n = 500)*  *To be allocated to trial (n = 450)*  *To be analyzed (n = 400 in ITT analysis; n=300 per protocol)* |
| **Statistical analysis** | This study is intended to allow for two types of adaptations: 1) blinded confirmation or modification of the day selected for the primary endpoint and 2) ability to add a new experimental arm if one becomes available. Details will be described in the statistical analysis plan.  The primary outcome uses an ordinal severity scale with 7 categories, analysed using the proportional odds model. This model assumes that the treatment to placebo odds ratio of being classified in a given severity category “i” or better is the same for each category. The null hypothesis being tested is whether the odds of improvement on the ordinal scale is the same for the placebo and experimental treatment arms (i.e., whether the common odds ratio differs is 1). |
| **Participating Organization** | TBA |
| **Funding** | TBA |

## Rationale for Proposed Clinical Study

In December 2019, the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus RNA was quickly identified in some of these patients. This novel coronavirus has been designated SARS-CoV-2, and the disease caused by this virus has been designated COVID-19. Currently there are no approved therapeutic agents available for coronaviruses.

## Study Design

This study is an adaptive, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adult patients diagnosed with COVID-19.

The study is a multi-center trial that will be conducted in up to 50 sites globally with multiple Sponsors.

*Conducting a double-blind trial is important, especially if the primary endpoint is not all cause mortality (ACM) but rather one that involves caregiver judgment (such as the ordinal scale for clinical severity).*

*An important issue is whether it would be feasible to blind. One potentially achievable approach to conducting blinded trials involving multiple experimental interventions would be that used by the NIAID-sponsored CPCRA 007 HIV treatment trial, as discussed in Example 5.10 and Figure 5.1 of the Ellenberg S, Fleming T and DeMets DMC textbook (Second edition).*

The study will compare different investigational therapeutic agents to a placebo. There will be interim monitoring to introduce new arms and allow early stopping for futility, efficacy, or safety. If one therapy proves to be efficacious, this treatment will then become the control arm for comparison(s) with new experimental treatment(s).

Because of the possibility that background standards of supportive care may evolve/improve over time as more is learned about successful management of COVID-19, comparisons of safety and efficacy will be based on data from concurrently randomized participants.

An independent data and safety monitoring board (DSMB) is proposed to actively monitor interim data to make recommendations to the sponsor about early study closure or changes to study arms.

Subjects will be assessed daily while hospitalized. Discharged patients will be asked to attend study visits at Days 15, and 29. All subjects will undergo a series of efficacy, safety, and laboratory assessments. Blood samples and oropharyngeal (OP) swabs will be obtained on Day 1; 3, 5, 8, 11 (while hospitalized); and Day 15 and 29 (if able to return to clinic or still hospitalized).

*The visits post discharge may not be feasible in some sites, especially if the study is multicounty, multi-sites. Therefore, follow up visits by phone if physical visit is not feasible, can be considered.*

*Limitation to OP swabs and blood for virological testing may need to be revisited, if feasible, to enlarge to other specimens as pertinent and feasible. A central lab is warranted.*

*Pharmacokinetics evaluation in principle should be included as there I as need to better understand if the exposure in humans is adequate (e.g. ventilated patients or coadministration with other antivirals) and to perform exposure-response analyses. It is however understood that if only few sparse samples can be feasibly collected with a very heterogenous background of concomitant therapy, this might turn out not informative.*

The proposed primary outcome, a 7-point ordinal scale at Day 15, will be defined based on blinded review of data from the first 100 subjects. The pilot study data will be used to evaluate the ordinal scale on other days and may collapse parts of the ordinal scale if there are few subjects represented in certain categories.

The pilot study data will be included in the primary analysis of the ‘pivotal’ stage of the trial as long as those using the pilot stage data to enlighten decisions about finalizing the design of the pivotal stage do not have access to information from the pilot stage that would be directly or indirectly informative about the efficacy and safety of the experimental regimens being evaluated in the pivotal stage. Principles for endpoint selection will be defined a priori in a separate document.

The pilot study will also evaluate the different constructs of the ordinal scale (different days and different number of categories) by severity (severe vs. mild-moderate).

Different primary endpoints may be chosen for different severity populations. In addition, data from the pilot study will be used to determine the utility of the secondary endpoints, and to down select and prioritize the secondary endpoints.

*After the pilot phase, it could emerge that more profound changes than day of primary evaluation could be warranted, which would need reflection on how to progress the study and whether a seamless approach would still be appropriate.*

*In addition, other considerations about how the study will progress if Remdesivir* ***[used as example]*** *or another therapeutic is found to be effective needs to be fully deliberated as assessing for superiority to an effective antiviral might not always be obvious ( at least for monotherapy).*

Randomization will be stratified by:

• Site

• Severity of illness at enrolment:

o Severe disease: requiring mechanical ventilation or oxygen, a SpO2 ≤ 94% on room air, or tachypnoea (respiratory rate ≥ 24 breaths/min)

o Mild-moderate disease: SpO2 > 94% and respiratory rate < 24 breaths/min without supplemental oxygen.

# Schedule of Assessments

*please adapt if necessary*

**Table 1. Schedule of Assessments**

|  |  |  |
| --- | --- | --- |
|  | Screen | Baseline |
| **Day +/- Window** | **−1 or 1** | **1** | **Daily until hospital**  **discharge** | **156**  **± 2** | **296**  **± 3** |
| **Time** |  |  |  |  |  |
| **Assessments/Procedures** |  |  |  |  |  |
| **ELIGIBILTY** |  |  |  |  |  |
| Informed consent | x |  |  |  |  |
| Demographics & Medical History | x |  |  |  |  |
| Review SARS-CoV-2 results | x |  |  |  |  |
|  |  |  |  |  |  |
| **STUDY INTERVENTION** |  |  |  |  |  |
| Randomization |  | x |  |  |  |
| Administration of Remdesivir | control |  | Daily administration until discharge or  Day 10 | |  |  |
|  |  |  |  |  |  |
| **STUDY PROCEDURES** |  |  |  |  |  |
| Vital signs including SpO2 |  | x5 | Daily until discharge | x | x |
| Clinical data collection1 |  | x5 | Daily until discharge | x | x |
|  |  | x5 | Daily until discharge | x | x |
|  |  | x | Daily until discharge | x | x |
|  |  |  |  |  |  |
| **SAFETY LABORATORY** |  |  |  |  |  |
| Safety haematology, chemistry and liver  tests2 | X3 | X4,5 | Day 3, 5, 8, 11 (all ± 1 day)  if hospitalized |  |  |
| Pregnancy test for females of  childbearing potential | X3 |  |  |  |  |
|  |  |  |  |  |  |
| **RESEARCH LABORATORY** |  |  |  |  |  |
| Blood for serum |  | x5 | Day 3, 5, 8, 11 (all ± 1 day)  if hospitalized | x | x |
| Blood for PCR SARS-CoV-2 |  | x5 | Day 3, 5, 8, 11 (all ± 1 day)  if hospitalized |  |  |
| Oropharyngeal swab |  | x5 | Day 3, 5, 8, 11 (all ± 1 day)  if hospitalized | x | x |

*Notes:*

*1. Refer to Section 9.1 of the protocol for details of clinical data to be collected. This includes ordinal score, NEWS, oxygen requirement, Mechanical ventilator requirement, etc.*

*2. White cell count, haemoglobin, platelets, creatinine, glucose, total bilirubin, ALT/SGPT, AST/SGOT.*

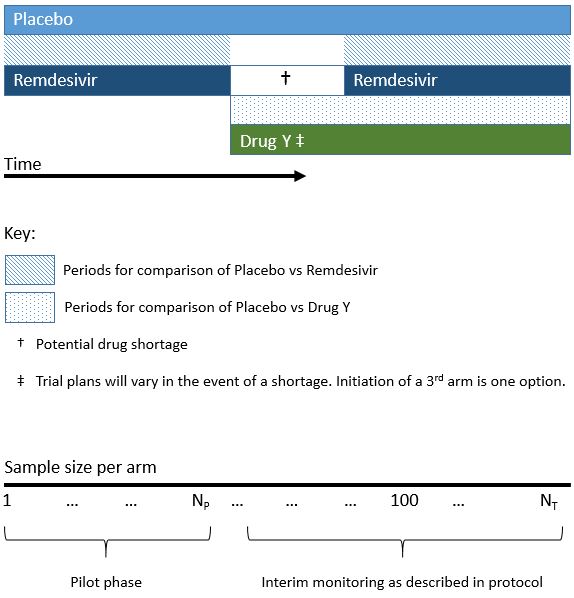
*3. Laboratory tests performed in the 48 hours prior to enrolment will be accepted for determination of eligibility.*

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

*5. Baseline assessments should be performed prior to study drug administration*

*6. In person visits are preferred but recognizing quarantine and other factors may limit the subject’s ability to return to the clinic. In this case, these visits may be conducted by phone.*

# Study schema



# Introduction

## Study rational

COVID-19 is a respiratory disease caused by a novel coronavirus (SARS-CoV-2) and causes substantial morbidity and mortality. There is currently no vaccine to prevent infection with SARS-CoV-2 or therapeutic agent to treat COVID-19. This clinical trial is designed to evaluate potential therapeutics for the treatment of adult patients hospitalized with COVID-19.

## Background

### Purpose of the Study

Coronavirus (CoVs) are positive-sense single stranded enveloped RNA viruses, many of which are commonly found in humans and cause mild symptoms. Over the past two decades, emerging pathogenic CoVs capable of causing life-threatening disease in humans and animals have been identified, namely severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle Eastern respiratory syndrome coronavirus (MERSCoV).

In December 2019, the Wuhan Municipal Health Committee (Wuhan, China) identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus RNA was quickly identified in some of these patients. This novel coronavirus has been abbreviated as SARSCOV-2 and has 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV (1). Most of the infections outside China have been travel associated cases in those who had recently visited Wuhan City and are thought to have acquired the virus through contact with infected animals or contact with infected people.

This novel coronavirus has been designated SARS-CoV-2, and the disease caused by this virus has been designated COVID-19.

Outbreak forecasting and mathematical modeling suggest that these numbers will continue to rise (2).

Global efforts to evaluate novel antivirals and therapeutic strategies to treat COVID-19 have intensified. There is currently no vaccine to prevent SARS-CoV-2 infection or therapeutic agent to treat COVID-19. Therefore, there is an urgent public health need for rapid development of novel interventions.

### Potential therapeutics

WHO has convened an independent panel of experts to deliberate on potential therapeutic candidate that could be further evaluated in the current COVID-19 epidemic[[1]](#footnote-1). This review will be conducted regularly as more data becomes available. The intention was to assess the evidence available for these candidates with regards to safety and efficacy and recommend those that should be advanced for clinical care through a compassionate protocol and/or evaluated in a clinical trial.

Based on the evidence available on January 27, 2020[[2]](#footnote-2), on the different therapeutic options, Remdesivir was considered the most promising candidate based on the broad antiviral spectrum, the in vitro and in-vivo data available for coronaviruses and the extensive clinical safety database (in particular coming from the Ebola virus disease clinical trial and MEURI) in eastern Congo). Further, studies in mice using Remdesevir showed superior efficacy over Kaletra + IFNbeta. Among the repurposed drugs, the investigation of the antiretroviral medicine (HIV protease inhibitors), lopinavir/ritonavir, either alone or in combination with IFNbeta1b, was considered a suitable second option for rapid implementation in clinical trials. Preclinical data available and limited clinical experience in the context of MERS, would suggest that it could provide some degree of clinical benefit and would be worth investigating particularly in severe cases.

## RISK/BENEFIT ASSESSMENT

### Known Potential Risks

For each new therapeutic agent under investigation, findings from the preclinical and clinical studies will be briefly described in this section and a summary of the findings described in the IB will be in an appendix.

*Example using Remdesivir*

*Remdesivir (GS-5734) is a broad-spectrum nucleotide prodrug that inhibits RNA-dependent RNA polymerase activity among a diverse group of RNA viruses including filoviruses (e.g. Ebola, Sudan, Marbrurg), paramyxoviruses (e.g. RSV, Nipah, Hendra) and pathogenic coronaviruses (3-5). Multiple nonhuman primate studies demonstrated the therapeutic efficacy of Remdesivir against Ebola virus, supporting the development of Phase 2 clinical trials in Africa (4-6). Studies in human airway epithelial cell assays demonstrated that Remdesivir inhibits replication of coronaviruses, including MERS-CoV (7). In mouse infection models, Remdesivir had therapeutic efficacy against Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV) (7,8). In vitro studies with mouse hepatitis virus (murine coronavirus) found that Remdesivir inhibits coronavirus replication through interference with the viral polymerase, despite the presence of a viral proofreading exoribonuclease, and coronaviruses that were partially resistant to inhibition by Remdesivir, were still sensitive to higher concentrations of Remdesivir, and fitness was impaired in the resistant viruses as compared to wild-type MERS-CoV (9). In a recent nonhuman primate study, therapeutic Remdesivir treatment initiated 12 hours post inoculation with MERS-CoV provided clinical benefit with a reduction in clinical signs, reduced virus replication in the lungs, and decreased presence and severity of lung lesions (10,11). These nonclinical in vitro and in vivo data suggest that Remdesivir might be useful for the treatment of COVID-19 for which no medical countermeasures are currently approved and support testing the efficacy of Remdesivir treatment among hospitalized adults with COVID-19 (12).*

Example using Remdesivir

*The potential risks of participating in this trial are those associated with having blood drawn, the intravenous (IV) catherization, possible reactions to Remdesivir and breach of confidentiality. Drawing blood may cause transient discomfort and fainting. Fainting is usually transient and managed by having the subject lie down and elevate his/her legs.*

*Bruising at the blood collection sites may occur but can be prevented or lessened by applying pressure to the blood draw site for a few minutes after the blood is taken.*

*Intravenous catheterization may cause insertion site pain, phlebitis, hematoma formation, and infusate extravasation; less frequent but significant complications include bloodstream and local infections. The use of aseptic (sterile) technique will make infection at the site where blood will be drawn or at catheter site less likely.*

### Potential Risks

*Example using Remdesivir*

*Remdesivir is a relatively safe investigational therapeutic agent with few subjects experiencing constipation, heartburn, itching, unusual feelings in the ear, dizziness, loss of*

*appetite, nausea, vomiting, shaking of the leg and arm, headache, loose stool, or upset stomach. These adverse events were temporary, lasting only a few days, and none were serious. In clinical studies, transient elevations in ALT and AST have been observed with single doses of Remdesivir up to 225 mg and multiple once daily doses of Remdesivir 150 mg for up to 14 days, with mild, reversible PT prolongation in some subjects but without any clinically significant change in INR or other evidence of hepatic effects. The mechanism of these elevations is currently unknown. Patients with underlying chronic liver disease as evidenced by a screening ALT or AST >5 times the upper limit of normal will not be eligible for study enrolment. For subjects enrolled in the study, regular laboratory assessments be performed in subjects receiving Remdesivir in order to monitor hepatic function. Any observed liver function-related laboratory abnormalities or possibly related AEs will be treated appropriately and followed to resolution. In nonclinical animal studies, toxicity studies found dosedependent and reversible kidney injury and dysfunction. No clinical evidence of nephrotoxicity has been observed with single doses of Remdesivir up to 225 mg or multiple once daily doses of Remdesivir 150 mg for up to 14 days. A 150-mg dose of the solution and lyophilized formulations of Remdesivir contains 9 and 4.5 g, respectively, of SBECD, for which the maximum daily recommended dose (based on an EMA safety review) is approx. 250 mg/kg. Because SBECD is renally cleared, subjects with moderate or severe renal impairment may have SBECD exposures greater than those with less severe renal impairment or normal renal function. Patients with underlying renal disease as evidenced by a creatinine clearance < 30 ml/min will not be eligible for study enrolment. Remdesivir should not be used with other drugs that have significant hepatotoxicity. This includes other antivirals such as lopinavir/ritonavir. Although there have been no clinical studies, it is anticipated there would be additive hepatotoxicity.*

### Risks to Privacy

Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential according to regulatory requirements and national law. However, there is a chance that unauthorized persons will see the subject’s PHI. All study records will be kept in a locked file cabinet or maintained in a locked room at the participating clinical site. Electronic files will be password protected.

Only people who are involved in the conduct, oversight, monitoring, or auditing of this trial will be allowed access to the PHI that is collected.

Any publications from this trial will not use information that will identify subjects by name. Organizations that may inspect and/or copy research records maintained at the participating site for quality assurance and data analysis include groups such as the IRB, Sponsor or the pertinent regulatory authorities.

### Known Potential Benefits

The candidate therapeutic(s) being evaluated may or may not improve clinical outcome of an individual adult subject with COVID-19 who participates in this trial. However, there is potential benefit to society from their participation in this study resulting from insights gained about the therapeutic agents under study as well as the natural history of the disease. While there may not be benefits for an individual subject, there may be benefits to society if a safe, efficacious therapeutic agent can be identified during this global COVID-19 outbreak.

### Assessment of Potential Risks and Benefits

*Example using Remdesivir*

*Remdesivir is generally a well-tolerated medication. There are significant liver toxicities that have been observed in prior studies. These have been self-limited and resolved after cessation of the medication. There is the potential for renal toxicities as observed in preclinical data. By excluding those with significant underlying liver and renal disease, and appropriate monitoring during the study, the risk to subjects can be minimized.*

# Objectives and endpoints

The overall objective of the study is to evaluate the clinical efficacy and safety of different investigational therapeutics relative to the control arm among hospitalized adult patients who have COVID-19.

## Primary objectives and endpoints

|  |  |
| --- | --- |
| **Primary Objectives** | **Primary endpoint (outcome measures)** |
| The overall objective of the study is to evaluate the clinical efficacy of different investigational therapeutics relative to the control arm in patients hospitalized with COVID-19.   * The primary objective will be determined by a pilot study of the first defined subjects. * Subject clinical status (7-point ordinal scale) at Day 15 is the default primary endpoint. | Clinical status of subject at Day 15 (7-point ordinal scale):  1. Not hospitalized, no limitations on activities  2. Not hospitalized, limitation on activities;  3. Hospitalized, not requiring supplemental oxygen;  4. Hospitalized, requiring supplemental oxygen;  5. Hospitalized, on non-invasive ventilation or high flow oxygen devices; Hospitalized, on invasive mechanical ventilation or ECMO;  6. Death. |
|  |  |

## Secondary objectives and endpoints

|  |  |
| --- | --- |
| **Secondary objectives** | **Secondary endpoints** |
| 1. Evaluate the clinical efficacy of different  investigational therapeutics as compared to the  control arm as assessed by:  Clinical Severity   * **Ordinal scale:**   + Time to an improvement of one category from admission using an ordinal scale.   + Subject clinical status using ordinal scale at Days 3, 5, 8, 11, and 29.   + Mean change in the ordinal scale from baseline to Days 3, 5, 8, 11, 15 and 29 from * **National Early Warning Score (NEWS):**   + The time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.   + Change from baseline to Days 3, 5, 8, 11, 15, and 29 in NEWS * **Oxygenation:**   + Oxygenation free days in the first 28 days (to Day 29).   + Incidence and duration of new oxygen use during the study   + Mechanical Ventilation:     - § Ventilator free days in the first 28 days (to Day 29).     - § Incidence and duration of new mechanic * Hospitalization   + Duration of hospitalization (days). * Mortality   + 28-day mortality   2. Evaluate the safety of the intervention through 28 days of follow-up as compared to the control arm as assessed by:   * Cumulative incidence of serious adverse events (SAEs) through 29 days of follow-up. * Cumulative incidence of Grade 3 and 4 AEs. * Discontinuation temporary suspension of infusions (for any reason) * Changes in white cell count, haemoglobin, platelets, creatinine, glucose, total bilirubin, ALT and AST over time. | * Ordinal outcome assessed daily while hospitalized and on Days 15 and 29. * NEWS assessed daily while hospitalized and on Days 15 and 29. * Duration of supplemental oxygen (if applicable). * Duration of mechanical ventilation (if applicable). * Duration of hospitalization. * Date and cause of death (if applicable). * Grade 3 and 4 adverse events * SAEs. * White cell count, haemoglobin, platelets, creatinine, glucose, total bilirubin, * ALT, and AST on Days 1; 3, 5, 8, 11 (while hospitalized); and Day 15 and 29 (if able to return to clinic or still hospitalized). |
|  |  |

|  |  |
| --- | --- |
| **exploratory** |  |
| Evaluate the virologic efficacy of different investigational therapeutics as compared to the control arm as assessed by:  • Percent of subjects with SARS-CoV-2 detectable in OP sample at Day 3, 5, 8, 11, 15, and 29.  • Quantitative SARS-CoV-2 virus in OP sample at Day 3, 5, 8, 11, 15, and 29.  • Development of resistance of SARS-CoV-2 in OP sample at Day 3, 5, 8, 11, 15, and 29.  • Quantitative SARS-CoV-2 virus in blood at Day 3, 5, 8, and 11 | • Qualitative and quantitative PCR for SARS-CoV-2 in OP swab on Days 1; 3, 5, 8, 11(while hospitalized); and Day 15 and 29 (if able to return to clinic or still hospitalized).  • Qualitative and quantitative PCR for SARS-CoV-2 in blood on Days 1; 3, 5, 8, 11 (while hospitalized). |

# Study design

## OVERALL DESIGN

This study is an adaptive, randomized, blinded, controlled trial to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adult patients diagnosed with COVID-19. The study is a multicenter trial that will be conducted in up to XX sites. The study will be a series of 2-arm comparisons between different investigational therapeutic agents and a placebo. There will be interim monitoring to introduce new arms and allow early stopping for futility, efficacy, or safety. If one therapy proves to be efficacious, this treatment will then become the control arm for comparison(s) with new experimental treatment(s). Because of the possibility that background standards of supportive care may evolve/improve over time as more is learned about successful management of COVID-19, comparisons of safety and efficacy will be based on data from concurrently randomized participants. An independent data and safety monitoring board (DSMB) will actively monitor interim data to make recommendations about early study closure or changes to study arms.

Randomization will be stratified by:

* Site
* Severity of illness at enrolment:
  + Severe disease: requiring mechanical ventilation or oxygen, a SpO2 ≤ 94% or tachypnoea (respiratory rate ≥ 24 breaths/min)
  + Mild-moderate disease: SpO2 > 94% and respiratory rate < 24 breaths/min without supplemental oxygen.

*please adapt*

*Stratification by site is fine, given the site investigators are blinded to treatment assignment in this current version of the Master Protocol. In an open label trial, it would be problematic if the randomization scheme would use permuted blocks by site. In open label trials, this could be resolved using dynamic balancing or by stratifying by groups of like sites, such as by region.*

*Notwithstanding that the number of strata should kept to the minimum and the ones selected are agreed as of major importance, the time of onset of symptoms can be rather critical and should be considered for stratification - at least proper data collection in this respect is essential for proper subgroup analyses, and after the pilot it might be one key factor to consider.*

Subjects will be assessed daily while hospitalized. Follow-up is for approximately 29 days. Discharged patients will be asked to attend study visits at Days 15, and 29. All subjects will undergo a series of efficacy, safety, and laboratory assessments. Blood samples and oropharyngeal (OP) swabs will be obtained on Day 1; 3, 5, 8, 11 (while hospitalized); and Day 15 and 29 (if able to return to clinic or still hospitalized).

The proposed primary outcome, a 7-point ordinal scale at Day 15, will be defined based on blinded review of data from the first 100 subjects. The pilot study data will be used to evaluate the ordinal scale on other days and may collapse parts of the ordinal scale if there are few subjects represented in certain categories. As long as the primary endpoint remains the ordinal scale, the pilot study data will be included in the primary analysis.Principles for endpoint selection will be defined a priori in a separate document.

The pilot study will also evaluate the different constructs of the ordinal scale (different days and different number of categories) by severity (severe vs. mild-moderate). Different primary endpoints may be chosen for different severity populations. In addition, data from the pilot study will be used to determine the utility of the secondary endpoints, and to down select and prioritize the secondary endpoints.

## SCIENTIFIC RATIONALE FOR STUDY DESIGN

At present, there is no specific antiviral therapy for coronavirus infections.

Few treatment studies have been done because most human coronavirus strains cause self-limited disease and care is supportive. See section 4.4 potential therapeutics.

After the severe acute respiratory syndrome (SARS) coronavirus was identified in 2002 and caused a large global outbreak, there was an increased interest in the development of a specific therapeutic agent. SARS CoV case-patients were treated with corticosteroids, type 1 IFN agents, convalescent plasma, ribavirin, and lopinavir or ritonavir, and except for ribavirin, many of these agents have in vitro pre-clinical data that support their efficacy (13-28). Since the SARS outbreak, new therapeutic agents targeting viral entry proteins, proteases, polymerases, and methyltransferases have been tested, however, none of them has been shown to be efficacious in clinical trials (29-31).

This study utilizes an adaptive design that maximizes our efficiency in identifying a safe and efficacious therapeutic agent for COVID-19 during the current outbreak. Some investigational products may be in limited supply and this study design enables continuation of the study even if a product becomes unavailable. In addition, the adaptive design allows for the evaluation of new therapeutic agents as they are identified.

As the study will be a monocentre / multicentre / multinational randomized controlled study, we will be able to acquire rigorous data about the safety and efficacy of investigational therapeutic agents for COVID-19 that will lead to generalizable evidence.

Randomization is essential for establishing efficacy of these new therapeutic agents. Last, collecting clinical and virologic data on enrolled patients using a standardized timeline and collection instruments should provide valuable information about the clinical course of and morbidities associated with severe COVID-19 in a diverse group of hospitalized adult patients.

## JUSTIFICATION FOR DOSE

*Example Remdesivir*

*The dose of Remdesivir used in this study will be the same dose that was has been used in the human Ebola clinical trials.*

# Timetable

FPI to Last Patient Out (Visit XX) XX

Estimated total duration of the trial XX

Planned FPI (First Patient in): XX

Planned LPO (Last Patient out): XX

# Study population

Approximately XX male and non-pregnant female adults ≥18 years of age or older with COVID-19 and who meet all eligibility criteria will be enrolled at up to XX clinical trial sites. The target population should reflect the community at large.

The estimated time from screening (Day -1 or Day1) to end of study for an individual subject is approximately 29 days.

Subject Inclusion and Exclusion Criteria must be confirmed by a study clinician named on the delegation log.

## Inclusion criteria

In order to be eligible to participate in this study, a patient must meet all of the following criteria:

1. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures.
2. Understands and agrees to comply with planned study procedures.
3. Agrees to the collection of OP swabs and venous blood per protocol.
4. Male or non-pregnant female adult ≥18 years of age at time of enrollment.
5. Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen < 72 hours prior to randomization.
6. Illness of any duration, and at least one of the following:

* Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR
* Clinical assessment (evidence of rales/crackles on exam) AND SpO2 ≤ 94% on room air, OR
* Requiring mechanical ventilation and/or supplemental oxygen.

1. No participation in other clinical trials according to AMG (x months before and after) at the time of this trial
2. (if applicable) XX

## Exclusion criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

* ALT/AST > 5 times the upper limit of normal.
* Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30)
* Pregnancy or breast feeding.
* Anticipated transfer to another hospital which is not a study site within 72 hours.
* Allergy to any study medication
* Patients unwilling to consent to saving and propagation of pseudonymized medical data for study reasons
* Subjects who are legally detained in an official institution
* (if applicable) XX

## Lifestyle Considerations

During this study, subjects are asked to:

* Refrain from drinking alcohol for 14 days after they begin receiving Remdesivir.
* Avoid taking paracetamol (acetaminophen) for 14 days after they begin receiving Remdesivir.
* Avoid getting pregnant during the study from Day 1 through Day 29 if female subject.

## Screen Failures

After the screening evaluations have been completed, the investigator or designee is to review the inclusion/exclusion criteria and determine the subject’s eligibility for the study.

Only the reason for ineligibility will be collected on screen failures. Subjects who are found to be ineligible will be told the reason for ineligibility.

Individuals who do not meet the criteria for participation in this study (screen failure) because of an abnormal laboratory finding may be rescreened once.

### Strategies for Recruitment and Retention

#### Recruitment

It is anticipated that patients with COVID-19 will present to participating hospitals, and that no external recruitment efforts towards potential subjects are needed. Recruitment efforts may also include dissemination of information about this trial to other medical professionals / hospitals.

Patients that are confirmed to have SARS-CoV-2 will be assessed for eligibility.

Screening will begin with a brief discussion with study staff. Some will be excluded based on demographic data and medical history i.e. pregnant, < 18 years of age, renal failure, etc. Information about the study will be presented to potential subjects (or legally authorized representative) and questions will be asked to determine potential eligibility. Screening procedures can begin only after informed consent is obtained.

#### Retention

Participating subjects will be reminded of subsequent visits.

*For a trial conduct issue having such influence on interpretability of trial results, more clarity should be provided about approaches to enhance retention (i.e, to reduce levels of loss-to-follow-up’). Consideration of such issues, for example, is provided in ‘Addressing Missing Data in Clinical Trials’, Ann Intern Med. 2011;154:113-117.*

#### Compensation Plan for Subjects

Compensation, if any, will be determined locally and in accordance with local IRB requirements, and subject to local IRB approval.

#### Costs

There is no cost to subjects for the research tests, procedures/evaluations and study product while taking part in this trial. Procedures and treatment for clinical care including costs associated with hospital stay may be billed to the subject, subject’s insurance or third party.

# STUDY PRODUCT

## Description of study medication / investigational medicinal product and administration

**Study Product Description**

*Example Remdesivir*

*Remdesivir is a single diastereomer monophosphoramidate prodrug designed for the intracellular delivery of a modified adenine nucleoside analog GS-441524. In addition to the active ingredient, the lyophilized formulation of Remdesivir contains the following inactive ingredients: water for injection, sulfobutylether β-cyclodextrin sodium (SBECD), and hydrochloric acid and/or sodium hydroxide.*

The supplied matching placebo lyophilized formulation is identical in physical appearance to the active lyophilized formulation and contains the same inactive ingredients.

### Dosing and Administration

Subjects will be randomized to receive either active product or placebo. Initially, the trial will have 2 arms. Subjects will be randomized to receive either active product or placebo.

*Example Remdesivir*

*Remdesivir will be administered as a 200 mg intravenous loading dose on Day 1, followed by a 100 mg once-daily intravenous maintenance dose for the duration of the hospitalization up to a 10 days total course.*

A matching placebo will be given at an equal volume at the same schedule.

See the protocol-specific Manual of Procedures (MOP) Appendices for detailed information on the preparation, labelling, storage, and administration of Remdesivir and placebo. Drug preparation will be performed by the participating site’s research pharmacist on the same day of administration to the subject. All missed doses are not made up.

### Dose Escalation

Not Applicable

### Dose Modifications

There are no clinical safety or pharmacokinetic data available for Remdesivir in patients with renal and/or hepatic impairment. Given the benefit-to-risk ratio in patients with COVID-19, these subjects are excluded from the study.

If the estimated creatinine clearance decreased by more than ≥ 50% from baseline, the study infusion should not be given. The infusion may be resumed when the estimated creatinine clearance returns to baseline.

If the liver function tests (ALT and/or AST) increase to > 3 times upper limits of normal, the dose of Remdesivir should be held. Dosing may be resumed when the ALT and/or AST returns to baseline. Dosing may be given later the same day. If a day’s dosing is missed, the dosing is not made up.

If any of the following occur, the dose of Remdesivir should be stopped and should not be restarted:

* ALT ≥3 × upper limits of normal and bilirubin ≥2 × upper limits of normal,
* ALT and/or AST increases to > 5 times upper limits of normal

*Example Remdesivir*

*If any level of hepatic/renal impairment is excluded, the use in renal/hepatic impairment is tailored based on current knowledge on Remdesivir, but might be worth considering whether further clinical data could be generated to possibly help in the future to enlarge the use considering the patient population and investigation of follow-on drug.*

### matching placebo

please state where appropriate

### Preparation/Handling/Storage/Accountability

#### Acquisition and Accountability

Therapeutic agents will be shipped to the site either directly from participating companies, from the sponsor, or from other regional or local drug repositories. All other supplies will be provided by the site.

#### Accountability

The site PI is responsible for study product distribution and disposition and has ultimate responsibility for study product accountability. The site PI may delegate to the participating site’s research pharmacist responsibility for study product accountability.

The participating site’s research pharmacist will be responsible for maintaining complete records and documentation of study product receipt, accountability, dispensation, storage conditions, and final disposition of the study product(s). Time of study drug administration to the subject will be recorded on the appropriate data collection form (CRF).

All study product(s), whether administered or not, must be documented on the appropriate study product accountability record or dispensing log. The sponsor’s monitoring staff will verify the participating site’s study product accountability records and dispensing logs per the site monitoring plan. Refer to the protocol-specific MOP for details on storing active and placebo medications.

#### Destruction

After the study treatment period has ended or as appropriate over the course of the study after study product accountability has been performed, disposition of unused and used active and placebo vials should occur as noted:

Unused and Used active and placebo vials:

* Should be returned to the sponsor or destroyed on-site following applicable site procedures or by the site’s selected destruction vendor. Following the site’s procedure for the destruction of hazardous material or study product destruction policy/standard operating procedure (SOP) when destroying used and unused items.
* A certificate of destruction should be provided to the sponsor and retained in the Pharmacy Binder once completed.

*Example Remdesivir*

*The lyophilized formulation of Remdesivir is a preservative-free, white to off-white or yellow, lyophilized solid containing 150 mg of Remdesivir to be reconstituted with 29 mL of sterile water for injection and diluted into IV infusion fluids prior to IV infusion. Following reconstitution, each vial contains a 5 mg/mL Remdesivir concentrated solution with sufficient volume to allow withdrawal of 30 mL (150 mg of Remdesivir). It is supplied as a sterile product in a single-use, 50 mL, Type 1 clear glass vial. In addition to the active ingredient, the lyophilized formulation of Remdesivir contains the following inactive ingredients: water for injection, SBECD, hydrochloric acid, and/or sodium hydroxide. Hydrochloric acid and/or sodium hydroxide are used to adjust the formulation to a final pH of 3.0 to 4.0.*

### Formulation, Appearance, Packaging, and Labelling

#### Placebo to match

The supplied matching placebo lyophilized formulation is identical in physical appearance to the active lyophilized formulation and contains the same inactive ingredients.

*Example Remdesivir*

*The lyophilized formulation of matching placebo is filled in a 50-mL glass vial closed with a rubber stopper and aluminium seal with a plastic flip-off cap. Each single-use vial contains sufficient volume to allow withdrawal of 30 mL of Remdesivir 5 mg/mL concentrate or placebo following reconstitution.*

Each of the study products will be labelled according to manufacturer specifications and include the statement “Caution: New Drug Limited by Regulatory Authority to Investigational Use.”

### Product Storage and Stability

*Example Remdesivir*

*Ambient vials of the lyophilized formulation of Remdesivir should be stored below 30°C. The lyophilized formulation needs to be reconstituted and then diluted into IV infusion fluids before use. After reconstitution, the total storage time before administration (including any time before or after dilution) should not exceed 4 hours at room temperature or 24 hours at refrigerated temperature (2°C to 8°C). See MOP for additional information.*

*Placebo to match*

*Vials of the lyophilized formulation of matching placebo should be stored below 30°C. The lyophilized formulation needs to be reconstituted and then diluted into IV infusion fluids before use. After reconstitution, the total storage time before administration (including any time before or after dilution) should not exceed 4 hours at room temperature or 24 hours at refrigerated temperature (2°C to 8°C).*

### Preparation

Refer to the protocol-specific MOP for details about preparation.

Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures.

### Treatment schedule

Please refer to table 1.

### Treatment compliance

Each dose of study product will be administered by a member of the clinical research team, that is qualified and licensed to administer the study product. Administration and date, time, and location of injection will be entered into the case report form (CRF).

### Concomitant medication / concomitant therapy

Therapy prior to enrolment with antivirals including lopinavir/ritonavir (Kaletra) or other therapeutic agents (e.g. corticosteroids) are permitted. These should, however, be discontinued on enrolment.

If the local standard of care per written policies or guidelines (i.e., not just an individual clinician decision) includes lopinavir/ritonavir (Kaletra) or other agents, then continuing these during the study is permitted, but may require additional safety monitoring by the site. Additionally, there should be plans on how the concomitant drugs are stopped for transaminase elevations, and prior to the thresholds for Remdesivir dose modification above (Section 0). Otherwise, concomitant use of lopinavir/ritonavir (Kaletra) and Remdesivir is prohibited due to lack of evidence on additive or synergistic effects and potential for an increased risk of transaminase elevations.

*The current wording, “is permitted,” seems proper, given the interest in understanding relative efficacy and relative safety of randomized interventions in real world settings. On the other hand, even if background interventions would be supported by local guidelines, stronger wording such as “is required” would be problematic if the relative efficacy and safety of such background interventions had not been reliably established.*

Concomitant medications in a hospitalized population change daily and are difficult to collect and attribute to success and failure of therapy and impact on safety. Therefore, only select concomitant medications will be captured in this trial. The list of medications will be assessed only from 7 days prior to enrollment to Day 11 and will be detailed in the MOP.

### Rescue Medicine

*Not Applicable*

### Non-Research Standard of Care

*Not Applicable*

### Adverse drug reactions and restrictions, contra-indications, drug interactions

*please adapt if necessary*

### Procedures in case of emergency

*please adapt if necessary*

### Blinding procedures

*please adapt*

### Unblinding

*please adapt*

# Study assessments and procedures

## Recruitment / screening procedures

After the informed consent, some or all of the following assessments are performed to determine eligibility requirements as specified in the inclusion and exclusion criteria:

* Confirm the positive SARS-CoV-2 test result.
* Focused medical history, including the following information:
  + Day of onset of COVID-19 symptoms
  + History of chronic medical conditions related to inclusion and exclusion criteria
  + Medication allergies
  + Review medications and therapies for this current illness and record on the appropriate CRF.
* Counsel subjects to use adequate birth control methods required during the trial to avoid pregnancy.
* Obtain weight
* Review recent radiographic imaging (x-ray or CT scan)
* Targeted physical exam focused on lung auscultation
* SpO2
* Obtain blood for screening laboratory evaluations if not done in the preceding 48 hours:
  + ALT
  + AST
  + Cr (and calculate creatinine clearance)
  + Urine or serum pregnancy test (in women of childbearing potential)

Clinical screening laboratory evaluations will be performed locally by the site laboratory. The overall eligibility of the subject to participate in the study will be assessed once all screening values are available. The screening process can be suspended prior to complete assessment at any time if exclusions are identified by the study team. Study subjects who qualify will be immediately randomized.

The volume of venous blood to be collected is presented in Table 3.

## Methods of obtaining informed consent

*please adapt if necessary*

In order to enroll a subject into the trial an informed consent will be obtained from each individual participating in this study prior any trial related interventions could occur.

First, patients will be informed in written and oral form regarding the key facts of the study, the procedures that will follow, and the reasonably foreseeable risks or discomforts as well as potential benefits. As a second step, the research team will give each participant an informed consent document with details about the study including its purpose, duration, procedures, and key contacts, as well as risks and potential benefits. The patients then will decide whether to give written and oral consent. Patients unwilling or unable to consent will not be included in the study.

## Methods of avoiding simultaneous enrolment in other trials

*please adapt if necessary*

The patient information sheet points out that there is no possibility of participating in other clinical trials at the same time. The patient will be informed about this issue in the interview with the investigator and it is part of the informed consent form.

## Enrolment and randomisation (assignment of study medication)

*please adapt*

*Patients, who meet all inclusion criteria and who have given their written informed consent will be reported to the trial centre (the Sponsor, the biometrical centre)*

*List the following data:*

* *Name and address of the responsible trial centre / institution*
* *Name of person responsible for clinical trial or contact person*
* *Telephone / fax numbers*
* *Times, at which trial centre can be contacted*
* *Study site, Investigator*
* *Pseudonym of patients who need randomization*
* *Gender*
* *Diagnosis / Staging result*
* *Stratification criteria (if applicable)*

### Measures to Minimize Bias: Randomization and Blinding

The study will randomize participants 1:1 to placebo or investigational product. If additional arms are added to or dropped from the trial, randomization will proceed with an equal probability of assignment to each of the remaining arms. Randomization will be stratified by:

* Site
* Severity of illness at enrolment:
  + Severe disease: requiring mechanical ventilation or oxygen, a SpO2 ≤ 94% on room air, or tachypnoea (respiratory rate ≥ 24 breaths/min)
  + Mild-moderate disease: SpO2 > 94% and respiratory rate < 24 breaths/min without supplemental oxygen.

The randomization procedure will be described in a corresponding SOP, which will define procedures for blinding.

## Clinical examinations and trial-related deviations from clinical practice

*please adapt*

### Pre-trial examinations (screening / inclusion examination)

*please adapt*

### Examinations during trial

*please adapt*

### Final examination

*please adapt*

## Efficacy Assessments

### Measures of clinical support

At each study day while hospitalized, the following measure of clinical support should be assessed:

1. Hospitalization
2. Oxygen requirement
3. Non-invasive mechanical ventilation (via mask)
4. Mechanical ventilator requirement (via endotracheal tube or tracheostomy tube)
5. ECMO requirement

### Ordinal Scale

The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. Each day, the worse score for the previous day will be recorded. i.e. on Day 3, Day 2 score is obtained and recorded as Day 2. The scale is as follows:

1. Not hospitalized, no limitations on activities
2. Not hospitalized, limitation on activities;
3. Hospitalized, not requiring supplemental oxygen;
4. Hospitalized, requiring supplemental oxygen;
5. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
6. Hospitalized, on invasive mechanical ventilation or ECMO;
7. Death.

### NEW Score

The NEW score has demonstrated an ability to discriminate patients at risk of poor outcomes. (Smith, 2016). This score is based on 7 clinical parameters. The NEW Score is being used as an efficacy measure. This should be evaluated at the first assessment of a given study day. These parameters can be obtained from the hospital chart using the last measurement prior to the time of assessment. This is recorded for the day obtained. i.e. on Day 3, Day 3 score is obtained and recorded as Day 3.

**Table 2: NEW Score**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Physiological Parameters** | **3** | **2** | **1** | **0** | **1** | **2** | **3** |
| **Respiration Rate** | ≤ 8 |  | 9 - 11 | 12 - 20 |  | 21 - 24 | ≥ 25 |
| **Oxygen Saturation** | ≤ 91 | 92 - 93 | 94 - 95 | ≥ 96 |  |  |  |
| **Any Supplemental Oxygen** |  | Yes |  | No |  |  |  |
| **Temperature** | ≤ 35.0 |  | 35.1 – 36.0 | 36.1 – 38.0 | 38.1 – 39.0 | ≥ 39.1 |  |
| **Systolic BP** | ≤ 90 | 91 - 100 | 101 – 110 | 111 – 219 |  |  | ≥ 220 |
| **Heart Rate** | ≤ 40 |  | 41 – 50 | 51 – 90 | 91 – 110 | 111 – 130 | ≥ 131 |
| **Level of Consciousness** |  |  |  | A |  |  | V, P or U |

*Level of consciousness = alert (A), and arousable only to voice (V) or pain (P), and*

*unresponsive (U).*

## Exploratory assessments

### Viral Shedding

OP swabs will be collected on Days 1; 3, 5, 8, 11 (while hospitalized); and Day 15 and 29 (if able to return to clinic or still hospitalized) and stored as outlined in the MOP. These assays are not developed yet, and the ability to test samples at one central lab is not clear. Therefore, while viral shedding is thought to be an important endpoint, considering the limitations above it is listed as an exploratory endpoint.

If virology assays can be set up with enough numbers of specimens tested, this data will be submitted as part of the Clinical Study Report. This may be submitted separately, as a supplemental Clinical Study Report.

### Alternative Ordinal Scales

Given the limited structured clinical data available for COVID-19, the best construct of ordinal scale is not known. Additional data may be used to construct different ordinal scales to test their utility in a treatment study. These are hypothesis generating and will not be submitted as part of a final Clinical Study Report.

## Laboratory assessments

*please adapt*

## Safety and other assessments

Study procedures are specified in the SOA. A study physician licensed to make medical diagnoses and listed will be responsible for all trial-related medical decisions.

* Physical examination: A symptom-directed (targeted) physical examination will be performed to evaluate for any possible adverse event. No physical exam is needed for routine visits.
* Clinical laboratory evaluations:
  + Fasting is not required before collection of laboratory samples.
  + Blood will be collected at the time points indicated in the SOA. Clinical laboratory parameters include WBC, Hgb, PLT, Cr, glucose, total bilirubin, AST, ALT.
  + This testing will be performed at each clinical trial site in real time.

**Table 3: Venipuncture Volumes**

|  |  |  |
| --- | --- | --- |
|  | Screen | Baseline |
| Day +/- Window | -1 to 1 | 1 | 2 | 3 | 5 | 8 | 11 | 15 | 29 |
| Safety  haematology,  chemistry and liver  tests21 |  | X  6mL |  | X  6mL | X  6mL | X  6mL | X  6mL |  |  |
| Blood for Serum |  | X  24mL |  | X  24mL | X  24mL | X  24mL | X  24mL | X  24mL | X  24mL |
| Plasma (includes  PCR) |  | X  8mL |  | X  8mL | X  8mL | X  8mL | X  8mL |  |  |
| Total volume |  | 38ml |  | 38ml | 38ml | 38ml | 38ml | 24mL | 24mL |
| Total all study days |  |  |  |  |  |  |  |  | 238  mL |

### Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

If a physiologic parameter, e.g., vital signs, or laboratory value is outside of the protocol-specified range, then the measurement may be repeated once if, in the judgment of the investigator, the abnormality is the result of an acute, short-term, rapidly reversible condition or was an error.

A physiologic parameter may also be repeated if there is a technical problem with the measurement caused by malfunctioning, or an inappropriate measuring device (i.e., inappropriate-sized BP cuff).

## Individual trial duration

*Please refer to…. / please adapt*

# STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

## Individual Halting

For an individual subject, an individual infusion must be stopped if they have a suspected drug-related event of hypersensitivity (Grade 2 or higher) during the infusion.

Subjects who have an IV infusion stopped for a safety related issued will not continue with dosing. See 8.1.1 Individual Infusion Halting for information about dose modifications due to laboratory abnormalities.

## Study Halting

Given severity of illness in COVID-19, there are no pre-specified stopping rules. Instead there will be close oversight by the protocol team and frequent DSMB reviews for safety. Subject is found to be pregnant after randomization

### Withdrawal from Randomized Treatment or from the Study

Patients are free to withdraw from participation in the study at any time upon request, without any consequence. Patients should be listed as having withdrawn consent only when they no longer wish to participate in the study and no longer authorize the Investigators to make efforts to continue to obtain their outcome data. Every effort should be made to encourage patients to remain in the study for the duration of their planned outcome assessments. Patients should be educated on the continued scientific importance of their data, even if they discontinue study drug. In the case of a patients becoming lost to follow-up, attempts to contact the patient should be made and documented in the patient’s medical records.

### Discontinuation of Study Drug

A patient in this clinical study may discontinue study drug for any of the following reasons:

* Patient requests to discontinue study drug
* Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol
* Any serious adverse event (SAE), clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient
* Patient fails to comply with protocol requirements or study-related procedures

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

## Premature termination of the individual participant

### Withdrawal of Patients from the Study

A patient may be removed from the study for the following reasons post initial dosing; however, whenever possible the patient should be followed for safety evaluations per protocol:

* Patient withdraws consent or requests discontinuation from the study for any reason
* Death of the patient
* Termination of the study
* Lost to follow-up.

Patients who withdraw from this study or are lost to follow-up after signing the informed consent form (ICF) and administration of the study product, will not be replaced. The reason for patient discontinuation from the study will be recorded on the appropriate case report form.

### Lost to Follow-Up

A subject will be considered lost to follow-up if he or she fails to appear for a follow-up assessment and cannot be contacted with good effort. These efforts will be documented in the subject’s record.

## Premature termination of the clinical study

The study will be discontinued if the Sponsor or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP guidelines.

The following events, if applicable, may cause premature termination of the clinical study:

• Early evidence of overt inferiority of the treatment according to the recommendation of the DSMB (decision taken by the Sponsor);

* Unjustifiable risk and/or toxicity in risk-benefit analysis (decision taken by the Sponsor), e.g. when adverse events occur, unknown to date with respect to their nature, severity, duration or frequency in relation to the currently established safety profile (substantial changes to the risk-benefit ratio), and therefore medical and/or ethical reasons affect the continuation of the study;
* New scientific evidence provided during the study that could affect the patient’s safety (benefit-risk analysis no longer positive);
* Request of the Sponsor or regulatory agency.

## Follow-up and continuing treatment after regular / premature termination

*After completing all the protocol treatment and visits, patients will continue with regular visits according to usual practice of the transplant centre.*

*In the case of premature termination, the reason for withdrawal must be entered on the appropriate case report form (CRF) page and must be followed for safety and efficacy until XX (days / months) after discontinuation.*

# Adverse events

## Definitions (according to guideline 2001/20/EG)

**Adverse Event (AE)**

*An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment*

An AE could be diseases, signs or symptoms which occur or worsen after enrolment of the patient in the clinical trial.

Adverse Events are assessed as follows:

* Mild
* Moderate
* Severe
* If criteria for SAE apply

For every event the causality will be analysed:

* Sure
* Probable
* Possible
* Unlikely
* Not related
* Can not be evaluated

**Serious Adverse Event (SAE)**

*A ‘serious adverse event or serious adverse reaction’ is any untoward medical occurrence or effect that at any dose*

* *results in death,*
* *is life-threatening,*
* *requires hospitalisation or prolongation of existing hospitalisation,*
* *results in persistent or significant disability or incapacity,*
* *or is a congenital anomaly or birth defect;*

### Adverse Reactions

*Adverse reactions are all untoward and unintended responses to an investigational medicinal product related to any dose administered.*

### Suspected Unexpected Serious Adverse Reactions (SUSAR)

*A Suspected Unexpected Serious Adverse Reaction (SUSAR) is any suspected adverse reaction related to the study treatment that is both serious and unexpected.*

*“Unexpected” means that the nature and severity of the adverse reaction are not consistent with the information about the study medication in question set out in the reference safety information.*

## Treatment of (S)AEs

*All AEs should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization or any other medically required intervention.*

## Assessment of SAEs

*As far as possible, each AE should be evaluated to determine:*

1. *the severity grade (mild, moderate, severe or CTCAE v5.0)*
2. *its relationship to the study drug (assessment of causality)*
3. *its duration (start and end dates or if continuing at final exam)*
4. *action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this AE; hospitalization)*
5. *whether it constitutes a serious adverse event (SAE)*

### Assessment of Seriousness

*Seriousness shall be determined according to the definition above.*

*Furthermore medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room, or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug addiction or drug abuse.*

### Assessment of intensity

Mild: The Adverse Event is transient and can be tolerated easily.

Moderate: The Adverse Event causes discomfort and impedes normal activities

Severe: The Adverse Event causes severe impairment of normal activities

**CTCAE grading:**

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL\*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL\*\*.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

### Assessment of causality

To assess causality between administration of the investigational product and the Adverse Event the following definitions apply:

Sure:

The reaction comprehensively follows the administration of the investigational product in the right timeframe or can be measured in body tissues or fluids or represents a known or expected response to the study medication or disappears after discontinuation or dose reduction and reoccurs after re-exposure.

Probable:

The reaction comprehensively follows the application of the investigational product in the right timeframe or represents a known or expected response to the study medication or disappears after discontinuation or dose reduction and cannot be explained by known characteristics of the patient’s disease.

Possible:

The reaction comprehensively follows the application of the investigational product in the right timeframe or represents a known or expected response to the study medication, but could easily be caused by other factors.

Unlikely:

Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible); disease or other drugs provide plausible explanations

Not related:

Adequate Information supporting the assumption that there is no causality

Cannot be evaluated:

The causality cannot be determined.

## Documentation of AEs and SAEs

All Serious Adverse Events (SAEs) and all Adverse Events (AEs) need to be documented, no matter if the Investigator suspects a causal connection to the investigational product or not. The documentation needs to include the type of event, start, duration, severity and causality.

Related signs symptoms and laboratory changes should be summarized to a specific disease. The event will be recorded in the CRF (Appendix \_\_\_). SAEs need to be documented on a separate SAE form.

Out of normal range laboratory data need to be analysed concerning their clinical relevance by the Investigator – and if relevant documented as an AE itself.

*All adverse events need to be followed until they subside or stabilize.*

The Sponsor will carefully document all SAEs reported by the Investigator. His documentation will be sent to the relevant regulatory authorities and to relevant authorities of other European member states and other contracting states of the EWR agreement, if the study is run in their territory and if they so request.

## Reporting of SAEs

The Investigator will report any Serious Adverse Event within 24 hours after becoming aware to the Sponsor (or < insert name > ) and will afterwards send an extended written record

This announcement will be done via fax or email to:

Sponsor: name, address, telephone, fax or see section XX.

Every event will be documented on a record form and will immediately be sent to the above given address. If at that point all required information is not available, succeeding records will be sent. In the event of death a copy of the autopsy record could be added.

Exceptional rules:

In this clinical trial the following SAEs are excluded from the reporting requirement:

* Serious or unexpected events which occur after enrolment, but before treatment was initiated
* Hospitalization required for therapeutical procedures (administration of investigational product, blood transfusions), e.g. …
* Other events: For example events that cause hospitalization but were planned before enrolment (e.g. (planned surgery)
* Symptoms related to underlying disease, for example…….
* Expected serious events, which could occur because of the administration of the investigational product and represent known effects of the investigational product.

## Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Sponsor will report all suspicious cases of Suspected Unexpected Serious Adverse Reactions (SUSARs) which had been occurred in one of clinical trials conducted by the same sponsor with the same drug substance/IMP to the relevant Ethics Committee, the relevant regulatory authorities and to relevant regulatory authorities of other European member states and other contracting states of the EWR agreement, if the study is run in their territory immediately, at the latest 15 days after it becomes known. He will also inform all Investigators involved in the trial.

In case of a fatal or life threatening SUSAR the Sponsor will report all information relevant for judging the event immediately, at the latest 7 days after the event becomes known to the relevant Ethics Committee, the relevant regulatory authorities and to relevant regulatory authorities of other European member states and other contracting states of the EWR agreement, if the study is run in their territory as well as to all Investigators involved in the trial. After a further 8 days all further relevant information must be available.

## Other safety issues requiring expedited reporting

The Sponsor will immediately, at the latest 15 days after it becomes known report all circumstances that require a revision of the risk-benefit analysis to the relevant Ethics Committee, the relevant regulatory authorities and to relevant regulatory authorities of other European member states and other contracting states of the EWR agreement, if the study is run in their territory. This especially includes:

* + Singular cases of expected severe adverse events with an unexpected outcome.
  + Increased incidence of expected severe adverse events that are judged as being clinically relevant.
  + SUSARs which occur after termination of the clinical trial (….weeks,……months,…..years after termination or exclusion)
  + Events related to study procedures or development of the study medication, which could affect a subject’s safety.

All person-related data will always be transmitted pseudonymised. Before reporting a SUSAR the subject will be unblinded.

## Follow-up of adverse events

*Once an AE is detected, it should be followed until its resolution or stabilisation, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study, the interventions required to treat it and the outcome.*

*Follow-up information is sent to the same address to which the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or withdrew from study participation.*

*For a follow-up report to the authorities, the investigator may be required to collect further information for a detailed description and a final evaluation of the case, including copies of hospital reports, autopsy reports, or other relevant documents.*

## Reporting Events to Subjects

*please adapt*

## Contact / person responsible for reporting

|  |  |
| --- | --- |
| Name |  |
| Study centre |  |
| Address |  |
| Tel. |  |
| Fax |  |

## UNANTICIPATED PROBLEMS

### Definition of Unanticipated Problems (UP)

*please adapt if required*

### Unanticipated Problem Reporting

*please adapt if required*

### Reporting Unanticipated Problems to Subjects

*please adapt if required*

## Data Safety Monitoring Committee

*The**study will be monitored by an independent Data Data Safety Monitoring Board (DSMB) that was specifically chosen to include an expert in …, in biostatistics and in … to ensure utmost competence and vigilance. The DSMB will meet before the start of the trial, then every … months in order to review the trial’s progress, safety data (SAEs) and adherence to protocol. (please refer to the DSMB charter)*

# Documentation

## Case Report Forms (CRF)

*This trial will be performed using an electronic case report form eCRF) (\_\_\_). The investigator and the trial site staff will receive system documentation, training and support for the use of the eCRF. In case of new trial site staff the training can be performed by experienced personnel of the respective trial site.*

*All protocol-required information collected during the trial must be documented in the eCRF by the investigator, or a designated representative. All data entry, modification or deletion will be recorded automatically in an electronic audit trail indicating the individual subject, the original value, the new value, the reason for change, who made the change and the time and date of the change. All data changes will be clearly indicated. Former values can be viewed in the audit trail. All electronic data will be entered by the site (including an electronic audit trail) in compliance with applicable record retention regulations in a web- based data capturing system known as \_\_\_\_.*

*The software as well as the support will be provided \_\_\_*

*ADRESS*

*The system will be secured to prevent unauthorized access to the data or the system. Only people provided with a user ID and a password will be able to enter or change data. The investigator will maintain a list of individuals who are authorized to enter or correct data.*

## Investigator Site File (ISF)

*All essential documents will be kept in the Investigator Site File which will be stored at the study site in accordance with ICH GCP chapter 8. The sponsor will provide the investigator with an investigator's file. This file should be used for all trial-related documents. The investigator will be responsible for keeping the investigator's file updated and ensuring that all required documents, as specified in ICH-GCP guidelines, are filed. The file will be made available for monitoring and/or auditing by the sponsor or its representative and regulatory agencies.*

# Quality management

## Monitoring, Data Quality Assurance

*The trial site will be monitored by…..to ensure the quality of the data collected. The objectives of the monitoring procedures are to ensure that the trial subject’s safety and rights as a study participant are respected, that accurate, valid and complete data are collected, and that the trial is conducted in accordance with the trial protocol, the principles of GCP and local legislation.*

*All investigators agree that the monitor regularly visits the trial site and assure that the monitor will receive appropriate support in his activities at the trial site. The declaration of informed consent includes a statement to the effect that the monitor has the right – while observing the provisions of data protection legislation – to compare the case report forms (eCRFs) with the trial subject’s medical records (doctor’s notes, ECGs, laboratory printouts etc.). The investigator will secure access for the monitor to all necessary documentation for trial-related monitoring. The aims of the monitoring visits are as follows:*

* *To check the declarations of informed consent.*
* *To monitor trial subject safety (occurrence and documentation/reporting of AEs and SAEs).*
* *To check the completeness and accuracy of entries on the eCRF.*
* *To validate the entries on the eCRF against those in the source documents (source data verification, SDV).*
* *To evaluate the progress of the trial.*
* *To evaluate compliance with the trial protocol.*
* *To assess whether the trial is being performed according to GCP at the trial site.*
* *To discuss with the investigator aspects of trial conduct and any deficiencies found.*

*A monitoring visit report is prepared for each visit describing the progress of the clinical trial and any problems (e.g. refusal to give access to documentation).*

*The investigators allow the monitor to have access to any or all of the study materials needed for source data verification and proper review of the study progress. At all times, the sponsor/investigators/monitors will maintain the confidentiality of the study documents. Furthermore, problems with inconsistent and incomplete data will be discussed. By signing the declaration of informed consent the participants allow access to their documents. With the signature in the protocol, the investigators confirm that auditors and health authority inspectors may have access to the study documentation and accordant medical records. Auditors and inspectors are bound by professional confidentiality and may not pass on any personal information that comes to their knowledge. In the course of audits or inspections, data in the case report forms will be compared with the data for medical records. All the documentation held by the investigators within the scope of the clinical trial, as well as the drug logs of the study medications will be verified.*

## Data Quality Assurance

*The sponsor assumes responsibility for implementing and maintaining quality assurance and quality control systems with written Standard Operation Procedures (SOPs) to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice, and the applicable regulatory requirements. The sponsor also takes responsibility for securing agreement from all involved parties to ensure direct access to the trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor and inspection by authorities. Quality control will be applied to each stage of the study to ensure that all data are reliable and have been processed correctly.*

## Audits / inspections

*Authorised representatives of the Sponsor, a regulatory authority, may visit the centre to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements.*

## Standardisation and validation

*if required (please adapt)*

## Reference institutions

*if required (please adapt)*

# Data entry und data management

All patient related data will be recorded under a pseudonym. Every patient will receive a patient number / pseudonym which will be unique for this individual patient. The Investigator will compile a confidential list, which relates these patient numbers to the patient’s full name. This list will only be accessible to the study team and the monitor. Original patient files may be viewed by monitors, auditors and inspectors.

## Source Data and Patient Files

*The information in original documents and records (e. g. patient files, laboratory notes) are defined as Source Data and will be reviewed by the Monitor for Source Data Verification. All data that will be recorded directly in the CRF without prior written or electronic record will be described in the protocol and considered to be Source Data.*

## Data processing

The study centre / Sponsor / biometrical centre will file all data electronically. To verify accuracy of the data, range, validity and consistency checks will be performed. Implausible or missing data can be corrected or added after consulting the Investigator. Documentation for these corrections will be stored with the CRFs.

All validated data will be stored in a database\_\_\_\_\_\_\_ (Access / Lotus / FoxPro / Oracle). After termination of the study and after all entries have been completed, the database will be closed for further entries. This process will be documented.

The analysis will be performed using the following commercial software:

SAS / SPSS\_\_\_\_\_\_\_\_\_ (Program / version).

Other programs \_\_\_\_\_\_\_\_\_\_ used in the study are validated.

## Generation of pseudonym

*if required (please adapt)*

# Statistical Analysis

This study is intended to allow for two types of adaptations: 1) blinded confirmation or modification of the day selected for the primary endpoint and 2) ability to add a new experimental arm if one becomes available. A brief summary is provided here. Details will be described in the statistical analysis plan.

## Blinded endpoint confirmation or modification

The current plan is to evaluate the primary endpoint on Day 15. Because there is uncertainty about the clinical course and potential different trajectories according to baseline disease severity, the day of the primary endpoint may be modified based on a blinded evaluation of various timepoints (e.g., days 7-21). [Posch, 2012] This will occur after approximately 100 participants have been enrolled, by a blinded endpoint evaluation committee without knowledge of treatment assignment. Analyses will be evaluated by baseline severity (mild/moderate vs severe). For example, in mild disease, recovery may occur rapidly such that all with mild disease have resumed normal activities by Day 15. Hence, the final timepoint selected may vary accordingly.

*With this approach, there is considerable potential that the pilot study data could be*

## Addition of new experimental therapies

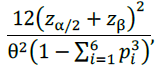
If additional data become available to add an experimental therapy, analyses of experimental arms will be performed comparing concurrently enrolled control subjects. If one treatment crosses an efficacy stopping boundary, this treatment may become the new control arm for comparisons. This approach was used in the recent PALM Ebola therapy RCT [Mulangu ,2019].

## STATISTICAL HYPOTHESES

The primary outcome uses an ordinal severity scale with 7 categories, analysed using the proportional odds model. This model assumes that the treatment to placebo odds ratio of being classified in a given severity category “i” or better is the same for each category. The null hypothesis being tested is whether the odds of improvement on the ordinal scale is the same for the placebo and experimental treatment arms (i.e., whether the common odds ratio differs is 1). It is worth noting that, for large sample sizes, the test based on the proportional odds model is nearly the same as the Wilcoxon rank sum test.

## Sample size determination

The proportions of patients in the different categories of the ordinal scale at Day 15 in the placebo and treatment arm assuming an odds ratio (OR) of 2 are given below. The odds ratio represents the odds of improvement in the ordinal scale for treatment relative to placebo control [Whitehead, 1993] shows that the sample size to detect a given odds ratio for 1:1 randomization using a 2-tailed test at level α is given by



where θ is the log odds ratio, 𝑝% is the overall probability (combined over both arms) of being in the ith category of the ordinal outcome, and 𝑧!/# and 𝑧\* are the 1 − α/2 and βth quantiles of the standard normal distribution.

Table 4 displays four scenarios considered for outcomes under placebo for sample size determination. There is significant uncertainty with these assumptions given the limited data available.

Table 5 shows a range of sample sizes for odds ratios ranging from 1.5 to 2.5 for 85% power. For 90% power, increase the sample size by 17%. Table 6 displays the probabilities of being in different categories of the ordinal scale under an odds ratio of 2. A total sample size of 354 gives approximately 85% power to detect an odds ratio of 2 using a 2-tailed test at level α = 0.05. To allow for approximately 10% of participants to be lost to follow-up, the targeted sample size will be 394.

**Table 4. Possible scenarios for outcomes at day 15.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Severity Outcome** | **Anticipated** | ***Alternative Scenarios*** | | | |
| **Scenario 1** | **Scenario 2** | **Scenario 3** | **Scenario 4** | **Scenario 5** |
|  | ***more mild disease ↔ more severe***  ***disease*** | | | |
| outcome  (%) | outcome  (%) | outcome  (%) | outcome  (%) | outcome  (%) |
| Death | 2 | 1 | 1 | 2 | 3 |
| Hospitalized, on  mechanical ventilation  or ECMO | 1 | 1 | 1 | 1 | 3 |
| Hospitalized, on noninvasive  ventilation or  high flow oxygen  devices | 2 | 1 | 1 | 2 | 4 |
| Hospitalized, requiring  supplemental oxygen | 7 | 2 | 5 | 5 | 9 |
| Hospitalized, not  requiring supplemental  oxygen | 8 | 5 | 7 | 17 | 23 |
| Not hospitalized,  limitation on activities | 38 | 40 | 40 | 36 | 33 |
| Not hospitalized, no  limitations on activities | 42 | 50 | 45 | 37 | 25 |

**Table 5. Sample size calculations for scenarios in Table 4 for a two-arm study assuming 85% power and various true odds ratios.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **True odds ratio** | **Total sample size** | | | | |
| Scenario 1 | Scenario 2 | Scenario 3 | Scenario 4 | Scenario 5 |
| 1.5 | 774 | 837 | 798 | 746 | 709 |
| 1.75 | 412 | 447 | 425 | 396 | 374 |
| 2.0 | 272 | 296 | 281 | 261 | 245 |
| 2.25 | 201 | 220 | 208 | 193 | 180 |
| 2.5 | 159 | 175 | 165 | 152 | 143 |

**Table 6. Treatment ordinal outcome proportions under odds ratio of 2 for five cenarios in Table 4 at day 15.**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Scenario 1 | | Scenario 2 | | Scenario 3 | | Scenario 4 | | Scenario 5 | |
|  | Anticipated | | more mild disease ↔ more severe  disease | | | | | | | |
| **Severity Outcome** | Control % | Treatment % | Control % | Treatment % | Control % | Treatment % | Control % | Treatment % | Control % | Treatment % |
| Death | 2 | 1 | 1 | 0.5 | 1 | 0.5 | 2 | 1 | 3 | 1.5 |
| Hospitalized, on  mechanical ventilation  or ECMO | 1 | 0.5 | 1 | 0.5 | 1 | 0.5 | 1 | 0.5 | 3 | 1.6 |
| Hospitalized, on noninvasive  ventilation or  high flow oxygen  devices | 2 | 1 | 1 | 0.5 | 1 | 0.5 | 2 | 1 | 4 | 2.2 |
| Hospitalized, requiring  supplemental oxygen | 7 | 3.8 | 2 | 1 | 5 | 2.6 | 5 | 2.7 | 9 | 5.2 |
| Hospitalized, not  requiring supplemental  oxygen | 8 | 4.7 | 5 | 2.7 | 7 | 3.9 | 17 | 10.3 | 23 | 16.1 |
| Not hospitalized,  limitation on activities | 38 | 29.7 | 40 | 28.1 | 40 | 29.8 | 36 | 30.4 | 33 | 33.4 |
| Not hospitalized, no  limitations on activities | 42 | 59.2 | 50 | 66.7 | 45 | 62.1 | 37 | 54 | 25 | 40 |

Note that columns may not sum to exactly 100 due to rounding errors.

## POPULATIONS FOR ANALYSES

The primary analysis will be based on an intention-to-treat population, including participants randomized. Similarly, safety analyses will be based a modified intent-totreat population consisting of all participants who received at least one infusion.

## STATISTICAL ANALYSES

### General Approach

This is a double-blind placebo controlled randomized trial testing a superiority hypothesis with a two-sided type I error rate of 0.05. Secondary hypotheses have been ordered according to relative importance. These will be described according to the appropriate summary statistics (e.g., proportions for categorical data, means with 95% confidence intervals for continuous data, median for time-to-event data).

A statistical analysis plan (SAP) will be developed and filed with the study sponsor prior to unblinding of study and database lock.

### Analysis of the Primary Efficacy Endpoint

The ordinal scale will be used to estimate a proportional odds model. The primary hypothesis test will be based on a test of whether the common odds ratio for treatment is equal to one. As noted earlier, the hypothesis test is, for large sample sizes, nearly the same as the Wilcoxon rank sum test.

Therefore, the procedure produces a valid p-value regardless of whether the proportional odds model is correct. Nonetheless, estimation and confidence intervals do require the model to be correct. Accordingly, we will evaluate model fit using a goodness-of-fit likelihood ratio test. A stratified hypothesis test to account for baseline severity of disease will be used.

The distribution of severity results will be summarized by treatment arm as percentages. The validity of the proportionality assumption will be evaluated and tested. Efforts to minimize loss-to-follow-up will be considerable. However, small amounts of missing data may occur. In such cases, participants without final outcome data will be excluded from the analysis. Sensitivity analyses will evaluate the impact of making different assumptions about missing observations. These sensitivity analyses will be fully defined in the SAP.

### Analysis of the Secondary Endpoint(s)

1) Differences in time-to-event endpoints (e.g., time to a one category improvement in ordinal scale) by treatment will be summarized with Kaplan-Meier curves and 95% confidence bounds.

2) Change in ordinal scale at specific time points will be summarized by proportions (e.g., proportion who have a 1-, 2-, 3-, or 4-point improvement or 1-, 2-, 3-, 4-point worsening).

3) Duration of event (e.g., duration of mechanical ventilation) will be summarized according to median days with quartiles.

4) Incidence data (e.g., incidence of new oxygen use) will be summarized as a percent with 95% confidence intervals.

5) Categorical data (e.g., 28-day mortality or ordinal scale by day) will be summarized according to proportions with confidence intervals on the difference or odds ratios for a binary or multiple category scale, respectively.

Missing data procedures will be described in the SAP.

### Safety Analyses

Safety endpoints include death through Day 28, SAEs, discontinuation of study infusions, and severe AEs. These events will be analyzed univariately and as a composite endpoint. Time-to-event methods will be used for death and the composite endpoint. Each AE will be counted once for a given participant and graded by severity and relationship to COVID-19 or study intervention. AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented by system organ class, duration (in days), start- and stop-date. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs should be presented either in a table or a listing.

### Baseline Descriptive Statistics

Baseline characteristics will be summarized by treatment arm. For continuous measures the mean and standard deviation will be summarized. Categorical variables will be described by the proportion in each category (with the corresponding sample size numbers).

### Planned Interim and Early Analyses

**Early analyses**

An initial blinded endpoint-evaluation phase will be enrolled prior to specification of the primary endpoint. Analysis and decision making will be restricted to a blinded endpoint evaluation committee (a BEEC). BEEC membership will be defined elsewhere and will consist only of individuals who are blinded to treatment assignment. Principles of blinded endpoint-evaluation will be defined in a separate document.

Additional early analyses include monitoring enrollment, baseline characteristics, and follow-up rates throughout the course of the study by the study team. Analyses will be conducted blinded to treatment assignment.

**Interim analyses**

A data and safety monitoring board (DSMB) will monitor ongoing results to ensure patient well-being and safety as well as study integrity. The DSMB will be asked to recommend early termination or modification only when there is clear and substantial evidence of a treatment difference. More details about the interim analyses are described in section 0 and 0 below as well as a separate guidance document for the DSMB.

**Interim Safety Analyses**

Interim safety analyses will occur at approximately 25%, 50%, and 75% of total enrollment. Safety analyses will evaluate serious AEs by treatment arm and test for differences using a Pocock spending function approach with a one-sided type I error rate of 0.025. This approach is less conservative than what will be used to test for early efficacy results because proving definitive harm of the experimental agents is not the focus of this study. Pocock stopping boundaries at the looks described correspond to z-scores of (2.37, 2.37, 2.36, & 2.35). This contrasts with the z-score stopping boundaries for the Lan-DeMets spending function that mimics O’Brien-Fleming boundaries: (4.33, 2.96, 2.36 & 2.01). The unblinded statistical team will prepare these reports for review by the DSMB.

**Interim Efficacy Review**

The Lan-DeMets spending function analog of the O’Brien-Fleming boundaries will be used to monitor the primary endpoint as a guide for the DSMB for an overall two-sided type-I error rate of 0.05. Interim efficacy analyses will be conducted after the BEEC has selected the primary efficacy endpoint at approximately 50%, 75% and 100% of total information.

Conditional power will be presented as an additional guide to the DSMB. Conditional power allows computation of the probability of obtaining a statistically significant result by the end of the trial given the data accumulated thus far, incorporating and assuming a hypothesized treatment effect (e.g., the treatment effect assumed for sample size determination) thereafter. If conditional power is less than 20% under the original trial assumptions, consideration should be given to stopping the trial.

The unblinded statistical team will prepare these closed reports for DSMB review and recommendations. Analyses will be presented with blinded codes for treatment arms to protect against the possibility that the DSMB report may fall into the wrong hands. A DSMB charter will further describe procedures and membership. An additional document on statistical issues related to monitoring will be provided to the DSMB prior to interim analyses.

### Sub-Group Analyses

Subgroup analyses for the primary outcomes will evaluate the treatment effect across the following subgroups: geographic region, duration of symptoms prior to enrollment, age and sex. A forest plot will display confidence intervals across subgroups. Interaction tests will be conducted to determine whether the effect of treatment varies by subgroup.

### Exploratory Analyses

An exploratory analysis will compare treatment efficacy estimates according to the various scales outlined in section \_\_\_. Specifically, the probability of falling into category “i” or better will be compared between arms for each i.

# Reporting

## Statistical report

The statistical analysis and composition of a biometrical report will be performed by……… in cooperation with the Sponsor and the Principal Investigator. All data in this report is confidential.

## Final report

The composition of a final integrated report will be conducted in accordance with ICH E3: Structure and Contents of Clinical Study Reports.

After termination of the biometrical analysis ……………. will compose an integrated report.

This report contains a clinical record, a statistical record, single value tables and conclusions. It will be signed by …………. (Principal Investigator, Sponsor, biometricians, data managers, monitor, trial centre manager)

*Due to the following organisational structure \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ it is guaranteed, that the biometrician named in the protocol (see list of responsibilities) will be able to supervise the statistical analysis.*

## Publication (policy)

The study results will be published irrespective of the study outcome.

# Ethical, legal and regulatory aspects

## ICH-GCP-guidelines

*This trial will be conducted in accordance with the current ICH-GCP-guidelines. Good Clinical Practice (ICH-GCP (E6(R2)) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.*

## Legal requirements of the study

* Approval of Ethics Committee
* Approval of competent authority
* Notification to local authorities
* Informed Consent
* Insurance
* Data privacy and confidentiality

### Approval of Ethics Committee

Proposal

Study protocol, patient information and consent form will be presented to the relevant Ethics Committee (Name, address) for survey. The study will only start after ethics approval has been granted. The Ethics Committee will immediately be informed (by the Sponsor) of all changes to the protocol and of all events that could affect a patients safety. The Ethics Committee will also be informed of all suspected SUSARs and of regular or premature termination of the study.

The Investigators have to register with the Ethics Committee (enter proof of qualification) before they enrol any patients.

### Approval of competent authority

*Proposal*

*The trial will be submitted to the relevant federal authorities (BfArM, PEI) for approval. The trial will only start after approval has been granted*

### Notification to local authorities

*The trial will be submitted to the relevant local authorities. The Sponsor and all Investigators will be reported by full name.*

### Patient information and informed consent

Proposal

Patient Information

Before enrolment every patient will receive full oral and written information about the nature, purpose, expected advantages and possible risks of the trial.

Consent to participation in the trial:

The patient will agree to participation in the trial by signing the informed consent form. Patients must be given an opportunity to enquire about details of the study. After a sufficient period of time for the individual’s consideration and decision, comprehension and consent shall be documented on the consent form by the dated signature of the patient and the Investigator/ treating doctor. If a patient is able to consent but cannot sign himself/herself, oral information and written consent need to be testified and signed by a witness.

Adults who cannot give their consent must be represented by a legal carer.

If applicable: The parent(s) or a legally acceptable representative of minors must read, sign, and date a consent form before his or her child enters the study, takes study treatment, or undergoes any study-specific procedures. If a minor is able to comprehend the study he will also sign an informed consent form.

Design and language will be adjusted to the study site’s needs. The final versions of patient information and consent will be presented to the Ethics Committee. Both the patient information and the patient consent form are prepared in duplicate. One of each form for the Investigator, a duplicate will be handed to the patient.

### Patient insurance

*For participating patients, an insurance (according to. AMG § 40 paragraph 1 Sentence 3 Nb. 8) has been established. The insurance \_\_\_\_\_\_\_\_\_\_ (name, address) policy number \_\_\_\_\_\_will cover for incidents from\_\_\_\_\_\_\_\_\_\_\_ (the commencement of the study/date). The insurance is limited to a maximum of 500.000 Euro per patient.*

### Data Privacy and confidentiality

*The participants’ data will be saved in a pseudonymous form, which will neither contain initials nor full date of birth. All regulative requirements applying to data protection will be met. Re-identification of a participant subject’s name is possible from the patient identification log, which is kept in a locked research office at the Trial site where access is only possible by the principal Investigator or persons authorised by the principal Investigator.*

Patients will be informed that their disease-related data will be saved for scientific purpose (Publication, etc.) using a pseudonym. Consenting patients have got the right to be informed about the data recorded. Patients will also be informed that their pseudonymised data will be forwarded to the ‘Competent Authority and to the Ethics Committee responsible (if necessary), in accordance with legal notification obligation for drug safety. Patients, who disagree with this process of data transfer, are not allowed to participate in this study.

## Archiving of data / access to records

*Originals of all study-related report forms will be stored in the study headquarters at the trial site for at least 10 years after completion of the trial (GCP-V § 13(10)).*

*The Investigator / principle Investigator stores all administrative documents (correspondence with the Ethics Committee, the Supervising Authority, trial centre, study site), patient identification log, the signed patient consent forms, copies of the data documentation form and common study documentation (protocol, amendments) for the duration mentioned above. Original data of study patients (medical records) will be stored for at least 10 years.*

*A list allowing patient identification will be kept for 15 years (directive 2001/83/EG)*

## Financing

*please adapt*

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# Appendices

1. https://apps.who.int/iris/bitstream/handle/10665/330680/WHO-HEO-RDBlueprint%28nCoV%29-2020.1-eng.pdf [↑](#footnote-ref-1)
2. https://www.who.int/blueprint/priority-diseases/key-action/Table\_of\_therapeutics\_Appendix\_17022020.pdf?ua=1 [↑](#footnote-ref-2)