La science pour la santé
From science to health

Réservé au promoteur	N° Inserm	EU-DRACT	CPP	MR	N° Clinical Trial
	C20-15	2020-000936-23	Réf. CPP : 3777 Réf. CNRIPH : 20.03.06.51744	001	NCT04315948
	Qualification Réglementaire	☒ RIPH du 1° médicament ☐ RIPH du 1° médicament thérapie innovante ☐ RIPH du 1° dispositif médical ☐ RIPH du 1° hors produit de santé		☐ RIPH du 2° à risques et contraintes minimes ☐ RIPH du 3° non interventionnelle	

Etude multicentrique, randomisée, adaptative, de l'efficacité et de la sécurité des traitements des patients adultes hospitalisés pour une infection COVID-19

Multi-centre, adaptive, randomized trial of the safety and efficacy of treatments of COVID-19 in hospitalized adults

DisCoVeRy

VERSION N°7.0 DU 05/04/2020

CONFIDENTIEL

Investigateur coordonnateur : **Florence Ader** **Fonction** : **PU-PH** **Unité Inserm d'affiliation : Centre International de Recherche en Infectiologie (CIRI) - Inserm 1111** **DR de rattachement : DR Auvergne Rhône Alpes** **Adresse :** **Service des Maladies infectieuses** **Hopital de la Croix-Rousse, Hospices Civils de Lyon** 104, Grande-Rue de la Croix-Rousse 69317 LYON cedex 04, FRANCE **Tel :** 33 (0)4 72 07 15 60 Mail : florence.ader@chu-lyon.fr	**Méthodologie et statistique :** **Cédric LAOUENAN / France MENTRE** **Unité Inserm d'affiliation : Infection. Antimicrobials. Modelling. Evolution (IAME), UMR 1137** **Adresse :** 46 rue Henri Huchard, 75018 Paris, France **Tel :** 33 (0)1 40 25 79 41 **Email :** cedric.laouenan@inserm.fr, france.mentre@inserm.fr

☐ **Monocentrique** ☐ **Nationale**

☒ **Multicentrique** ☒ **Européenne/Internationale**

Promoteur :	**Contact France :**	**Contact Europe**
Inserm - Pôle Recherche Clinique (PRC) Biopark, Bâtiment A, 8 rue de la Croix Jarry, 75013 Paris	Christelle Delmas, Cheffe de projet christelle.delmas@inserm.fr rqrc.siege@inserm.fr Tél: 01 82 53 33 68 Fax: 01 44 23 67 10	Juliette Saillard, Cheffe de projet juliette.saillard@inserm.fr rqrc.siege@inserm.fr Tél: 01 44 23 67 20 Fax: 01 44 23 67 10

Summary of DisCoVeRy

Terminology: The novel coronavirus-induced disease described in December 2019 in Wuhan is designated COVID-19, and the coronavirus itself (an RNA virus) is designated SARS-CoV-2.

Background: In early 2020, as this protocol was being developed, there were no approved treatments for COVID-19. As soon a January 2020, WHO identified remdesivir and lopinavir/ritonavir as being candidates of interest to be tested in clinical trials [1]. Additional considerations based on emerging literature data have led to consider other drugs such as hydroxychloroquine and interferon ß-1a to be tested. However, other drugs might soon emerge that also require evaluation. The purpose of this randomised trial is to provide substantial evidence on the efficacy, or lack of efficacy and safety of these treatments given the large number of cases.

Randomisation: This protocol therefore describes a randomised trial among adults (≥18) hospitalised for COVID-19 that randomly allocates them between 5 arms: Standard of Care (SoC) alone *versus* SoC + remdesivir *versus* SoC + lopinavir/ritonavir *versus* SoC + lopinavir/ritonavir plus interferon ß-1a *versus* SoC + hydroxychloroquine. Other arms can be added as evidence emerges from other candidate therapeutics.

Adaptive design: The interim trial results will be monitored by a Data Monitoring Committee, and if at any stage evidence emerges that any treatment arm is definitely inferior then it will be decided that that arm will be discontinued. If at any stage evidence emerges that any treatment arm is definitely superior, it will be decided that that arm will become the standard of care. If good evidence emerges while the trial is continuing that some other treatment(s) should also be being evaluated then it will be centrally decided that one or more extra arms will be added while the trial is in progress.

Outcomes to be recorded: At randomisation, information will be collected on the identity of the randomising physician and of the patient, and on age, sex, and an ordinal 7-point scale of severity. The main outcome will be the clinical status on the ordinal 7-point scale at day 15.

Numbers to be randomised: The larger the number randomised the more accurate the results will be, but the numbers that can be randomised will depend critically on how large the epidemic becomes. If substantial numbers are hospitalised in the participating centres then it may be possible to randomise several thousand with moderate disease and a few thousand with severe disease.

Simplicity of procedures: To facilitate collaboration even in hospitals that suddenly become overloaded, patient entry and all of the other trial procedures have been greatly streamlined.

Need for DisCoVeRy protocol: if many hospitals in several different countries collaborate through a compatible master protocol then reliable results will emerge more rapidly than if different hospitals or countries were to establish separate trials, and the findings are therefore more likely to be helpful in controlling the present pandemic. The interim results will be monitored confidentially, allowing the trial to continue across sites and countries without release of results in settings where an outbreak would wane before the trial study had reliably answered the principal questions it was designed to address.

[1] Notes on treatment options: remdesivir is a prodrug, infused once daily and metabolised into an adenosine nucleoside analogue that interferes with the viral RNA polymerase. Lopinavir/ritonavir 200mg-50 mg (widely used in HIV disease) is an orally administered tablets combination of an antiretroviral protease inhibitor (lopinavir) and a pharmacokinetic booster (ritonavir). Hydroxychloroquine 200mg is an orally administered tablet. Interferon ß-1a is an injectable subcutaneous treatment.

LINK WITH WHO SOLIDARITY TRIAL

The DisCoVeRy protocol is based on the WHO Master protocol version 3.0 of March 3, 2020.

That WHO master protocol was largely based on a series of deliberations of the WHO R&D Blueprint Clinical Trials Expert Group, including clinical trialists, coronavirus experts, regulatory and ethics experts, and clinicians,some treating COVID-19 patients.[1] Based on these deliberations, the National Institute of Allergy and Infectious Diseases (NIAID) at the US National Institutes of Health drafted a Master Protocol, which was then adapted by the WHO to facilitate international implementation of the global SOLIDARITY protocol.

As of April 2, 2020, DisCoVeRy is an add-on trial of the SOLIDARITY Trial (protocol v10.0, March 20, 2020)

The randomization of DisCoVeRy patients will be performed on the SOLIDARITY website, the follow-up of patients on DiSCoVeRy E-CRF. At the end of follow-up of each patient the three outcomes of the SOLIDARITY trial will be uploaded by the inverstigator on the specific website.

[1] https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf
https://apps.who.int/iris/bitstream/handle/10665/330694/WHO-HEO-RDBlueprintnCoV-2020.4-eng.pdf
https://apps.who.int/iris/bitstream/handle/10665/330692/WHO-HEO-RDBlueprintnCoV-2020.2-eng.pdf

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with the following, as applicable:

- All National and Local Regulations and Guidance applicable at each site
- The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6(R2) Good Clinical Practice, and the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research,
- National and ethical regulations

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol including statements regarding confidentiality, and according to local legal and regulatory requirements, and ICH E6(R2) GCP guidelines.

Site Investigator Signature:

Signed: _____ Date: _____

Name:

Title:

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

Synopsis

1.1 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. The purpose of this randomised trial is to provide substantial evidence on the efficacy, or lack of efficacy and safety of these treatments given the large number of cases.

This protocol is based on the protocol produced by the National Institute of Health for the World Health Organization (WHO), version of March 3, 2020, which further led to the Solidarity protocol of WHO. This study supports the integration of the Solidarity WHO trial worldwide.

The supplementary investigations in the DisCoVeRy trial correspond to the add-on studies planned by the WHO Solidarity protocol: "Particular countries, or particular groups of hospitals, may want to collaborate in making further measurements or observations, such as serial virology, serial blood gases or chemistry, serial lung imaging, or serial documentation of other aspects of disease status (eg, through linkage to electronic healthcare records and routine medical databases)."

1.2 Study Design

This study is an adaptive, randomized, open clinical trial to evaluate the safety and efficacy of possible therapeutic agents in hospitalized adult patients diagnosed with COVID-19.

The study is a multi-centre/country trial that will be conducted in various sites in Europe with Inserm as sponsor.

The study will compare different investigational therapeutic agents to a control group managed with the Standard of Care (SoC). There will be interim monitoring to allow early stopping for futility, efficacy, or safety and to introduce new therapies as they become available. If one therapy proves to be superior to others

in the trial, this treatment will then become part of the SoC arm for comparison(s) with new experimental treatment(s).

This protocol therefore describes a randomised trial among adults (≥18) hospitalised for COVID-19 that randomly allocates them between 5 arms: Standard of Care (SoC) alone *versus* SoC + remdesivir *versus* SoC + lopinavir/ritonavir *versus* SoC + lopinavir/ritonavir plus interferon ß-1a *versus* SoC + hydroxychloroquine. Other arms can be added as evidence emerges from other candidate therapeutics.

Because of the possibility that standards of supportive care may vary between trial centres and may also be optimized 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.

A global independent data and safety monitoring board (DSMB) is proposed to monitor interim data to make recommendations about early study closure or changes to conduct, including adding or removing treatment arms.

Subjects will be assessed daily while hospitalized. For discharged patients, follow-up assessments will be organized (see Table 1: Schedule of assessments). All subjects will undergo a series of efficacy and safety assessments, including laboratory assays. Blood samples and nasopharyngeal swabs (NP) or lower respiratory tract samples will be obtained on days 1, 3 (while hospitalized); and on days 5, 8, 11, 15 and 29 (in the hospital or in the outpatient setting). Thoracic computed tomography (CT)-scan or chest X-ray, on days 1, 8, 15 and 29 will be made if available depending on the centre imagery capacities over the course of COVID-19 patient management. In-hospital mortality and mortality at day 29 and day 90 will be assessed.

The proposed primary outcome is the condition of the patient on a 7-point ordinal scale on Day 15 (see below).

The larger the number randomised the more accurate the results will be, but the numbers that can be randomised will depend critically on how large the epidemic becomes. If substantial numbers are hospitalised in the participating centres then it may be possible to randomise several thousand with mild disease and a few thousand with severe disease, but realistic, appropriate sample sizes could not be estimated at the start of the study.

As of April 2, 2020, randomization will be performed on the SOLIDARITY WHO clinical trial platform. There is no stratification.

1.3.1 Primary Objective

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

The primary endpoint is subject clinical status (on a 7-point ordinal scale) on Day 15.

1.3.2 Secondary Objectives

Clinical efficacy

Evaluate clinical efficacy of different investigational therapeutics as compared to the control arm as assessed by:

Ordinal scale:

- Time to an improvement of one category from admission on an ordinal scale.
- Subject clinical status on an ordinal scale on Days 3, 5, 8, 11, and 29.
- Mean change in the ranking on an ordinal scale from baseline to Days 3, 5, 8, 11, 15 and 29 from baseline.

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, non-invasive ventilation or high flow oxygen devices during the study.

Mechanical Ventilation:

- Ventilator free days in the first 28 days (to Day 29).
- Incidence and duration of new mechanical ventilation use during the study.

Hospitalization

- Duration of hospitalization (days).

Mortality

- In-hospital mortality
- 28-day mortality.
- 90-day mortality

Safety

Evaluate the safety of different investigational therapeutics through 28 days of follow-up as compared to the control arm as assessed by:

- Cumulative incidence of serious adverse events (SAEs)
- Cumulative incidence of Grade 3 and 4 adverse events (AEs).
- Discontinuation or temporary suspension of antiviral drugs (for any reason).
- Grade changes (according to DAIDS table) in blood white cell count, haemoglobin, platelets, creatinine, blood electrolytes (including kaliemia), prothrombine time and international normalized ratio (INR), glucose, total bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) over time.

1.3.3 Exploratory Objective

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 NP or lower respiratory tract samples on Days 3, 5, 8, 11, 15, and 29.
- Quantitative SARS-CoV-2 virus in NP or lower respiratory tract samples on Days 3, 5, 8, 11, 15, and 29.
- Quantitative SARS-CoV-2 virus in blood at days 3, 5, 8, and 11.

Development of resistance of SARS-CoV-2 in NP or respiratory tract samples sample on Days 3, 5, 8, 11, 15, and 29.

Evaluate concentrations of study medications

- For lopinavir as assessed by:
    - On Day 1, plasma concentration 4 hours after the first administration (peak), and before the second administration (trough at H12)
    - On Days 3, 6, 8 and 11, trough plasma concentration (before dose administration) while hospitalized

- For hydroxychloroquine as assessed by:
    - On Day 1, plasma concentration 4 hours after the first administration (peak), and before the second administration (trough at H12)
    - On Days 3, 5, 8 and 11, trough plasma concentration (before dose administration) while hospitalized

- For remdesivir, as assessed by:
    - On Day 1, plasma concentration after end of infusion (peak)
    - On Day 2 trough plasma and intracellular concentration before dose administration (24 hours after Day 1 infusion)
    - On Days 5 and 8 trough plasma concentration (before dose administration) while hospitalized

- For interferon beta-1a as assessed by:
    - On Days 3, 6 trough plasma concentration (before dose administration) while hospitalized

Evaluate evolution of imagery abnormalities under different investigational therapeutics as compared to the control arm as assessed by:

- Improvement of chest X-ray or thoracic CT scan from baseline on Days 8, 15 and 29 in centres where it could be performed for COVID 19-patients.

Identify genetic variants having an impact (1) in the development of severe clinical disease in individuals infected by SARS-CoV-2 (2) in the response in term of safety and efficacy to investigational antiviral drugs

1.4 Study Endpoints

1.4.1 Primary Endpoint

Clinical status of subject on Day 15 (on a 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;
6. Hospitalized, on invasive mechanical ventilation or ECMO;
7. Death.

Participants who answer yes to the question "are you able to carry out all the activities, including physicial activities, that you carried out before the first symptoms of COVID-19?" will have a score of 1 (Not hospitalized, no limitations on activities). Participants who answer no to the question "are you able to carry

out all the activities, including physical activities, that you carried out before the first symptoms of COVID-19?" will have a score of 2 (Not hospitalized, limitations on activities).

1.4.2 Secondary Endpoints

- Status on an ordinal scale 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.
- In-hospital mortality, 28-day mortality and 90-day mortality with date and cause of death (if applicable).
- Grade 3 and 4 adverse events
- SAEs.
- White cell count, haemoglobin, platelets, creatinine, blood electrolytes (including kaliemia), prothrombin time and international normalized ratio (INR), glucose, total bilirubin, ALT, and AST on Days 1, 3, 5, 8, 11 (while hospitalized or in the outpatient setting); and Days 15 and 29 (in the hospital, or, if discharged in the outpatient setting).

1.4.3 Exploratory Endpoint

- Qualitative and quantitative PCR for SARS-CoV-2 in NP or lower respiratory tract samples on days 1, 3, 5, 8, 11 (while hospitalized or in the outpatient setting); and days 15 and 29 (in the hospital, or, if discharged in the outpatient setting).
- Qualitative and quantitative PCR for SARS-CoV-2 in blood on days 1; 3, 5, 8, 11 (while hospitalized or in the outpatient setting).
- Development of resistance of SARS-CoV-2 in NP or respiratory tract samples at days 3, 5, 8, 11, 15 and 29.
- Whole genome sequencing of participants to identify genetic variants having an impact (1) in the development of severe clinical disease in individuals infected by SARS-CoV-2 (2) in the response in term of safety and efficacy to investigational antiviral drugs
- Imagery assessement through chest X-ray or thoracic CT scan on days 1, 8, 15, 29, depending on availability in centre.

- For lopinavir:

- On Day 1, plasma concentration 4 hours after the first administration (peak), and before the second administration (trough at H12)
- On Days 3, 6, 8 and 11, trough plasma concentration (before dose administration) while hospitalized

- For interferon beta-1a as assessed by:
  - On Days 3, 6 trough plasma concentration (before dose administration)

- For hydroxychloroquine:
  - On Day 1, plasma concentration 4 hours after the first administration (peak), and before the second administration (trough at H12)
  - On Days 3, 5, 8 and 11, trough plasma concentration (before dose administration) while hospitalized

- For remdesivir, as assessed by:
  - On Day 1, plasma concentration after end of infusion (peak)
  - On Day 2 trough plasma and intracellular concentration before dose administration (24 hours after Day 1 infusion)
  - On Days 5 and 8 trough plasma concentration (before dose administration) while hospitalized

1.5 Inclusion criteria

1. Adult ≥18 years of age at time of enrolment.
2. 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.
3. Hospitalized patients with illness of any duration, and at least one of the following:
   - Clinical assessment (evidence of rales/crackles on exam) AND SpO2 ≤ 94% on room air,
     OR
   - Acute respiratory failure requiring supplemental oxygen, high flow oxygen devices, non-invasive ventilation, and/or mechanical ventilation.
4. Women of childbearing potential must agree to use contraception for the duration of the study. Acceptable birth control methods are listed in section 7.3

1.6 Exclusion criteria

1. Refusal to participate expressed by patient or legally authorized representative if they are present
2. Spontaneous blood ALT/AST levels > 5 times the upper limit of normal.
3. Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30 mL/min)
4. Pregnancy or breast-feeding.
5. Anticipated transfer to another hospital, which is not a study site within 72 hours.
6. Patients previously treated with one of the antivirals evaluated in the trial (i.e. remdesivir, interferon ß-1a, lopinavir/ritonavir, hydroxychloroquine) in the past 29 days
7. Contraindication to any study medication including allergy
8. Use of medications that are contraindicated with lopinavir/ritonavir i.e. drugs whose metabolism is highly dependent on the isoform CYP3A with narrow therapeutic range (e.g. amiodarone, colchicine, simvastatine).
9. Use of medications that are contraindicated with hydroxychloroquine: citalopram, escitalopram, hydroxyzine, domperidone, pipéraquine.
10. Human immunodeficiency virus infection under highly active antiretroviral therapy (HAART).
11. History of severe depression or attempted suicide or current suicidal ideation
12. Corrected QT interval superior to 500 milliseconds (as calculated with the Fridericia formula)

1.7 Study Phase

Phase 3

1.8 Study Population

Hospitalized adult (≥18 years old) patients with COVID-19.

1.9 Sites

Site selection will be determined as information becomes available about the epidemiology of COVID-19, and sites will be activated based on the number of local/regional cases and the willingness of local investigators to participate in the study. Multiple sites will be IRB approved, but activation will be dependent on the incidence of COVID-19 at the site.
In France, the trial will be embedded in the French COVID-19 cohort, so that all sites opened will be encourage to participate to the trial.

1.10 Study intervention:

The study will compare different investigational therapeutic agents to a control group. There will be interim monitoring to allow early stopping for futility, efficacy, or safety and to introduce new therapies as they become available. If one therapy proves to be superior to others in the trial, this treatment will then become part of the SoC arm for comparison(s) with new experimental treatment(s). As soon a January 2020, WHO identified remdesivir and lopinavir/ritonavir as being candidates of interest to be tested in clinical trials [1]. Additional considerations based on emerging literature data have led to consider other drugs such as hydroxychloroquine and interferon ß-1a to be tested. However, other drugs might soon emerge that also require evaluation. The purpose of this randomised trial is to provide substantial evidence on the efficacy, or lack of efficacy and safety of these treatments given the large number of cases.

This is randomised trial among adults (≥18) hospitalised for COVID-19 that randomly allocates them between 5 arms: SoC alone *versus* SoC + remdesivir *versus* SoC + lopinavir/ritonavir *versus* SoC + lopinavir/ritonavir plus interferon ß-1a *versus* SoC + hydroxychloroquine. Other arms can be added as evidence emerges from other candidate therapeutics.

The study will randomize participants 1:1:1:1:1 to standard of care alone (control) or with investigational product added. 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.

As new interventions are added, the protocol will be amended and reviewed by IRBs/IECs and applicable regulatory agencies before implementation.

Based on the evidence available on March 29th, 2020 on the different therapeutic options, remdesivir, hydroxychloroquine, lopinavir/ritonavir either

alone or in combination with IFN-ß-1a were considered drug candidates to be evaluated based on their broad antiviral activity, the in vitro and in vivo data showing activity against coronaviruses, preliminary clinical data in patients with COVID-19 and extensive clinical safety database (see below). As a consequence, they were considered suitable options for rapid implementation in clinical trials.

The current protocol lays out the general principles of how the multi-intervention trial would be implemented.

1.11 Study Duration

The study will last for up to 3 years.

1.11.1 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. In addition, in-hospital mortality will be recorded as well as 28-day and 90-day mortality.

1.11.2 Safety

- Given the severity of illness in COVID-19, there is no pre-specified study stopping rules for safety. The protocol team will review AE / SAE data every 2 weeks. If there are a concerning number of unexpected AEs, the DSMB will be asked to review safety data in an *ad hoc* meeting.
- The DSMB will review safety data after every 100 subjects are entered into the study and ad hoc reviews will be undertaken if there are other specific safety concerns. The study will not stop enrolment awaiting these DSMB reviews, though the DSMB may recommend temporary or permanent cessation of enrolment based on their safety reviews.

1.12 Schedule of Assessments

Table 1: Schedule of Assessments

Day +/- Window	Screening[1]	Baseline[2]	1	2-14[3]	15[3] ± 2	29[3] ± 3
Time						
Assessments/Procedures						
ELIGIBILTY						
Informed consent	X					
Demographics & Medical History	X					
EKG	X					
Review SARS-CoV-2 results	X					
STUDY INTERVENTION						
Randomization		X				
Standard of Care (SoC)						
Or SoC plus administration of Lopinavir/ritonavir			Lopinavir/ritonavir for 14 days			
Or SoC plus administration of lopinavir/ritonavir in association with interferon ß1a			Lopinavir/ritonavir for 14 days Interferon ß-1a day 1, day 3 day 6 or until discharge (after at least 2 doses)			
Or SoC plus administration of remdesivir			Daily administration until discharge (after at least 5 days) or Day 10			
Or SoC plus administration of hydroxychloroquine			Daily administration until Day 10			
STUDY PROCEDURES						
Vital signs including SpO_2		X	X	Daily until discharge	X	X
Clinical data collection[4]		X[4]	X[4]	Daily until discharge[4]	X[4]	X[4]
Electrocardiogram (EKG)[5]	X[5]			Day 3, 5, 8[5]		
Medication review	X		X	Daily until discharge	X	X
Adverse event evaluation			X	Daily until discharge	X	X
SAFETY LABORATORY						
Safety haematology, chemistry and liver tests[6,7]	X[6,7,8]	X[9]		Day 3, 5, 8, 11 (all ± 1 day)[6,7,10]	X[6,7,10]	X[6,7,10]
Pregnancy test for females of childbearing potential	X[8]				X[10]	X[10]
Plasma concentration of lopinavir			X[11]	Day 3, 6, 8, 11[11,12] (all ± 1 day)		
Plasma concentration of hydroxychloroquine			X[11]	Day 3, 5, 8, 11[11,12] (all ± 1 day)		
Plasma and intracellular concentration of remdesivir[13]			X[13]	Day 2, 5, 8, 11[13] if hospitalized		
Plasma concentration of interferon ß-1a[14]				Day 3, 6[14] if hospitalized		
RESEARCH LABORATORY						
Blood for serum (serum bank)			X	Day 3, 5, 8, 11 (all ± 1 day)[10]	X[10]	X[10]

Plasma for PCR SARS-CoV-2			X	Day 3, 5, 8, 11 (all ± 1 day)[10]		
Whole blood for blood bank[15]			X[15]			
Nasopharyngeal swab or lower respiratory tract samples			X[5]	Day 3, 5, 8, 11 (all ± 1 day)[8,10]	X[10]	X[10]
Thoracic CT scan or chest x-ray[16]			X[16]	Day 8 (± 1 day)[16]	X[10,16]	X[10,16]
Whole blood for genetic analysis			X			

Notes:

1. *Refer to Section 9.1 of the protocol for details of data to be collected at screening.*
2. *If discharged from the hospital, visits and safety assessments will be conducted in the outpatient setting.*
3. *Baseline assessments should be performed prior to study drug administration*
4. *Refer to Section 9.2 of the protocol for details of clinical data to be collected. This includes ordinal score, NEWS, oxygen requirement, mechanical ventilator requirement, etc.*
5. *An electrocardiogram (EKG) with calculation of the corrected QT (Fridericia formula) will be reviewed at screening and monitored at Day 3, 5, 8 in patients treated with hydroxychloroquine*
6. *White cell count, haemoglobin, platelets, creatinine, blood electrolytes (including kaliemia), prothrombin time and international normalized ratio (INR), glucose, total bilirubin, ALT/SGPT, AST/SGOT.*
7. *Any laboratory tests performed as part of routine clinical care within the specified visit window can be used for safety laboratory testing.*
8. *Laboratory tests performed in the 48 hours prior to enrolment will be accepted for determination of eligibility.*
9. *Any laboratory tests performed in the 24 hours before randomization can be used for baseline and Day 1*
10. *While hospitalized or in the outpatient setting*
11. *Plasma concentration of lopinavir and hydroxychloroquine 4 hours (peak) and 12 hours (trough) after first administration on day 1 and only trough afterwards*
12. *if the drug (lopinavir-ritonavir or hydroxychloroquine) is pursued in the outpatient setting*
13. *Plasma concentration of redemsivir after end of first infusion (peak) and trough on Day 2, 5, 8, 11(24 hours after the infusion on the previous day). Intracellular trough concentration of remdesivir on Day 2.*
14. *Plasma trough concentration of interferon ß-1a on Day 3 and Day 6 (before the administration)*
15. *Whole blood stored for further analysis including dosage of hydroxychloroquine and/or lopinavir before administration of the study drugs if judged necessary*
16. *If available for COVID-19 patients.*

1.13 Study Schema

This is a randomised trial among adults (≥18) hospitalised for COVID-19 that randomly allocates them between 5 arms: SoC alone *versus* SoC + remdesivir *versus* SoC + lopinavir/ritonavir *versus* SoC + lopinavir/ritonavir plus interferon ß-1a *versus* SoC + hydroxychloroquine. Other arms can be added as evidence emerges from other candidate therapeutics.

2. INTRODUCTION

2.1 Study Rationale

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 COVID-19 or infection with SARS-CoV-2 or therapeutic agent to treat COVID-19. This clinical study is designed to evaluate potential therapeutics for the treatment of adult patients hospitalized with COVID-19.

2.2 Background

2.2.1 Purpose of 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 (MERS-CoV).

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 SARS-COV-2 and has 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV[1].

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 modelling 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 an urgent public health need for rapid development of novel interventions.

If many hospitals in several different countries collaborate through DisCoVeRy protocol then reliable results will emerge more rapidly than if different hospitals or countries were to establish separate trials, and the findings are therefore more likely to be helpful in controlling the present outbreak. The interim results will be monitored confidentially, allowing the study to continue across sites and countries without release of results in settings where an outbreak would wane before the study had reliably answered the principal questions it was designed to address.

2.2.2 Potential therapeutics

As soon a January 2020, WHO identified remdesivir and lopinavir/ritonavir as being candidates of interest to be tested in clinical trials [1]. Additional considerations based on emerging literature data available on March 29th, 2020 have led to consider other drugs such as hydroxychloroquine and interferon ß-1a to be tested.

Consequently, remdesivir, hydroxychloroquine, lopinavir/ritonavir either alone or in combination with IFN-ß1a were considered drug candidates to be evaluated based on their broad antiviral activity, the in vitro and in vivo data showing activity against coronaviruses, preliminary clinical data in patients with COVID-19 and extensive clinical safety database (see below). Consequently, they were considered suitable options for rapid implementation in clinical trials.
However, other drugs might soon emerge that also require evaluation. This review will be conducted regularly as more data become available. The intention is to assess the evidence available for these candidates regarding safety and efficacy.

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, Marburg), paramyxoviruses (e.g. RSV, Nipah, Hendra) and pathogenic coronaviruses.[3–5] Multiple nonhuman primate studies have 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 proof reading 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 non-human 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] Remdesivir has recently shown an *in vitro* activity on SARS-CoV-2.[12] 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 (NCT04257656).

Lopinavir/ritonavir

Lopinavir is an antiviral of the protease inhibitor class that disrupts the protease enzyme by forming an inhibitor-enzyme complexe preventing the production of infectious viral particles. Ritonavir substantially increases lopinavir drug exposure by inhibiting cytochrome P450 isoenzyme 3A4 (pharmacokinetic booster). Lopinavir/ritonavir is a fixed dose combination mostly used for the treatment and prevention of HIV infection. It has shown an *in vitro* activity against SARS-CoV in several studies[13] and appears to have activity against MERS-CoV in animal studies[14].

Lopinavir and ritonavir were shown *in vitro* to bind to the active site of the SARS-CoV protease[15] and early virtual docking studies confirmed that the spatial structure of the lopinavir/ritonavir binding site was conserved between SARS-CoV and SARS-CoV-2.[16] Treatment with lopinavir/ritonavir improved clinical, radiological pathological findings and reduced viral load in a nonhuman primate model of marmoset infected with MERS-CoV.[14] In a cohort of 111 patients with SARS infection, the use lopinavir/ritonavir was associated with better clinical outcomes.[17] The use of this agent for treatment of COVID-19 has been described in case reports[18,19] and in a case series of patients infected with SARS-CoV-2 in Singapore. In this article five patients who required supplemental oxygen were treated with lopinavir/ritonavir with no severe adverse events and variable clinical outcomes: three improved and two deteriorated with progressive respiratory failure.[20] These data have led researchers to register a number of clinical trials on the USA clinical trial registry (e.g. trials number NCT04261907, NCT04252885) and the Chinese clinical trial registry (e.g. trials number ChiCTR2000029539, ChiCTR2000029603) evaluating the effect of lopinavir/ritonavir on patients with COVID-19.

The results of the Chinese trial were published on March 18, 2020.[21] It is an open randomized clinical trial comparing 99 patients receiveing lopinavir/ritonavir (400/100 mg bid for 14 days) and 100 patients receiving standard of care (SoC). Patients were adults, with confirmed infection at SARS-CoV-2 and hypoxemia (SaO_2 < 94 %). Primary end point was a clinical endpoint: time to clinical improvement on the 7-item ordinal scale. No significant difference between the 2 groups was observed (HR of improvment 1.24; CI95% 0.90 - 1.72). Mortality at day 28 was not significantly different (19,2% in lopinavir/ritonavir arm vs. 25.0% in SoC arm: différence −5.8 %; CI95% −17.3 - + 5.7). No differences were observed in the proportion of patients with detectable viral loads. In the modified intention to treat analysis (with exclusion of 3 patients that died before taking

lopinavir/ritonavir), time to improvment was shorter by one day in patients with lopinavir/ritonavir (HR 1.39; CI95% 1.00 - 1.91). Mortality was lower (19 % vs. 27,1 %) in the subset of patients reveing lopinavir/ritonavir less that 12 days after the beginning of the symptoms. There were more digestive adverse events in the lopinavir/ritonavir arm but more serious adverse event in the SoC arm.
The authors concluded that treatment by lopinavir/ritonavis did not show a benefit in hospitalized patients with severe COVID-19. However, this trial clearly lacks power, as reconized by the authors, and all clinical outcomes are in favor of the lopinavir/ritonavir arm. Therefore, there is a need for further evaluation of this treatment in a large randomized clinical trial.

Interferon ß1

Interferon (IFN)-ß-1 is a broad-spectrum antiviral drug belonging to the type 1 interferons. Viral components induce a strong type 1 IFN response when detected by pattern-recognition receptors.[22] As a consequence, type 1 IFNs are among the first cytokines produced during a virus infection. These IFNs are produced by fibroblasts and plasmacytoid dendritic cells and bind to a specific cell surface receptor complex known as the IFN-α/β receptor (IFNAR) that consists of IFNAR1 and IFNAR2 chains.[23] The activation of IFNAR induces a number of genes involved in antiviral response via an activation of the innate and adaptive immune response. Type 1 IFNs then induce an array of genes involving host defense, inflammation, signaling, immunomodulation that interfere with virus replication in order to restrict and limit viral spread from cell to cell.[24] They also promote the activation and expansion of lymphocytes that are important for control of viruses during an acute infection. The protective role of type 1 IFNs during virus infection has been highlighted by the increased mortality observed in mice deficient in the type I IFN receptor in comparison to their control counterparts when infected with various viruses.[25,26] Type 1 IFNs have shown a major importance in the immune response against numerous viruses, including human papillomavirus (HPV), Hepatitis C Virus (HCV), Hepatitis B Virus (HBV) and coronaviruses.[24,27]

Regarding specific host-virus interaction, coronaviruses may attenuate the IFN response of the innate immune system and impair the adaptive T-cell immune response. Administering IFN-ß-1 could restore part of this immune response. Among the IFN family biologics, IFN-ß-1a has been reported to be a potently inhibitor of SARS-CoV *in vitro*.[27] In a recent in vitro study, IFN-ß-1a had an antiviral *in vitro* activity equivalent to remdesivir and superior to lopinavir/ritonavir against MERS-CoV.[8] In mice with MERS-CoV, lopinavir/ritonavir combined with IFN-ß-1a improved pulmonary function but did not reduce virus replication or severe lung pathology.[8] In addition, IFN-ß-1a has shown immunomodulatory properties through improvement of pulmonary endothelial barrier function. IFN-ß-1a up

regulates cluster of differentiation 73 (CD73) on pulmonary endothelial cells. Production and increased concentration of CD73-mediated anti-inflammatory extracellular adenosine helps maintain endothelial barrier function, through junctional reorganization, cytoskeleton rearrangement, and further transcriptional up regulation of CD73. Clinical data suggest that IFN-ß-1a, which increases CD73 synthesis, could reduce vascular leakage that is a major feature of early in acute respiratory distress syndrome (ARDS).[28] However, in a recent randomized clinical trial, a 6-day intravenous IFN-ß-1a treatment did not improve mortality in patients with ARDS.[29]

In a study with nonhuman primates, treatment with IFN-ß-1b was as effective as lopinavir/ritonavir to improve outcomes of MERS-CoV infected marmosets.[30] As a consequence, the combination of lopinavir/ritonavir and IFN-ß-1b is currently tested as a potential treatment for MERS-CoV in a randomized controlled trial in Saudi Arabia.[31] Clinical trials have been recently registered to evaluate a combination of lopinavir/ritonavir and IFN (ChiCTR2000029387) or a combination of lopinavir/ritonavir with ribavirin and IFN-ß-1b (NCT04276688) for the treatment of COVID-19.

Thus, we propose to evaluate a recombinant human type 1 IFN: IFN-ß-1a. IFN-ß-1b and -ß-1a both have the same sequence of amino acids than the generic IFN-ß. As such, we expect the main aspects of tolerance to be comparable between the two. We chose IFN-ß-1a preparation because: (i) it is a relatively safe medication, that has been used for more than 2 decades with more than 20,000 patients in the setting of multiple sclerosis (marketing authorization in France in 1998); (ii) it was shown in an *in vitro* model to have antiviral activity 14 times greater than IFN-ß-1b[32]; (iii) its production and supply chain is secured and can sustain the need for the clinical study. Indeed, IFN-ß-1a is produced with Chinese hamster ovary CHO-K1 mammalian cells with a recombinant DNA method and we do not anticipate a problem on the production lines for supply.

Hydroxychloroquine

The *in vitro* antiviral activity of chloroquine has been known for a long time[33] and was described on a number of viruses including SARS-CoV.[34] Hydroxychloroquine as well has been suggested for the treatment of a number viral diseases following *in vitro* data.[35] However, chloroquine failed to demonstrate a benefit in the treatment of viral diseases such as influenza, dengue or chikungunya.[36–38] Regarding COVID-19, a recent publication reported an activity of chloroquine on SARS-CoV-2[12] and another encouraged the use of chloroquine for patients with COVID-19 on the basis of preliminary clinical results.[39] The *in vitro* and pre-clinical

evidence supporting the use of chloroquine for COVID-19 has been recently reviewed.[40]
In light of these encouraging data, on March the 7th, 18 clinical trials evaluating hydroxychloroquine or chloroquine were registered in clinical trial registries.
The mechanism of action between chloroquine and hydroxychloroquine is known to be similar.[41] In animals, both drugs share similar tissue distribution patterns, with high concentrations in the liver, spleen, kidney, and lung reaching levels of 200–700 times higher than those in the plasma.[42] Experts in China have suggested the use of chloroquine for patients infected with SARS-CoV-2 but few clinical data have been provided yet to support this announcement.[43,44] A recent *in* vitro study suggests that hydroxychloroquine is as effective as chloroquine in inhibiting SARS-CoV-2.[42] However, pharmacokinetic data from another study show that hydroxychloroquine is more potent on SARS-CoV-2 infected cells than chloroquine phosphate.[45] In the same article, physiologically-based pharmacokinetic models predict that hydroxychloroquine might have a better diffusion in lung fluids.[45] In a recent single arm trial in France, hydroxychloroquine provided preliminary results showing a decrease of the duration of viral excretion in patients infected with SARS-CoV-2. In this study, the dose of hydroxychloroquine was 600 mg daily. Chinese guidelines for COVID-19 currently recommend hydroxychloroquine 400 mg twice daily for 2 days, followed by 200 mg daily for 4 days. Italian guidelines also use a loading dose of 400 mg twice daily for 2 days with a maintenance dose of 200 mg for 8 days.
For these reasons, we selected hydroxychloroquine as a study medication.

2.3 Risk/Benefit Assessment

2.3.1 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. The final decision to include or exclude women breastfeeding or pregnant and children depends on a risks and benefits assessment.

The potential risks of participating in this study are those associated with having blood drawn, the intravenous (IV) catherization, possible reactions to remdesivir, lopinavir/ritonavir or IFN-ß-1a 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, haematoma 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.

2.3.2 Potential Risks

Remdesivir is a relatively safe investigational therapeutic agent. A few subjects may experience 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 are temporary, lasting only a few days, and none are 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 100 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 should be performed in subjects receiving remdesivir in order to monitor hepatic function. Any observed liver function-related laboratory abnormalities or possibly related AEs should be treated appropriately and followed to resolution. In nonclinical animal studies, toxicity studies found dose-dependent 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 100 mg for up to 14 days. A 100 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.

In the remdesivir arm of the PALM trial with patients with Ebola virus disease, a severe case of hypotension leading to discontinuation of the loading dose infusion has been reported in one patient who subsequently died from cardiac arrest. Given the severity of Ebola virus disease, the causation of remdesivir is

difficult to determine, however, the infusion of remdesivir should be administered with caution.[6]

Lopinavir/ritonavir is a relatively safe combination therapy, approved for use in 2000 in the United States for people living with HIV. It belongs to the World Health Organization's List of Essential Medicines, listing the safest and most effective medicines needed in a health system. The most common adverse effects observed with lopinavir/ritonavir are diarrhea, vomiting, nausea, hypertriglyceridaemia and hypercholesterolemia. However, serious adverse events such as altered cardiac conduction or hepatotoxicity have been described in patients treated with lopinavir/ritonavir even for a short period. As such, lopinavir/ritonavir has to be used with caution in patients with underlying structural heart disease, conduction system abnormalities, ischemic heart disease or cardiomyopathies. 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. Lopinavir/ritonavir (400 mg lopinavir /100 mg ritonavir) will be administered every 12 h for 14 days in tablet form. For patients who are unable to take medications by mouth, the lopinavir/ritonavir (400 mg lopinavir /100 mg ritonavir) will be administered as a 5 mL suspension every 12 h for 14 days via a pre-existing or newly placed nasogastric tube. Lopinavir/ritonavir dose does not have to be adjusted for renal or hepatic impairment but it should be noted that its AUC may be increased in patients with hepatic impairment. Administration of lopinavir/ritonavir is not recommended in patients with severe liver impairment. For children and adolescents, the dose should be lopinavir 230 mg/m2/dose (maximum dose: 400 mg/dose) twice daily. This dose can be used in pregnant women. Lopinavir/ritonavir combination is contraindicated in persons with known hypersensitivity to one of the drugs and should be not be coadministered with drugs that are highly dependent on CYP3A for clearance, particularly drugs with a narrow therapeutic range.

IFN-ß-1a is an approved drug for multiple sclerosis in the USA and in Europe and being tested for ARDS, MERS-CoV and SARS-CoV. Common adverse effects include transient fever, headache, fatigue, pain, myalgia, chills, nausea, abdominal pain, leukopenia or dizziness. Flu-like symptoms are common but benign and transient. Transient elevations in ALT and AST have been observed with IFN-ß-1a. Injection site reactions are common but benign and transient. For subjects enrolled in the study, regular laboratory assessments should be performed in subjects receiving interferon in order to monitor hepatic and renal function. Any observed liver function-related laboratory abnormalities or possibly related AEs should be treated appropriately and followed to resolution. Rare autoimmune disorders including idiopathic thrombocytopenia, hyper- and

hypothyroidism and rarely autoimmune hepatitis have been reported following the use of IFN-ß. This concerns mostly patients with a long history of IFN therapy. Suicidal ideations have been reported with type 1 IFNs and IFN-ß-1a should not be administered to patients with severe depression and suicidal ideation. Hypersensitivity to IFN-ß is a contraincation. IFN-ß should not be used in pregnant women. IFN should be used with caution in patients with pre-existing cardiovascular disease and patients with underlying chronic liver disease, as evidenced by a screening ALT or AST >5 times the upper limit of normal. If administered subcutaneously, the drug should be injected into area where skin is irritated, red, bruised or scarred. There should be a rotation of injection sites. No dosage adjustment is provided for renal or hepatic impairment for IFN-ß-1a.

Hydroxychloroquine is a relatively safe drug with no contraindication other than known allergy or hypersensitivity to hydroxychloroquine or 4-aminoquinoline derivatives and the concomitant use of citalopram, escitalopram, hydroxyzine, domperidone, piperaquine. It belongs to the World Health Organization's List of Essential Medicines, listing the safest and most effective medicines needed in a health system. Hydroxychloroquine has been used for the prevention and treatment of chloroquine-sensitive malaria. Hydroxychloroquine is also approved for lupus erythematosus and rheumatoid arthritis and has been used for decades in a large number of patients (first approval in the USA in 1955). Although a large clinical experience has been obtained, safety data are limited in the COVID19 infection, but reconforting given the short-scheduled duration of use. Regarding safety, short-term therapy is not known to cause retinal toxicity which has only be described for treatment for more than 6 months.[46,47] A large majority of the cases of retinal toxicity occurred after 2 years[48,49] The use of hydroxychloroquine (400-800 mg daily) in infectious diseases for a duration between 1 and 18 months has been described in a number of case series with a good safety profile (35 patients[50], 24 patients[51], 19 patients[52], 22 patients[53], 103 patients[54]). Cardiac toxicity including conduction disorders and QT prolongation have mostly been described with chloroquine but reported with hydroxychloroquine after more than one year of use. [55,56 57 58] Hydroxychloroquine has to be used with caution in patients with underlying structural heart disease, conduction system abnormalities, ischemic heart disease or cardiomyopathies. An electrocardiogram (EKG) with calculation of the corrected QT is advised in these patients before beginning treatment with hydroxychloroquine to avoid the development of torsade de pointes. As recommended by the 2011 American Heart Association/American College of Cardiology (AHA/ACC) scientific statement on prevention of torsade de pointes in hospital settings, a QTc over 500 ms should be considered at risk of torsade de pointes.[59] A recent guidance for navigating the QTc prolonging and torsadogenic potential of potential drugs for

COVID-19 including hydroxychloroquine also suggested not to prescribe hydroxychloroquine in patients with a QTc over 500 ms.[60] We thus decided to exclude patients with a QTc over 500 milliseconds at baseline. The Fridericia formula for correction of the QT interval is the preffered formula as the Bazett correction tends to produce overlong QTc.[61]
This 2011 American Heart Association/American College of Cardiology (AHA/ACC) scientific statement also considered that a QTc over the 99th percentile is abnormally prolonged. This corresponds to a QTc of >470 milliseconds for men and pre-pubertal females, and >480 milliseconds for post-pubertal women.[59] This is in line with the 2015 guidelines of the European Society of Cardiology that recommend a QTc of ≥480 ms to diagnose long QT syndrome.[62]
In these patients, introduction of hydroxychloroquine is possible after correcting electrolytes abnormalities including kaliemia and discontinuing other QTc prolonging medications.[60]
Moreover those patients, as all the patients treated with hydroxychloroquine in this trial, will be monitored by an EKG with calculation of the corrected QT as part of the standard clinical management at day 3, 5, 8. As described earlier, a drug monitoring of hydroxychloroquine with peak and trough measurement will be done.

Myopathy and neurotoxicity has only been described on the long-term.[63] Gastro-intestinal symptoms including nausea, vomiting, diarrhea, abdominal pain are common adverse effects. Dividing doses (twice daily) may improve tolerability. Benign skin reactions may occur. Severe hypoglycemia has been reported in patients with and without concomitant use of antidiabetic agents. Investigators should advise patients of risk of hypoglycemia and associated signs/symptoms. Discontinuation of hydroxychloroquine should be considered in patients who develop severe hypoglycemia without other causes. Neuromuscular effects have been reported but only with long-term therapy. No dosage adjustment is provided for renal or hepatic impairment for hydroxychloroquine.

2.3.3 Risks to Privacy

Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the 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 study will be allowed access to the PHI that is collected.

Any publications from this study 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 and the pertinent regulatory authorities.

2.3.4 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 study. 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.

2.3.5 Assessment of Potential Risks and Benefits

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 pre-clinical data. By excluding those with significant underlying liver and renal disease, and appropriate monitoring during the study, the risk to subjects can be minimized.

Lopinavir/ritonavir is generally a well-tolerated medication that has been administered for more than fifteen years in a large number of patients. Adverse reactions are self-limited and resolved after cessation of the medication.

IFN-ß-1a adverse reactions are usually self-limited and resolved after cessation of the medication. Most of the severe adverse events with IFN-ß-1a have been reported in patients with a long history of taking the medication. The use of IFN-ß-1a for a short time minimizes the risks to subjects. By excluding those with significant underlying liver disease and patients with severe depression or suicidal ideations, and appropriate monitoring during the study, the risk to subjects can be minimized.

Hydroxychloroquine is generally a well-tolerated medication that has been used for decades in chloroquine-sensitive malaria prevention and treatment and in a large number of patients with lupus erythematosus and rheumatoid arthritis. Its first approval for use in the USA was in 1955. Adverse reactions for short-term use

including nausea, vomiting or diarrhea are self-limited and resolved after cessation of the medication. Short-term use is not expected to cause retinal toxicity nor neuromuscular toxicity. Cardiac adverse events are exceptional with use for less than 6 months. Patients with a corrected QT interval superior to 500 milliseconds (as calculated with the Fridericia formula) will be excluded because of the increased risk of torsade de pointes

An EKG at baseline and a monitoring with an EKG at day 3, day 5, day 8 is planned for all patients treated with hydroxychloroquine.

3. 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.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
1. The overall objective of the study is to evaluate the clinical efficacy of different investigational therapeutics relative to the control arm in adult patients hospitalized with COVID-19. • The primary endpoint is the subject clinical status (on a 7-point ordinal scale) at day 15.	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.
Secondary	

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
1. Evaluate the clinical efficacy of different investigational therapeutics as compared to the control arm as assessed by: **Clinical Severity** • Ordinal scale: o Time to an improvement of one category from admission using an ordinal scale. o Subject clinical status using ordinal scale on Days 3, 5, 8, 11, and 29. o Mean change in the ordinal scale from baseline to Days 3, 5, 8, 11, 15 and 29 from baseline.	• Ordinal outcome assessed daily while hospitalized and on Days 15 and 29.
• National Early Warning Score (NEWS): o The time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first. o Change from baseline to Days 3, 5, 8, 11, 15, and 29 in NEWS	• NEWS assessed daily while hospitalized and on Days 15 and 29
• Oxygenation: o Oxygenation free days in the first 28 days (to day 29). o Incidence and duration of new oxygen use, non invasive ventilation or high flow oxygen devices during the study	• Duration of supplemental oxygen (if applicable)
o Mechanical Ventilation: ▪ Ventilator free days in the first 28 days (to day 29). ▪ Incidence and duration of new mechanical ventilation use during the study.	• Duration of mechanical ventilation (if applicable)
• **Hospitalization** o Duration of hospitalization (days).	• Duration of hospitalization
• **Mortality** o In-hospital mortality o 28-day mortality o 90-day mortality	• Date and cause of death (if applicable)
2. Evaluate the safety of the intervention through 28 days of follow-up as compared to the control arm as assessed by:	• SAEs • Severe adverse events • White cell count, haemoglobin, platelets, blood electrolytes (including kalemia), creatinine,

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
• 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, blood electrolytes (including kaliemia), prothrombin time and international normalized ratio (INR), glucose, total bilirubin, ALT, and AST over time.	prothrombin time and international normalized ratio (INR), glucose, total bilirubin, ALT, and AST on days 1; 3, 5, 8, 11 (while hospitalized or in the outpatient setting); and Day 15 and 29 (in the hospital, or, if discharged, in the outpatient setting) • EKG at baseline and, in patients treated with hydroxychloroquine, at day 3, 5 and 8
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 NP or lower respiratory tract sample on Days 3, 5, 8, 11, 15, and 29. • Quantitative SARS-CoV-2 virus in NP or lower respiratory tract sample on Days 3, 5, 8, 11, 15, and 29. • Development of resistance of SARS-CoV-2 in NP or lower respiratory tract sample on Days 3, 5, 8, 11, 15, and 29. Quantitative SARS-CoV-2 virus in blood on Days 3, 5, 8, and 11	• Qualitative and quantitative PCR for SARS-CoV-2 in NP swab or lower respiratory tract sample on Days 1, 3, 5, 8, 11 (while hospitalized or in the outpatient setting); and Days 15 and 29 (in the hospital, or, if discharged in the outpatient setting). • Qualitative and quantitative PCR for SARS-CoV-2 in blood on Days 1; 3, 5, 8, 11 (while hospitalized or in the outpatient setting).
Evaluate evolution of thoracic CT scan or chest x-ray abnormalities under different investigational therapeutics as compared to the control arm as assessed by iImprovement of thoracic CT scan from baseline to Days 8, 15 and 29	• Thoracic CT scan or chest x-ray on Days 1, 8, 15, 29 when possible in centers for COVID-19 patients
Plasma concentrations of lopinavir	• On Day 1, plasma concentration 4 hours after the first administration (peak), and before the second administration (trough at H12) • On Days 3, 6, 8 and 11, trough plasma concentration (before dose administration) while hospitalized

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Plasma concenrations of hydroxychloroquine	• On Day 1, plasma concentration 4 hours after the first administration (peak), and before the second administration (trough at H12) • On Days 3, 5, 8 and 11, trough plasma concentration (before dose administration) while hospitalized
For remdesivir, as assessed by:	• On Day 1, plasma concentration after end of infusion (peak) • On Day 2 trough plasma and intracellular concentration before dose administration (24 hours after Day 1 infusion) • On Days 5 and 8 trough plasma concentration (before dose administration) while hospitallized •
For interferon beta-1a as assessed by:	• On Days 3, 6 trough plasma concentration (before dose administration)
Identify genetic variants having an impact (1) in the development of severe clinical disease in individuals infected by SARS-CoV-2 (2) in the response in term of safety and efficacy to investigational antiviral drugs	• Whole exome sequencing (WES) of the subjects

4. STUDY DESIGN

4.1 Overall Design

This study is an adaptive, randomized, open trial to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adult patients diagnosed with COVID-19. The study is a multicentre/country trial that will be conducted in various sites in Europe. It was decided to conduct an open trial as preparing placebo for the three treatment groups was not feasible to start rapidly. It is also complex to handle in a study with 4 active treatment groups and if additional arms might be added.

This randomised study among adults (≥18) hospitalised for COVID-19 randomly allocates them between 5 arms: SoC alone *versus* SoC + remdesivir *versus* SoC + lopinavir/ritonavir *versus* SoC + lopinavir/ritonavir plus interferon ß-1a *versus* SoC + hydroxychloroquine.
As of April 2, 2020, DisCoVeRy is an add-on trial to SOLIDARITY trial and the global randomization tool of SOLIDARITY will be used.

Other arms can be added as evidence emerges from other candidate therapeutics. 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 vary between centres and 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.

All decisions will be made globally by the Executive Group of the International Steering Committee of Solidarity from information of its DSMC.

Randomization will be stratified by:

- Region (according to the administrative definition in each country)
- Severity of illness at enrolment:
    - Severe disease: Patients requiring non-invasive ventilation OR high flow oxygen devices OR invasive mechanical ventilation OR ECMO;

- Moderate disease: Patients NOT requiring non-invasive ventilation NOR high flow oxygen devices NOR invasive mechanical ventilation NOR ECMO

Notwithstanding that the number of strata should kept to the minimum and the ones selected of major importance, the time of onset of symptoms should be considered for stratification or at least, collection of these data is essential for proper subgroup analyses, and in consideration of the pilot data it might be one key factor to consider as to whether there should be stratification on this variable.

Subjects will be assessed daily while hospitalized. Follow-up is for approximately 29 days and mortality will be assessed in-hospital and on Day 28 and Day 90. Discharged patients will be asked to attend study visits in the hospital on Days 15, and 29. All subjects will undergo a series of efficacy, safety, and laboratory assessments. Blood samples and nasopharyngeal (NP) swabs or lower respiratory tract samples will be obtained on Days 1, 3, 5, 8, 11 (while hospitalized or in the outpatient setting); and Days 15 and 29 (in the hospital, or, if discharged in the outpatient setting). Thoracic CT or chest x-ray, on Days 1, 8, 15 and 29 will be made if available in the center for COVID-19 patients.

The proposed primary outcome, assessed on a 7-point ordinal scale on Day 15.

4.2 Scientific Rationale for Study Design

At present, there is no specific antiviral therapy for coronavirus infections.
Few treatment studies have been conducted because most human coronavirus strains cause self-limited disease and care is supportive.
After the severe SARS coronavirus was identified in 2002 and caused a large outbreak, there was an increased interest in the development of specific therapeutic agents. 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 potential 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 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 multicentre, multinational randomized controlled study, it will be possible 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. Also, 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.

4.3 Justification for Dose

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

Lopinavir/ritonavir (400 mg lopinavir /100 mg ritonavir) will be administered every 12 h for 14 days in tablet form. This dose has been used in clinical reports of patients with SARS infection[17], is currently evaluated in a randomized controlled trial with MERS patients[31] and is the dose proposed in clinical trials registered on the USA (Identifiers NCT04295551, NCT04276688) and Chinese clinical trial registries (Identifiers ChiCTR2000029308, ChiCTR2000029541) for COVID-19.

We will deliver IFN-ß-1a subcutaneously at the dose commonly used in multiple sclerosis: 44 µg on D1, D3, and D6 (total of three doses), as already used for patients with MERS-CoV.[64] This administration schedule is adapted to the known half-life of IFN-ß-1a that is between 50 and 60 hours. The blood peaks of known impregnation biomarkers (ß2-microglobulin and neopterin) are reached 24-48 hours after a subcutaneous injection. Subcutaneously IFN-ß-1a at this dose has been tested in multiple randomized controlled trials in relapsing remitting multiple sclerosis and has shown a good safety profile. The subcutaneous dose that will be used is the one currently used and approved for multiple sclerosis patients in Europe and the USA.
The subcutaneous route of administration of 44 µg/0.5 mL is adapted to all patients hospitalized including in the intensive care unit. Regarding safety, there is no contraindication to the administration of subcutaneous IFN-ß-1a in patients with coagulation disorders. IFN-ß-1a can be administered in the hospital settings as well as in ambulatory settings if needed.

Hydroxychloroquine

Using physiologically-based pharmacokinetic models, hydroxychloroquine concentrations in lung fluid were optimal with a regimen of hydroxychloroquine 400 mg given twice daily for 1 day, followed by 200 mg twice daily for 4 days. When taking into account hydroxychloroquine half-life, which is over 20 days, this 5-day regimen allowed a lung concentration above the target concentration, as assessed by a ratio of free lung tissue trough concentration/EC50 on Day 10. In this model, the loading dose of hydroxychloroquine predicted a faster clinical effect.[45] In a recent article, the use of hydroxychloroquine 600 mg daily for COVID-19 patients provided a mean hydroxychloroquine serum concentration of 0.46 µg/mL+0.2 (N=20).[65] Following this article, the use of 600 mg daily has been suggested and allow a usual serum concentration of 1 µg/L. However, the lack of a loading dose may delay reaching the efficient concentration in the lungs.[45] An USA registered clinical trial is evaluated hydroxychloroquine loading dose of 800 mg orally, followed in 6 to 8 hours by 600 mg, then 600 mg once a day for 6 consecutive days in post-exposure prophylaxis for COVID-19 (NCT04308668). Another registered clinical trial in Korea evaluates hydroxychloroquine 400 mg twice daily for 7 to 10 days. Chinese guidelines for COVID-19 recommend 400 mg twice daily for 2 days, followed by 200 mg daily for 4 days. Italian guidelines also use a loading dose of 400 mg twice daily for 2 days with a maintenance dose of 200 mg for 8 days. Using more than 5 days of hydroxychloroquine might optimize the immunomodulatory effect of hydroxychloroquine. In light of these data, we chose to evaluate the following regimen: loading dose of 400 mg twice daily for one day followed by 400 mg once daily for 9 days. This regimen is in line with existing guidelines and available data regarding the importance of a loading dose and the half-life of hydroxychloroquine that allows a prolonged effective blood and lung concentration. Hydroxychloroquine tablets when crushed probably loose 20-50% biodisponibility. The loading dose of hydroxychloroquine when administered through a nasogastric tube will thus be increased to 600 mg twice a day for one day in order to obtain an effective concentration in the lungs as quickly as possible. This will be followed by the same maintenance dose of 400 mg once a day for 9 days.

There are available laboratory tests to check levels of hydroxychloroquine and its metabolites, thus encouraging pharmacokinetic/pharmacodynamic studies. Doses of hydroxychloroquine for infectious diseases were usually adjusted on the basis of drug monitoring (0·8–1·2 mg/mL for hydroxychloroquine).[53,54]

For therapeutic follow-up, hydroxychloroquine concentration will be measured at H4 (peak) and H12 (trough) on Day 1 (loading dose) then every 2 days (trough) for the duration of the treatment or until discharge.

5. STUDY POPULATION

Male and non-pregnant female adults ≥18 years of age with COVID-19 who meet all eligibility criteria will be enrolled at up to 50 clinical trial sites globally.

Children will be excluded from the study but the inclusion of adolescents could be considered after an amendment. Inclusion or exclusion of breastfeeding or pregnant women depends on a risks and benefits assessment. If this had to be modified in an amendment, it would be in line with the evolution of knowledge on COVID-19 pathology and on the effectiveness of treatments on SARS-CoV-2 infection.

The estimated time from screening (Day -1 or Day 1) to end of study for an individual subject is approximately 29 days. In-hospital mortality will be recorded as well as 28-day and 90-day mortality.

Information regarding this trial may be provided to potential subjects who have previously participated in other trials conducted at the sites and to medical care providers who have cases of COVID-19 admitted to their hospital or in the referral area. Other forms and/or mechanisms of recruitment may also be used. The IRB will approve the recruitment process and all materials prior to use.

Subject Inclusion and Exclusion Criteria must be confirmed by a study clinician named on the delegation log.
Precautions for use hydroxychloroquine:
Careful use of hydroxychloroquine in patients with psoriasis (worsening of lesions). For patients with intermittent porphyria, the intake of hydroxychloroquine can cause a severe crisis. Hydroxychloroquine belongs to the class of amino-4-quinolines. Other drugs in this class have caused acute hemolysis in people with G6PD enzyme deficiency.

5.1 Inclusion Criteria

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

1. Adult ≥18 years of age at time of enrolment.

2. 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.
3. Hospitalized patients with illness of any duration, and at least one of the following:
   - Clinical assessment (evidence of rales/crackles on exam) AND SpO2 ≤ 94% on room air,

     OR
   - Requiring supplemental oxygen, high flow oxygen devices, non invasive ventilation and/or mechanical ventilation
4. Women of childbearing potential must agree to use at least one primary form of contraception for the duration of the study. Acceptable birth control methods are listed in section 7.3.

5.2 Exclusion Criteria

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

1. Refusal to participate expressed by patient or legally authorized representative if they are present
2. Liver enzymes ALT/AST > 5 times the upper limit of normal.
3. Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30 mL/min)
4. Pregnancy or breast-feeding.
5. Anticipated transfer to another hospital, which is not a study site within 72 hours.
6. Patients treated with one of the antivirals evaluated in the study (i.e. remdesivir, interferon ß-1a, lopinavir/ritonavir, hydroxychloroquine) in the past 29 days
7. Contraindication to any study medication including allergy
8. Use of medications that are contraindicated with lopinavir/ritonavir i.e. drugs whose metabolism is highly dependent on the isoform CYP3A with narrow therapeutic range (e.g. amiodarone, colchicine, simvastatine)
9. Use of medications that are contraindicated with hydroxychloroquine: citalopram, escitalopram, hydroxyzine, domperidone, pipéraquine.
10. Human immunodeficiency virus infection under highly active antiretroviral therapy (HAART).
11. History of severe depression or attempted suicide or current suicidal ideation.
12. Corrected QT interval superior to 500 milliseconds (as calculated with the Fridericia formula)

5.2.1 Exclusion of Specific Populations

Children will be excluded from the study but adolescents could be considered after an amendment (regarding a risk benefit analysis for each specific candidate therapeutic).

The drug has only been used in a small number of paediatric patients. Initial information about the epidemiology of COVID-19 indicates that the overwhelming burden of severe disease occurs among older adults especially those with comorbidities. Given significant gaps in knowledge in children, and a low incidence of severe morbidity/mortality, the risk/benefits do not warrant inclusion of this population into this trial at this time.

In non clinical reproductive toxicity studies, remdesivir demonstrated no adverse effect on embryofoetal development when administered to pregnant animals. Embryonic toxicity was seen when remdesivir was initiated in female animals prior to mating and conception, but only at a systematically toxic dose. Because the effects on the foetus are not fully known, pregnant women will not be eligible for the study.

5.2.2 Inclusion of Vulnerable Participants

Not Applicable

5.3 Lifestyle Considerations

During this study, subjects are asked to:

- Refrain from drinking alcohol for 14 days after they begin receiving the antiviral drugs.

  Avoid getting pregnant during the study from Day 1 through Day 29 if female subject.

5.4 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.

5.5 Strategies for Recruitment and Retention

5.5.1 Recruitment

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

In France, the study will be embedded in the French COVID-19 cohort, so that all sites opened will be encouraged to participate to the study.

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, severe 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.

5.5.2 Retention

Participating subjects will be reminded of subsequent visits.

5.5.3 Compensation Plan for Subjects

No compensation is scheduled.

5.5.4 Costs

There is no cost to subjects for the research tests, procedures/evaluations and study product while taking part in this study.

6. STUDY PRODUCT

6.1 Study Product(s) and Administration

6.1.1 Investigational Therapeutic

Study Product Description

Remdesivir is a single diastereomer monophosphoramidate prodrug designed for the intracellular delivery of a modified adenine nucleoside analogue 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.

Lopinavir is an antiviral of the protease inhibitor class that disrupts the protease enzyme by forming an inhibitor-enzyme complexe preventing the production of infectious viral particles. Ritonavir substantially increases lopinavir drug exposure by inhibiting cytochrome P450 isoenzyme 3A4. The lopinavir/ritonavir tablets contain the following inactive ingredients: colloidal silicon dioxide, copovidone, sodium stearyl fumarate and sorbitan monolaurate. The following are the ingredients in the film coating: colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, polyethylene glycol 400, polyethylene glycol 3350, polysorbate 80, talc, titanium dioxide, and yellow ferric oxide E172. Lopinavir/ritonavir oral solution is available for oral administration as 80 mg lopinavir and 20 mg ritonavir per milliliter with the following inactive ingredients: Acesulfame potassium, alcohol, artificial cotton candy flavor, citric acid, glycerin, high fructose corn syrup, Magnasweet-110 flavor, menthol, natural & artificial vanilla flavor, peppermint oil, polyoxyl 40 hydrogenated castor oil, povidone, propylene glycol, saccharin sodium, sodium, chloride, sodium citrate, and water. Lopinavir/ritonavir oral solution contains 42.4% alcohol (v/v).

IFN-ß-1a SC formulation contains the following inactive ingredients: albumin (human), mannitol, sodium acetate, water for injection.

Hydroxychloroquine contains the following inactive ingredients: the excipients of the tablet core are maize starch, calcium hydrogen phosphate dihydrate, silica colloidal anhydrous, polysorbate 80, dried maize starch, talc and magnesium stearate and the excipients of the tablet coating are hypromellose 2910, macrogol 6000, titanium dioxide (E171) and purified talc.

Insofar as the information contained in the marketing authorizations is likely to evolve for IFN-ß-1a, hydroxychloroquine and lopinavir/ritonavir, it is mandatory to ensure at the time of the prescription of the drugs of the respect in particular of

the contraindications, warnings and precautions for use, drug interactions, and contraceptive measures. Refer to the information available on the French Public Drug Database, accessible at http://base-donnees-publique.medicaments.gouv.fr.

Dosing and Administration

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. Remdesivir is administered through a 30 to 60 minutes IV infusion. Patients must be under nurse or doctor surveillance during the infusion in order to detect hypersensitivy reactions or hypotension.
See the protocol-specific Manual of Procedures (MOP) Appendices for detailed information on the preparation, labelling, storage, and administration of remdesivir. Drug preparation will be performed by the participating site's research pharmacist on the same day of administration to the subject. Missed doses are not made up.

Lopinavir/ritonavir (400 mg lopinavir /100 mg ritonavir) will be administered every 12h for 14 days in tablet form. For patients who are unable to take medications by mouth, the lopinavir/ritonavir (400 mg lopinavir/100 mg ritonavir) will be administered as a 5-mL suspension every 12h for 14 days via a pre-existing or newly placed nasogastric tube. Data from patients treated with the suspension of lopinavir/ritonavir via a nasaogastric tube will be subject to special attention and will take into account compatibility aspects.

Interferon ß-1a will be administered subcutaneously at the dose of 44 µg on Day 1, Day 3, and Day 6 (total of 3 doses). No dosage adjustment is provided for renal or hepatic impairment for IFN-ß-1a.

For hydroxychloroquine, the following regimen will be used: loading dose of 400 mg twice daily for one day followed by 400 mg once daily for 9 days. This regimen was the one favored in the physiologically-based pharmacokinetic model studies with SARS-CoV-2 and is in line with available data regarding the importance of a loading dose and the half-life of hydroxychloroquine.

Precautions for use hydroxychloroquine:
An EKG with a corrected QT (Fridericia formula) will be reviewed at baseline and a monitoring at day 3, day 5, day 8 is recommended. In case of corrected QT interval > to 500 milliseconds, drugs should be definitively stopped.

Hydroxychloroquine tablets when crushed probably loose 20-50% biodisponibility. The loading dose of hydroxychloroquine when administered through a nasogastric tube will thus be increased to 600 mg twice a day for one day, followed by a maintenance dose of 400 mg once a day for 9 days (either with crushed tablets in the nasogastric tube if still needed or with orally administered tablets if possible).

Dose Escalation

Not Applicable

Dose Modifications

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

EKG will be monitored in participants in the arm SoC + hydroxychloroquine. In case of corrected QT interval > to 500 milliseconds, the drug should be definitively stopped.

If a participant in an arm containing lopinavir-ritonavir develops severe diarrhea or severe hypokaliemia requiring aggressive intravenous rehydration or intensive potassium delivery, lopinavir-ritonavir should be transiently stopped.
Administration may be resumed when the participant is rehydrated and the potassium returned within normal limits. If, after the reintroduction of drugs the patient develops again severe diarrhea or hypokaliemia, the drug will be definitely stopped.

If the estimated creatinine clearance decreases to less than 30 mL/min and the responsible clinician considers it attributable to the antiviral drug, the drug should be stopped. Administration should also be stopped when the estimated creatinine clearance decreases by 50% as compared to baseline level and the responsible clinician considers it attributable to the antiviral drug. Administration may be resumed when the estimated creatinine clearance increases by 50% as compared to the lowest level attained AND is higher than 30 mL/min.

If, in a patient with normal liver function tests at baseline, the ALT and/or AST increase to > 5 times the baseline level and the responsible clinician considers it attributable to the antiviral drug, the antiviral drug should be held. Administration

may be resumed when the ALT and/or AST decrease by 50% as compared to the highest level attained. If ALT and/or AST increase again after reintroduction of drugs to > 5 times baseline level, the drug will be definitely stopped.

If, in a patient with blood ALT/AST levels between 3 and 5 times the upper limit of normal at baseline, the liver function tests (ALT and/or AST) increase to > 8 times the baseline level and the responsible clinician considers it attributable to the antiviral drug, the antiviral drug should be held. Administration may be resumed when the ALT and/or AST decrease by 50% as compared to the highest level attained. If ALT and/or AST increase again after reintroduction of drugs to > 8 times baseline level, the drug will be definitely stopped.

Concentrations of study medications will not be used for dose modification of study medications as there are no data on the concentration needed for efficacy on COVID-19.

6.1.2 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 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 vials should occur as noted:

Unused and Used active 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.

6.1.3 Formulation, Appearance, Packaging, and Labelling

The lyophilized formulation of remdesivir is a preservative-free, white to off-white or yellow, lyophilized solid containing 100 mg of remdesivir to be reconstituted with 19 mL of sterile waterfor 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 20 mL (100 mg of remdesivir). It is supplied as a sterile product in a single-use, 30 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, hydrochloricacid, and/or sodium hydroxide. Hydrochloric acid and/or sodium hydroxide are used to adjust theformulation to a final pH of 3.0 to 4.0.

The oral tablets of lopinavir/ritonavir contain 200 mg lopinavir, 50 mg ritonavir. They have a yellow colour, film-coated, ovaloid shape debossed with the "a" logo and the code KA. The oral solution for patients who cannot swallow is a light yellow to orange colored liquid containing 400 mg lopinavir and 100 mg ritonavir per 5 mL (80 mg lopinavir and 20 mg ritonavir per mL). The lopinavir/ritonavir tablets contain the following inactive ingredients: colloidal silicon dioxide, copovidone, sodium stearyl fumarate and sorbitan monolaurate. The following are the ingredients in the film coating: colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, polyethylene glycol 400, polyethylene glycol 3350, polysorbate 80, talc, titanium dioxide, and yellow ferric oxide E172.

IFN-ß-1a is supplied as a sterile solution containing no preservative available in a prefilled syringe. It will be provided as a single-dose prefilled graduated syringe

with 44 µg per 0.5 mL. The liquid should be clear to slightly yellow. Do not use if the liquid is cloudy, discolored or contains particles. Use a different syringe. It contains the following inactive ingredients: albumin (human), mannitol, sodium acetate, water for injection

Hydroxychloroquine is supplied as film-coated 200 mg tablets. Hydroxychloroquine sulfate tablets are presented as white or whitish, peanut-shaped, oblong or round film-coated tablets containing 200 mg of hydroxychloroquine sulfate (equivalent to 155 mg base). The excipients of the tablet core are maize starch, calcium hydrogen phosphate dihydrate, silica colloidal anhydrous, polysorbate 80, dried maize starch, talc and magnesium stearate. The excipients of the tablet coating are hypromellose 2910, macrogol 6000, titanium dioxide (E171) and purified talc.

6.1.4 Product Storage and Stability

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.

Lopinavir/ritonavir tablets should be stored at 20°- 25°C (68°-77°F); excursions are permitted to 15°C- 30°C (59°- 86°F). Dispense in original container or equivalent tight container. Exposure of this product to high humidity outside the original container or equivalent tight container for longer than 2 weeks is not recommended. Lopinavir/ritonavir oral solution should be stored at 2°C- 8°C (36°-46°F) until dispensed and exposure to excessive heat should be avoided. Lopinavir/ritonavir oral solution remains stable until the expiration date printed on the label. If stored at room temperature up to 25°C (77°F), oral solution should be used within 2 months.

IFN-ß-1a should be stored refrigerated between 36°F to 46°F (2°C to 8°C) but should not be freezed. If needed, IFN-ß-1a may be stored between 36°F to 77°F (2°C to 25°C) for up to 30 days and away from heat and light, but refrigeration is preferred.

Hydroxychloroquine tablets should be stored at room temperature (15°- 30°C (59°-86°F)). Hydroxychloroquine should be dispensed in a tight, light-resistant container.

6.1.5 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.

7. Measures to Minimize Bias: Randomization

The study will randomize participants 1:1:1:1:1 to standard of care alone or with investigational product added. 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.

As of April 2, 2020, randomization will be performed on the SOLIDARITY WHO clinical trial platform. There is no stratification.
v

The randomization procedure and link with DisCoVeRy e-CRF will be described in an SOP.

7.1 Study Intervention 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).

7.2 Concomitant Therapy

Patients treated with one of the antivirals evaluated in the study (lopinavir/ritonavir, IFN-ß-1a, remdesivir, hydroxychloroquine) cannot be included.

Included participants cannot be treated with antivirals other than the study medication that are administered in the clinical trial according to randomization. Included participants can be treated with other investigational drugs that are not antivirals including - but not limited - to steroids, tocilizumab, sarulimab, etc. These

drugs can be used as part of the standard of care or as part of another clinical trial.

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 6.1.1).

Lopinavir/ritonavir should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events especially CYP3A inhibitors (e.g. amiodarone, colchicine, simvastatine).
An exception is allowed for patients hospitalized in the intensive care unit and for which sedation is needed, midazolam can be used as part of standard sedation regimen. Starter dose of midazolam will be divided by four and subsequently adjusted through individual titration of daily doses according to an internationally validated sedation score. The sedation will be adjusted using the local sedation score and protocols.

Hydroxychloroquine should not be co-administered with citalopram, escitalopram, hydroxyzine, domperidone, piperaquine. Generally, for patients with cardiac conditions co-administration of known QT prolongation drug should be used with caution (see section 2.3.2).

- Last intake of citalopram, escitalopram, hydroxyzine, domperidone : 7 days before inclusion
- Last intake of piperaquine: 4 months before inclusion

The list of medications will be assessed only from 7 days prior to enrolment to day 15 and will be detailed in the MOP.

7.3 Acceptable birth method control

Women of childbearing age potential must use an acceptable birth method control. These acceptable methods are: Intrauterine device with copper, hormonal contraception and sterilization.
Hormonal contraception must be compatible with study drug. Sterilization is defined by physically incapable of becoming pregnant with documented tubal ligation, hysterectomy or bilateral oophorectomy.
Patients treated with remdesivir: in the case of hormonal contraception (including intrauterine device with hormonal release), a barrier contraceptive must be used in addition.

7.4 Rescue Medicine

Not Applicable

7.5 Non-Research Standard of Care

Not Applicable

8. STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

8.1 Halting Criteria and Discontinuation of Study Intervention

8.1.1 Individual antiviral drugs 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 6.1.1 for information about dose modifications due to laboratory abnormalities.

8.1.2 Study Halting for Safety

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. Treatment should be stopped if a patient is found to be pregnant after randomization

8.1.3 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.

8.1.4 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.

8.1.5 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
- Discontinuation from the study is requested by the patient for any reason
- Discontinuation from the study is requested by or one of the investigators upon medical judgment
    - Particularly in the arm standard of care alone for patients with severe disease
- 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.

8.1.6 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.

9.STUDY ASSESSMENTS AND PROCEDURES

9.1 Screening Assessment

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 by PCR.
- Focused medical history, including the following information:
    - Day of onset of COVID-19 symptoms
    - Day of hospitalisation
    - History of chronic medical conditions related to inclusion and exclusion criteria
    - Medication allergies or contraindication
    - 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 study to avoid pregnancy.
- Obtain age and sex
- Obtain weight and height
- Obtain country of birth and ethnicity
    - In the context of a new disease, the ethnicity might be a prognostic factor for COVID-19. Moreover, the ethnicity is known to be an important factor for drug concentrations and the pharmacodynamics / pharmacokinetic of study drugs may be different according to ethnicity.
- Review electrocardiogram (EKG) and calculate corrected QT interval (Fridericia formula)
- Obtain blood for screening laboratory evaluations if not done in the preceding 48 hours:

- ALT
- AST
- Creatinine (and calculate creatinine clearance)
- Blood electrolytes (including kaliemia)
- Prothrombin time and international normalized ratio (INR)
- Urine or serum pregnancy test (in women of childbearing potential)

The following data collected before randomization will be reported centrally to the WHO Solidarity trial:

- Country, hospital (from a list of approved hospitals) and randomising doctor
- Confirmation that informed consent has been obtained
- Patient identifiers, admission date, age and sex
- Patient characteristics (yes/no): current smoking, diabetes, heart disease, chronic lung disease, chronic liver disease, asthma, HIV, Tuberculosis.
- COVID-19 severity at entry (yes/no): shortness of breath, being given oxygen, already on a ventilator, and, if lungs imaged, major bilateral abnormality
- Whether any of the study drugs are currently not available at the hospital.

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 one or more exclusion criteria 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.

9.2 Efficacy Assessment

For all baseline assessments and follow-up visits, refer to SOA for procedure to be done, and details below for each assessment.

Measures of clinical support

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

- Hospitalization
- Oxygen requirement
- High flow oxygen devices
- Non-invasive mechanical ventilation (via mask)

- Mechanical ventilator requirement (via endotracheal tube or tracheostomy tube)
- 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. onday 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.

Participants who answer yes to the question "are you able to carry out all the activities, including physicial activities, that you carried out before the first symptoms of COVID-19?" will have a score of 1 (Not hospitalized, no limitations on activities). Participants who answer no to the question "are you able to carry out all the activities, including physical activities, that you carried out before the first symptoms of COVID-19?" will have a score of 2 (Not hospitalized, limitations on activities).

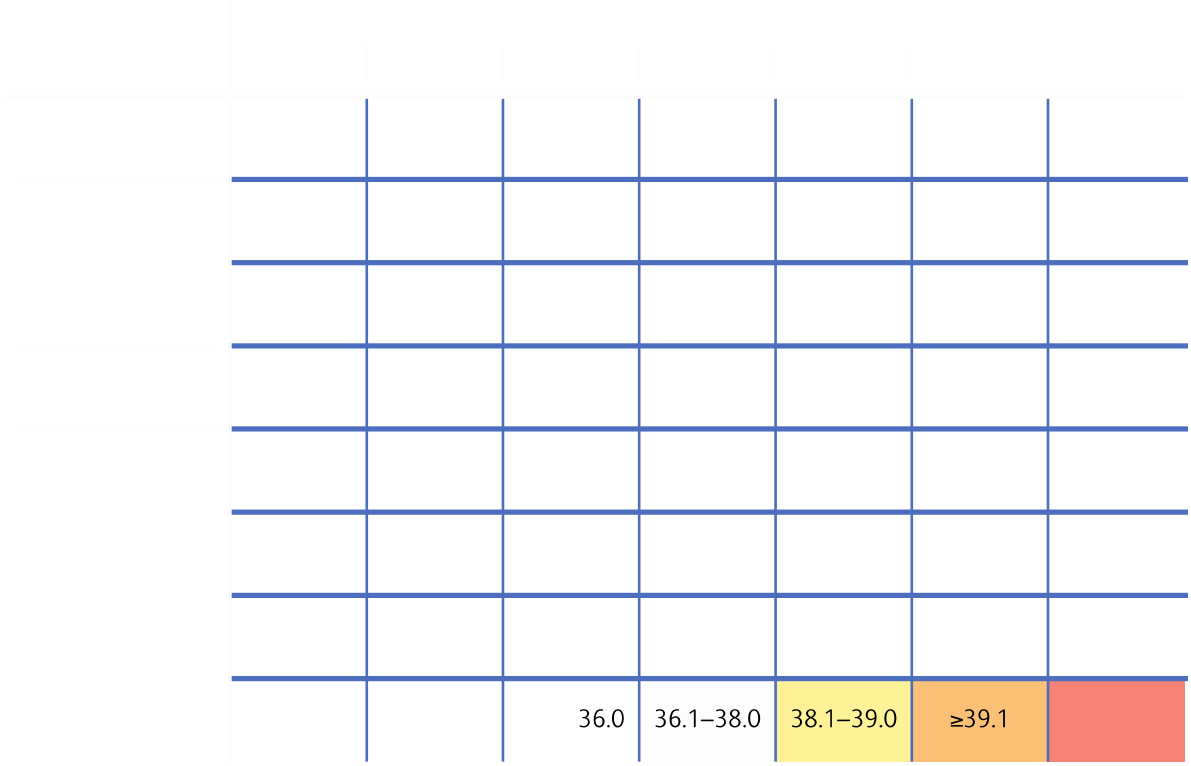
NEW Score

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 2

Chart 1: The NEWS scoring system



SpO2 scale: For patients confirmed to have hypercapnic respiratory failure on blood gas analysis on either a prior or their current hospital admission, and requiring supplemental oxygen, we recommend (i) a prescribed oxygen saturation target range of 88–92%, and (ii) that the dedicated SpO2 scoring scale (Scale 2) on the chart should be used to record and score the oxygen saturation for the NEWS. The decision to use SpO2 scale 2 should be made by a competent clinical decision maker and should be recorded in the patient's clinical notes. In all other circumstances, the regular NEWS SpO2 scale 1 should be used.

CVPU: Confusion or arousable only to voice (V) or pain (P), or unresponsive (U).

In addition, following clinical information should be collected:

- Symptoms
- Complications
- Assessment of measures of clinical support
    - Oxygen requirement and flow
    - High flow oxygen devices requirement
    - Non-invasive mechanical ventilation and parameters of ventilation

- Mechanical ventilator requirement (via endotracheal tube or tracheostomy tube) and parameters of ventilation
- Hemodynamic support, drug and dose
- ECMO requirement and parameters

The following data collected during follow-up will be reported centrally to the WHO Solidarity trial:

- When patients die or are discharged, follow-up ceases and it is reported
- Which study drugs were given (and for how many days)
- Whether ventilation or intensive care was received (and, if so, when)
- Date of discharge, or date and cause of death.

9.3 Exploratory Assessment

Viral Shedding

NP swabs or lower respiratory tract samples will be collected on days 1; 3, 5, 8, 11 (while hospitalized); and Day 15 and 29 (in the hospital, or, if discharged in the outpatient setting) and stored as outlined in the MOP. Development of resistance of SARS-CoV-2 in NP or respiratory tract samples will be analyzed.

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. In France, these samples can be centralized and analyzed in the National Reference Center (CNR) of virology in Lyon.

Concentrations of study medications

Concentration of lopinavir/ritonavir, hydroxychloroquine, interferon ß-1a and remdesivir will be measured at different time points for each drug (see Table 1). The drug concentration can be assessed centrally if not available in the study centre.

Evolution of Thoracic CT scan or chest x-ray

Thoracic CT-scan or chest X-ray will be performed on Days 1, 8, 15, 29 whenever possible in centers managing COVID-19 patients. A standardized framework will be used to assess the CT scans in each centre.

Genetic variants associated with severity of disease and/or drug response

Whole blood for whole exome sequencing will be collected at baseline in subjects who agree to participle in the genetic analysis.

9.4 Safety and Other Assessments

9.4.1 Safety procedures

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. If follow-up assessments are conducted in the outpatient setting, each center has to manage the collection of the data and the completion of the CRF.

- Physical examination: A symptom-directed (targeted) physical examination will be performed to evaluate for any possible adverse event.

- Electrocardiogram: the electrocardiogram with calculation of the corrected QT (Fridericia formula) will be monitored at day 3, day 5 and day 8 in patients treated with hydroxychloroquine.

- 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, blood electrolytes, glucose, total bilirubin, AST, ALT.
    - This testing will be performed at each clinical trial site in real time.
    - Urine or serum pregnancy test on Day 15 and Day 29 (in women of childbearing potential)

Table 3: Venepuncture Volumes

	Screen	***Baseline***								
Day +/- Window	**−1 to 1**	**1**	**2**	**3**	**5 ±1**	**6**	**8 ± 1**	**11 ± 1**	**15 ± 2**	**29 ± 3**
Safety haematology, chemistry and liver tests[21]		X 6mL		X 6mL	X 6mL		X 6mL	X 6mL	X 6mL	X 6mL
Blood for Serum		X 7mL		X 7mL	X 7mL		X 7mL	X 7mL	X 7mL	X 7mL
Plasma (includes PCR)		X 6mL		X 6mL	X 6mL		X 6mL	X 6mL		

Blood for drug concentration (EDTA)		X 2 x 5mL	X[1] 5mL[1] 21mL[1]	X 5mL	X 5mL	X 5mL[2]	X 5mL	X 5mL		
Blood for genetic analysis (EDTA)		X 5mL								
Whole blood for blood bank (EDTA)		X 5mL								
Total volume		39mL	26mL	24mL	24mL	5mL	24mL	24mL	13mL	13mL
Maximum total for all study days										187mL

[1]Only for the participants in the remdesivir arm
[2]Only for the participants in the arm containing interferon

9.4.2 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).

9.5 Adverse Events and Serious Adverse Events

9.5.1 Definition of Adverse Event (AE)

AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it should be recorded as an AE.

Given the nature of severity of the underlying illness, subjects will have many symptoms and abnormalities in vitals and laboratory. All Grade 3 and 4 AEs will be captured as AEs in this trial and will be considered as notable events.

9.5.2 Definition of Serious Adverse Event (SAE)

An SAE is defined as "An AE or suspected adverse reaction is considered serious if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death,
- a life-threatening AE,
- prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- or a congenital anomaly/birth defect.
- important medical events

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse."

"Life-threatening" refers to an AE that at occurrence represents an immediate risk of death to a subject. An event that may cause death if it occurs in a more severe form is not considered life-threatening. Similarly, a hospital admission for an elective procedure is not considered a SAE.

All SAEs, as with any AE, will be assessed for severity and relationship to study intervention.

All SAEs will be recorded on the appropriate SAE CRF.

All SAEs will be followed through resolution or stabilization by a licensed study physician (for IND studies, a physician listed on the Form FDA 1572 as the site PI or Sub-Investigator).

All SAEs will be reviewed and evaluated and will be sent to the SMC (for periodic review), and the IRB/IEC.

9.5.3 Suspected Unexpected Serious Adverse Reactions (SUSAR)

A SUSAR is any SAE where a causal relationship with the study product is at least reasonably possible but is not listed in the Investigator Brochure (IB), Package Insert, and/or Summary of Product Characteristics. All SUSAR and SAR will be sent to DSMB in real time for a safety review.

9.5.4 Classification of an Adverse Event

The determination of seriousness, severity, and causality will be made by an on-site investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment. This includes but is not limited to physicians, physician assistants, and nurse practitioners.

Severity of Adverse Events

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

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- Mild (Grade 1): Events that are usually transient and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the subject's usual activities of daily living.

- Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

- Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.

- Severe (Grade 4): Events that are potentially life threatening.

AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop Duration of each reported AE will be recorded on the appropriate CRF. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity.

Relationship to Study Intervention

For each reported adverse reaction, the PI or designee must assess the relationship of the event to the study product using the following guideline:

- Related – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

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

9.5.5 Time Period and Frequency for Event Assessment and Follow-Up

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.

Investigators Reporting of AEs

Information on all AEs should be recorded on the appropriate CRF. All clearly related signs, symptoms, and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis. If the AE is a laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the

individual laboratory abnormality. Each AE will also be described in terms of duration (start and stop date), severity, association with the study product, action(s) taken, and outcome.

9.5.6 Serious Adverse Event Reporting

Investigators Reporting of SAEs

- **e-CRF Notification :**

Any AE that meets a protocol-defined criterion as a SAE must be notified immediately (within 24 hours of site awareness) on an SAE form.

When the eCRF SAE notification form is completed, dated and signed by the investigator, an automatic email is sent immediately to the Inserm safety department.

- **Back up circuit when eCRF is unavalaible:**

The investigator must report all SAE/SAR using the CRF SAE printed form, dated and signed to:

- Institut Thématique Santé Publique – Recherche Clinique et Thérapeutique (ITSP – RCT)
- Mission Réglementation et Qualité et Recherche Clinique (RQRC)

Fax: 01 53 94 60 02
Email: pharmacovigilance.prc@inserm.fr

If an SAE is declared by paper circuit, it is the responsibility of the site to re-enter the form in the eCRF

- **Relevant documentation related to SAE** (e.g. hospitalization report, laboratories results…):

The investigator sends all relevant coded documentation related to the SAE to the Inserm safety department, by fax: 01 53 94 60 02 or by email: pharmacovigilance@anrs.fr.
The designated Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

At any time after completion of the study, if the site PI or appropriate sub-investigator becomes aware of an SAE, the site PI or appropriate sub-investigator will report the event to the Inserm safety department.

Regulatory Reporting of safety data

All Suspected Unexpected Adverse Reactions (SUSAR) have to be reported, within the legal timeframe, by the sponsor to the National Competent Authority of the Member State concerned.

The timelines for expedited initial reporting (day 0) starts as soon as the information containing the minimum reporting criteria has been received by the sponsor.

For fatal and life-threatening SUSAR, the sponsor should report at least the minimum information without delay after being made aware of the case.
SUSAR which are not fatal and not life-threatening are to be reported within 15 calendar days.

If significant new information on an already reported case is received by the sponsor, this information should be reported as a follow-up report within 8 days after being made aware of the relevant complementary information.

Once a year throughout the clinical trial, the sponsor should submit to the national competent authority and the Ethics Committee of the Member States, an annual safety report.

9.5.7 Reporting of Pregnancy

Pregnancy is not an AE. However, any pregnancy that occurs during study participation should be reported to the sponsor on the appropriate CRF form. Pregnancy should be followed to outcome.

9.6 Safety concerns including unanticipated Problems

9.6.1 Definition of Unanticipated Problems (UP)

An Unanticipated Problem is any event, incident, experience, or outcome that meets the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the EC-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.6.2 Unanticipated Problem Reporting

To satisfy the requirement for prompt reporting, unanticipated problems (UP) will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB/EC and to the Statistical and Data Coordinating Centreand study sponsor within 24 hours of the investigator becoming aware of the event per the above describe SAE reporting process.
- Any other UP will be reported to the IRB/EC and to the SDCC/study sponsor within 3 days of the investigator becoming aware of the problem.

9.6.3 Reporting Unanticipated Problems to Subjects

Subjects will be informed of any UPs that occur as part of their participation in this study.

10 STATISTICAL CONSIDERATIONS

This study is intended to allow for adaptations with the 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.

The current plan is to evaluate the primary endpoint on Day 15.

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].

10.1 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

control 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 control and experimental treatment arms (i.e., whether the common odds ratio differs is 1).

10.2 Sample Size Determination

The larger the number randomised the more accurate the results will be, but the numbers that can be randomised will depend critically on how large the epidemic becomes. If substantial numbers are hospitalised in the participating centres then it may be possible to randomise several thousand with mild disease and a few thousand with severe disease, but realistic, appropriate sample sizes could not be estimated at the start of the study.

The samples sizes presented here are only illustrative. The larger the number randomised the more accurate the results will be, but the numbers that can be randomised will depend critically on how large the epidemic becomes.

The interim study results will be monitored by a Data Monitoring Committee, and if at any stage evidence emerges that any one treatment arm is definitely inferior then it will be communicated to the DSMC of SOLIDARITY trial. If at any stage evidence emerges that any treatment arm is definitely superior, it might be decided that that arm will become the standard of care. If good evidence emerges while the study is continuing that some other treatment(s) should also be being evaluated then it will be decided that one or more extra arms will be added while the trial is in progress. All those decisions will be made globally by the Executive Group of the International Steering Committee of Solidarity from information of its DSMC.

<u>Sample size estimates provided as a reference but not to indicate final number of patients to be randomised.</u>

The proportions of patients in the different categories of the ordinal scale on Day 15 in the control 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 control 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 $\alpha$is given by

$$\frac{12\left(z_{\alpha/2}+z_{\beta}\right)^{2}}{\theta^{2}\left(1-\sum_{i=1}^{6}p_{i}^{3}\right)},$$

where θ is the log odds ratio, p_i is the overall probability (combined over both arms) of being in the ith category of the ordinal outcome, and $z_{\alpha/2}$ and z_β are the $1-\alpha/2$ and βth quantiles of the standard normal distribution.

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

Table 4: Possible scenarios for outcomes on Day 15.

	Anticipated	***Alternative Scenarios***			
	Scenario 1	***Scenario 2***	***Scenario 3***	***Scenario 4***	***Scenario 5***
		more mild disease ⟷ more severe disease			
Severity Outcome	outcome (%)	*outcome (%)*	*outcome (%)*	*outcome (%)*	*outcome (%)*
Death	2	*1*	*1*	*2*	*3*
Hospitalized, on mechanical ventilation or ECMO	1	*1*	*1*	*1*	*3*
Hospitalized, on non-invasive 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*

The targeted strength of evidence for a stand-alone registration trial in essence is 2-sided p=0.05, which corresponds to a (one-sided) false positive error rate of 0.025.

Adjusting for multiplicity of 4 pairwise comparisons with the control arm in a 5-arm setting, the (one sided) false positive error rate would be 0.00625, (which requires achieving two-sided p=0.0125.)

Since a large proportion of patients are moderately ill patients, we power the study for an odds ratio 1.5.

We would need about 3,100 total patients or around 620 patients per arm.

10.3 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-to-treat population consisting of all participants who received at least one administration.

10.4 Statistical Analyses

10.4.1 General Approach

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

The interim trial results will be monitored by a Data Monitoring Committee, and if at any stage evidence emerges that any one treatment arm is definitely inferior then it will be communicated to the SOLIDARITY DSMC. If at any stage evidence emerges that any treatment arm is definitely superior, it will be decided that that arm will become the standard of care. If good evidence emerges while the trial is continuing that some other treatment(s) should also be being evaluated then it will be decided that one or more extra arms will be added while the trial is in progress.

All decisions will be made globally by the Executive Group of the International Steering Committee of Solidarity from information of its DSMC.

10.4.2 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.

The two-sided type I error of the trial is 0.01. As there are 4 comparaisons, each treatment group will be compared to the control group with a two-sided type I error of 0.0033. 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.

10.4.3 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.

10.4.4 Safety Analyses

Safety endpoints include death through Day 28, SAEs, discontinuation of study infusions, and severe AEs. These events will be analysed 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.

10.4.5 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).

10.4.6 Planned Interim and Early Analyses

Early analyses

Additional early analyses include monitoring enrolment, 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 communicate the results with the DSMC of SOLIDARITY trial when there is clear and substantial evidence of a treatment difference. More details about the interim analyses are described below as well as a separate guidance document for the DSMB. The composition and the charter of the DSMB will be communicated to the ANSM, as well as the minutes of each DSMB meeting.

The tree major outcomes of the SOLIDARITY trial will be analysed by the SOLIDARITY DSMC and not by the DIsCoVeRy DSMC. The two DSMC will get in relation before any decision is made about droping or adding an arm.

The 3 outcomes of the SOLIDARITY trial are

- Primary outcome: all-cause mortality, subdivided by severity of disease at the time of randomisation.
- Major secondary outcome: duration of hospital stay and time to first receiving ventilation (or intensive care)

Note the guidelines below recognize that we do not have a fixed target sample size, hence there are no alpha-spending functions nor conditional power. Also, formal corrections for multiple testing are not used: there are 4 active treatments

and an unknown number of interim reports (depending on recruitment) so such corrections were infeasible. The specifications below are in the spirit of statistical guidelines only, ie not rules. DSMB recommendations need to be based on the totality of evidence from primary, secondary and safety outcomes as well as any external evidence.

Interim Safety Analyses

Interim reports will be presented to the DSMB for efficacy and futility analyses every 100 patients when their day 15 data available for analysis. No pre-specify stopping guideline will be defined because there are various aspects of potential harm that could be studied. But to allow for some caution, any safety signal, ie active treatment worse than control, requires P<.01 to merit consideration of stopping that treatment arm.

Interim Efficacy Review

Interim reports will be presented to the DSMB for efficacy and futility analyses every 100 patients when their day 15 data available for analysis.

For EFFICACY, the statistical analysis will be done on the primary outcome, the 7-point ordinal scale at 15 days, and be based on the Haybittle Peto rule. That is, if any active treatment is superior to control at P<.001 then consideration be given to stopping early for efficacy. This would have major implications, hence the stopping boundary is stringent in the spirit of requiring proof beyond reasonable doubt.
For FUTILITY, ie stopping because an active treatment appears ineffective, the statistical analysis will be done with the primary outcome. Comparing an active treatment with control, if the upper 95% confidence limit for the common odds ratio is less than 1.25 then consideration be given to stopping that treatment for futility. Note that the odds ratio 1.5 was used for power calculations.

All the above is intended for all randomised patients. Analyses will be stratified by baseline severity of disease. Additionally, subgroup analyses for patients separated into moderate or severe baseline status could be done be with no pre-specify stopping guidelines for such subgroups.

An independent statistician, 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.

10.4.7 Sub-Group Analyses

Subgroup analyses for the primary outcomes will evaluate the treatment effect across the following subgroups: disease severity at inclusion, geographic region, duration of symptoms prior to enrolment, 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.

10.4.8 Exploratory Analyses

An exploratory analysis will compare treatment efficacy estimates according to the various scales outlined in section 9.1.3. Specifically, the probability of falling into category “i” or better will be compared between arms for each i.

11.SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 Regulatory, Ethical, and Study Oversight Considerations

This study will be conducted in conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research and the ICH E6(R2).

IRBs will review and approve this protocol, associated informed consent documents, recruitment material, and handouts or surveys intended for the subjects, prior to the recruitment, screening, and enrolment of subjects. Site IRBs may have additional national and local regulations.

Any amendments to the protocol or consent materials will be approved by the IRB before they are implemented. IRB review and approval will occur at least annually throughout the duration of the study. The investigator will notify the IRB of deviations from the protocol and SAEs, as applicable to the IRB policy.

The Sponsor must receive the documentation that verifies IRB-approval for this protocol, informed consent documents, and associated documents prior to the recruitment, screening, and enrolment of subjects, and any IRB-approvals for continuing review or amendments as required by the Sponsor.

11.1.1 Informed Consent Process

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Investigators or designated research staff will obtain a subject's informed consent in accordance with the national ethics and regulatory requirements and local regulations and policy, and ICH E6 GCP before any study procedures or data collection are performed.

Subjects will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. The key information about the study will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

ICFs will be IRB-approved, and subjects will be asked to read and review the consent form. Subjects (or legally authorize representatives) must sign the ICF prior

to starting any study procedures being done specifically for this trial. Once signed, a copy of the ICF will be given to the subject for their records.

New information will be communicated by the site PI to subjects who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated, and subjects will be re-consented per IRB requirements, if necessary.

Requirements for Permission by Parents/Guardians and Assent by Children (in case of a minor)

Not available

Other Informed Consent Procedures

Subjects may withdraw permission to use samples for secondary use at any time. They will need to contact the study site and the samples will be removed from the study repository after this study is completed and documentation will be completed that outlines the reason for withdrawal of permission for secondary use of samples.

11.1.2 Study Termination and Closure

In Section 8, Study Intervention Discontinuation and Subject Discontinuation/Withdrawal, describes the temporary halting of the study.

This study may be prematurely terminated if there is sufficient reasonable cause, including but not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Results of interim analysis
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or not evaluable
- Regulatory authorities

If the study is prematurely terminated, the site PI will promptly inform study subjects and the IRB as applicable. The site PI will assure appropriate follow-up for the subjects, as necessary.

The sponsor will notify regulatory authorities as applicable.

11.1.3 Confidentiality and Privacy

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover clinical information relating to subjects, test results of biological samples, and all other information generated during participation in the study. No identifiable information concerning subjects in the study will be released to any unauthorized third party. Subject confidentiality will be maintained when study results are published or discussed in conferences.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

All source records including electronic data will be stored in secured systems in accordance with institutional policies and federal regulations.

All study data and research specimens that leave the site (including any electronic transmission of data) will be identified only by a coded number that is linked to a subject through a code key maintained at the clinical site. Names or readily identifying information will not be released unless DMID approves and it aligns with the consent form, or according to laws for required reporting.

11.1.4 Secondary Use of Stored Specimens and Data

Secondary Human Subject Research is the re-use of identifiable data or identifiable biospecimens that were collected from some other ‘‘primary’’ or ‘‘initial’’ activity, such as the data and samples collected in this protocol. Any use of the sample or data for secondary research purposes, however, will be presented in a separate protocol and require separate IRB approval.

Each sample will be labelled only with a barcode and a unique tracking number to protect subject confidentiality. Secondary research with coded samples and data may occur, however, subject confidentiality will be maintained as described for this protocol. An IRB review of the secondary research using coded specimens is required.

The subject's decision can be changed at any time by notifying the study doctors or nurses in writing. If the subject subsequently changes his/her decision, the samples will be destroyed if the samples have not been used for research or released for a specific research project.

11.1.5 Data Sharing for Secondary Research

Data from this study may be used for secondary research. All of the individual subject data collected during the trial will be made available after de-identification. The SAP and Analytic Code will also be made available. This data will be available immediately following publication, with no end date.

The investigator may request removal of data on individual study subjects from data repositories in the event that a research subject withdraws or changes his or her consent. However, some data that have been distributed for approved research use cannot be retrieved.

11.2 Key Roles and Study Governance

Decisions related to the study will be made by a protocol team that includes representatives from all countries, and separate networks within a country.

11.2.1Safety Oversight

Protocol team oversight

The protocol team will review pools of AE data every 2 weeks to ensure there no significant number of unexpected AEs (AEs that do not fit with the known course of COVID-19). If there are a significant number of unexpected AEs, the DSMB will be asked to review unblinded safety data in an ad hoc meeting.

Data Safety Monitoring Committee

Safety oversight will be conducted (i) by a specific international independent DisCoVeRy DSMB that monitors subject safety treatment efficacyoutcomes specific to DisCoVeRy; (ii) by a Global international DSBM for the three outcomes shared with the WHO Solidarity protocol. The DisCoVeRy DSMB members will be separate and independent of study personnel participating in this trial and should not have scientific, financial or other conflict of interest related to this study.

The DisCoVeRy DSMB will consist of members with appropriate expertise to contribute to the interpretation of the data from this trial. The DisCoVeRy l DSMB should be as broadly informed as possible regarding emerging evidence from related studies as well as from the conduct of this DisCoVeRy Protocol. The DisCoVeRy DSMB will operate under the guidelines of a charter that will be written at the organizational meeting of the DSMB. The DSMB will review SAEs on a regular basis and ad hoc during this trial. The Medical Monitor will be responsible for reviewing SAEs in real time. All SAR and SUSAR will be sent to the DSMB in real time for a safety review.

The interim trial results will be monitored by a Data Monitoring Committee, and if at any stage evidence emerges that any one treatment arm is definitely inferior then it will be decided that that arm will be discontinued. If at any stage evidence emerges that any treatment arm is definitely superior, it will be decided that that arm will become the standard of care. If good evidence emerges while the trial is continuing that some other treatment(s) should also be being evaluated then it will be decided that one or more extra arms will be added while the trial is in progress

The study will not stop enrolment awaiting these DSMB reviews, though the DSMB may recommend temporary or permanent cessation of enrolment based on their safety reviews.

Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by DMID. The DSMB may receive data in aggregate and presented by treatment arm. The DSMB will review grouped data in the closed session only. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study interventions (as applicable), and to continue, modify, or terminate this study.

11.2.2 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial subjects are protected, that the reported trial data are accurate, complete, and verifiable. Clinical Monitoring also ensures conduct of the trial is in compliance with the currently approved protocol/ amendment(s), ICH, GCP, and with applicable regulatory requirement(s) and sponsor requirements. Clinical monitoring will also verify that any critical study procedures are completed following specific instructions in the protocol-specific MOP.

Monitoring for this study will be performed by DMID. Details of clinical site monitoring are documented in a clinical monitoring plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, CRFs, ICFs, medical and laboratory reports, site study intervention storage records, training records, and protocol and GCP compliance. Site monitors will have access to each participating site, study personnel, and all study documentation according to the DMID-approved site monitoring plan. Study monitors will meet with site PIs to discuss any problems and outstanding issues and will document site visit findings and discussions.

11.2.3 Data Handling and Record Keeping

Data Collection and Management Responsibilities

Data collection is the responsibility of the study personnel at the participating clinical study site under the supervision of the site PI. The site PI must maintain complete and accurate source documentation.

Clinical research data from source documentation (including, but not limited to, AE/SAEs, concomitant medications, medical history, physical assessments, clinical laboratory data) will be entered by the clinical study site into CRFs via a 21 CFR Part 11-compliant internet data entry system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Aes and concomitant medications will be coded according to the most current versions of MedDRA and WhoDrug, respectively.

The SDCC for this study will be responsible for data management, quality review, analysis, and reporting of the study data.

The IND sponsor is responsible for review of data collection tools and processes, and review of data and reports.

Aes will be coded according to the MedDRA dictionary version 23.0 or higher.

A separate study specific Study Data Standardization Plan (SDSP) appendix will be developed which describes the technical recommendations for the submission of human study data and related information in a standardized electronic format throughout product development.

At the end of the study, a copy of all datasets including annotated CRFs and data dictionary will be provided to DMID.

Study Record Retention

Study related records, including the regulatory file, study product accountability records, consent forms, subject source documents and electronic records should be maintained for a period of 2 years following the date a marketing application is approved for the investigational product for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation These documents should be retained for a longer period, however, if required by local policies or regulations. No records will be destroyed without the written consent of the sponsor. Consent forms with specimen retention linked to identifiable specimens will be maintained for as long as the specimens remain in identifiable format, and a minimum of three years after use of the identifiable specimens in non-exempt human subject research.

Source Records

Source data are all information in original records (and certified copies of original records) of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP, regulatory, and institutional requirements. Data recorded in the CRF derived from source documents should be consistent with the data recorded on the source documents.

Interview of subjects is sufficient for obtaining medical history. Solicitation of medical records from the subject's primary care provider is not required.

11.2.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, any process that is noted in the protocol and refers to details in the protocol-specific SOP, or GCP requirements or any critical study procedures with specific instructions in ancillary documents referenced in the protocol such as a protocol-specific MOP.

The noncompliance may be either on the part of the subject, the investigator, or the study site staff. Following a deviation(s), corrective actions should be developed by the site and implemented promptly. All individual protocol deviations will be addressed in subject study records.

It is the responsibility of the site PI and personnel to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported per the protocol deviation reporting procedures. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site PI and personnel are responsible for knowing and adhering to their IRB requirements. A completed copy of the Protocol Deviation Form must be maintained in the Regulatory File, as well as in the subject's chart if the deviation is subject specific.

11.2.5 Data Sharing Policy

To avoid premature release of data, this protocol specifies that efficacy data from a trial that has not yet been completed due to insufficient enrolment should not be released. After an outbreak has ended at a given site, the study would be paused.

An independent monitoring committee would review results from an interim analysis of study data to make recommendations regarding whether the study should continue or stop for efficacy, futility, or safety, guided by the pre-specified monitoring plan.

The study is registered on the clinicaltrials.gov site (NCT04315948).

Importantly, under this protocol, the investigators would remain blinded to any results of analyses; the study data would only be released if the trial were either stopped on the basis of a recommendation from the monitoring committee or had reached its targeted number of endpoints or amount of participant follow-up.

11.2.6 Human Data Sharing Plan

See above.

11.2.7 Publication

Following completion of the study, the lead PI is expected to publish the results of this research in a scientific journal, with consideration to the clarifications under section 10.1.10 above.

11.2.8 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

12. Additional Considerations

Research Related Injuries

For any potential research related injury, the site PI or designee will assess the subject.
Study personnel will try to reduce, control, and treat any complications from this study. Immediate medical treatment may be provided by the participating study site.

As needed, referrals to appropriate health care facilities will be provided to the subject. The site PI should then determine if an injury occurred as a direct result of the tests or treatments that are done for this study.

If it is determined by the participating site PI that an injury occurred to a subject as a direct result of the tests or treatments that are done for this trial, then referrals to appropriate health care facilities will be provided to the subject.

Study personnel will try to reduce, control and treat any complications from this trial. Immediate medical treatment may be provided by the participating site, such as giving emergency medications to stop immediate allergic reactions.

INSERM, as the sponsor, has taken out an insurance contract of civil responsibility under the number SYB16899689A4, in accordance with the French legal and regulatory guidelines.

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
EC	Ethics Committee
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
Hgb	Haemoglobin
HR	Heart Rate
IB	Investigator's Brochure
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IFN-ß-1a	Interferon beta-1a
IND	Investigational New Drug Application
IRB	Institutional Review Board
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
NP	Nasopharyngeal

PHI	Protected Health Information
PI	Principal Investigator
PLT	Platelet
PP	Per Protocol
PT	Prothrombin Time
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SDCC	Statistical and Data Coordinating Centre
SDSP	Study Data Standardization Plan
SMC	Safety Monitoring Committee
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

Protocol Amendment History

Version	Date	Description of Change	Brief Rationale

REFERENCES

1. Chan JF-W, Yuan S, Kok K-H, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet*. 2020;395(10223):514-523. doi:10.1016/S0140-6736(20)30154-9
2. Wu JT, Leung K, Leung GM. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. *The Lancet*. 2020;0(0). doi:10.1016/S0140-6736(20)30260-9
3. Lo MK, Jordan R, Arvey A, et al. GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses. *Sci Rep*. 2017;7:43395. doi:10.1038/srep43395
4. Lo MK, Feldmann F, Gary JM, et al. Remdesivir (GS-5734) protects African green monkeys from Nipah virus challenge. *Sci Transl Med*. 2019;11(494). doi:10.1126/scitranslmed.aau9242
5. Warren TK, Jordan R, Lo MK, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature*. 2016;531(7594):381-385. doi:10.1038/nature17180
6. Mulangu S, Dodd LE, Davey RT, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. *N Engl J Med*. 2019;381(24):2293-2303. doi:10.1056/NEJMoa1910993
7. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med*. 2017;9(396). doi:10.1126/scitranslmed.aal3653
8. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun*. 2020;11(1):1-14. doi:10.1038/s41467-019-13940-6
9. Agostini ML, Andres EL, Sims AC, et al. Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. *mBio*. 2018;9(2). doi:10.1128/mBio.00221-18
10. de Wit E, Rasmussen AL, Falzarano D, et al. Middle East respiratory syndrome coronavirus (MERS-CoV) causes transient lower respiratory tract infection in rhesus macaques. *Proc Natl Acad Sci USA*. 2013;110(41):16598-16603. doi:10.1073/pnas.1310744110
11. de Wit E, Feldmann F, Cronin J, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc Natl Acad Sci USA*. February 2020. doi:10.1073/pnas.1922083117
12. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30(3):269-271. doi:10.1038/s41422-020-0282-0
13. Groneberg DA, Poutanen SM, Low DE, Lode H, Welte T, Zabel P. Treatment and vaccines for severe acute respiratory syndrome. *Lancet Infect Dis*. 2005;5(3):147-155. doi:10.1016/S1473-3099(05)01307-1
14. Chan JF-W, Yao Y, Yeung M-L, et al. Treatment With Lopinavir/Ritonavir or Interferon-beta1b Improves Outcome of. *J Infect Dis*. 2015;212(12):1904-1913. doi:10.1093/infdis/jiv392
15. Nukoolkarn V, Lee VS, Malaisree M, Aruksakulwong O, Hannongbua S. Molecular dynamic simulations analysis of ritonavir and lopinavir as SARS-CoV 3CL(pro) inhibitors. *J*

Theor Biol. 2008;254(4):861-867. doi:10.1016/j.jtbi.2008.07.030
16. Liu X, Wang X-J. Potential inhibitors for 2019-nCoV coronavirus M protease from clinically approved medicines. *bioRxiv*. January 2020:2020.01.29.924100. doi:10.1101/2020.01.29.924100
17. Chu CM, Cheng VCC, Hung IFN, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004;59(3):252-256. doi:10.1136/thorax.2003.012658
18. Lim J, Jeon S, Shin HY, et al. Case of the Index Patient Who Caused Tertiary Transmission of COVID-19 Infection in Korea: the Application of Lopinavir/Ritonavir for the Treatment of COVID-19 Infected Pneumonia Monitored by Quantitative RT-PCR. *J Korean Med Sci*. 2020;35(6):e79. doi:10.3346/jkms.2020.35.e79
19. Wang Z, Chen X, Lu Y, Chen F, Zhang W. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. *Biosci Trends*. February 2020. doi:10.5582/bst.2020.01030
20. Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. *JAMA*. March 2020. doi:10.1001/jama.2020.3204
21. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med*. March 2020. doi:10.1056/NEJMoa2001282
22. Lee AJ, Ashkar AA. The Dual Nature of Type I and Type II Interferons. *Front Immunol*. 2018;9. doi:10.3389/fimmu.2018.02061
23. de Weerd NA, Samarajiwa SA, Hertzog PJ. Type I interferon receptors: biochemistry and biological functions. *J Biol Chem*. 2007;282(28):20053-20057. doi:10.1074/jbc.R700006200
24. Stetson DB, Medzhitov R. Type I interferons in host defense. *Immunity*. 2006;25(3):373-381. doi:10.1016/j.immuni.2006.08.007
25. Müller U, Steinhoff U, Reis LF, et al. Functional role of type I and type II interferons in antiviral defense. *Science*. 1994;264(5167):1918-1921. doi:10.1126/science.8009221
26. van den Broek MF, Müller U, Huang S, Zinkernagel RM, Aguet M. Immune defence in mice lacking type I and/or type II interferon receptors. *Immunol Rev*. 1995;148:5-18. doi:10.1111/j.1600-065x.1995.tb00090.x
27. Hensley LE, Fritz EA, Jahrling PB, Karp C, Huggins JW, Geisbert TW. Interferon-β 1a and SARS Coronavirus Replication. *Emerg Infect Dis*. 2004;10(2):317-319. doi:10.3201/eid1002.030482
28. Bellingan G, Maksimow M, Howell DC, et al. The effect of intravenous interferon-beta-1a (FP-1201) on lung CD73 expression and on acute respiratory distress syndrome mortality: an open-label study. *Lancet Respir Med*. 2014;2(2):98-107. doi:10.1016/S2213-2600(13)70259-5
29. Ranieri VM, Pettilä V, Karvonen MK, et al. Effect of Intravenous Interferon β-1a on Death and Days Free From Mechanical Ventilation Among Patients With Moderate to Severe Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. *JAMA*. 2020;323(8):725-733. doi:10.1001/jama.2019.22525
30. Jf C, Y Y, Ml Y, et al. Treatment With Lopinavir/Ritonavir or Interferon-β1b Improves Outcome of MERS-CoV Infection in a Nonhuman Primate Model of Common Marmoset. The Journal of infectious diseases. doi:10.1093/infdis/jiv392

31. Arabi YM, Alothman A, Balkhy HH, et al. Treatment of Middle East Respiratory Syndrome with a combination of lopinavir-ritonavir and interferon-β1b (MIRACLE trial): study protocol for a randomized controlled trial. *Trials*. 2018;19(1):81. doi:10.1186/s13063-017-2427-0
32. Antonetti F, Finocchiaro O, Mascia M, Terlizzese MG, Jaber A. A comparison of the biologic activity of two recombinant IFN-beta preparations used in the treatment of relapsing-remitting multiple sclerosis. *J Interferon Cytokine Res*. 2002;22(12):1181-1184. doi:10.1089/10799900260475696
33. Miller DK, Lenard J. Antihistaminics, local anesthetics, and other amines as antiviral agents. *PNAS*. 1981;78(6):3605-3609. doi:10.1073/pnas.78.6.3605
34. Keyaerts E, Vijgen L, Maes P, Neyts J, Ranst MV. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. *Biochemical and Biophysical Research Communications*. 2004;323(1):264-268. doi:10.1016/j.bbrc.2004.08.085
35. Rolain J-M, Colson P, Raoult D. Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century. *Int J Antimicrob Agents*. 2007;30(4):297-308. doi:10.1016/j.ijantimicag.2007.05.015
36. Paton NI, Lee L, Xu Y, et al. Chloroquine for influenza prevention: a randomised, double-blind, placebo controlled trial. *The Lancet Infectious Diseases*. 2011;11(9):677-683. doi:10.1016/S1473-3099(11)70065-2
37. Tricou V, Minh NN, Van TP, et al. A Randomized Controlled Trial of Chloroquine for the Treatment of Dengue in Vietnamese Adults. *PLOS Neglected Tropical Diseases*. 2010;4(8):e785. doi:10.1371/journal.pntd.0000785
38. Roques P, Thiberville S-D, Dupuis-Maguiraga L, et al. Paradoxical Effect of Chloroquine Treatment in Enhancing Chikungunya Virus Infection. *Viruses*. 2018;10(5):268. doi:10.3390/v10050268
39. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *BioScience Trends*. 2020;advpub. doi:10.5582/bst.2020.01047
40. Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *Journal of Critical Care*. March 2020. doi:10.1016/j.jcrc.2020.03.005
41. Colson P, Rolain J-M, Lagier J-C, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents*. March 2020:105932. doi:10.1016/j.ijantimicag.2020.105932
42. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov*. 2020;6(1):1-4. doi:10.1038/s41421-020-0156-0
43. Zhonghua Jie, He He, Hu Xi, Za Zhi. *Multicenter Collaboration Group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for Chloroquine in the Treatment of Novel Coronavirus Pneumonia. Expert Consensus on Chloroquine Phosphate for the Treatment of Novel Coronavirus Pneumonia [in Chinese]*.; 2020. 10.3760/cma.j.issn.1001-0939.2020.0019. Accessed March 12, 2020.
44. Touret F, de Lamballerie X. Of chloroquine and COVID-19. *Antiviral Res*.

2020;177:104762. doi:10.1016/j.antiviral.2020.104762
45. Yao X, Ye F, Zhang M, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. March 2020. doi:10.1093/cid/ciaa237
46. Costedoat-Chalumeau N, Dunogué B, Leroux G, et al. A Critical Review of the Effects of Hydroxychloroquine and Chloroquine on the Eye. *Clin Rev Allergy Immunol*. 2015;49(3):317-326. doi:10.1007/s12016-015-8469-8
47. Yam JCS, Kwok AKH. Ocular toxicity of hydroxychloroquine. *Hong Kong Med J*. 2006;12(4):294-304.
48. Mititelu M, Wong BJ, Brenner M, Bryar PJ, Jampol LM, Fawzi AA. Progression of hydroxychloroquine toxic effects after drug therapy cessation: new evidence from multimodal imaging. *JAMA Ophthalmol*. 2013;131(9):1187-1197. doi:10.1001/jamaophthalmol.2013.4244
49. Bergholz R, Schroeter J, Rüther K. Evaluation of risk factors for retinal damage due to chloroquine and hydroxychloroquine. *Br J Ophthalmol*. 2010;94(12):1637-1642. doi:10.1136/bjo.2009.174458
50. Raoult D, Houpikian P, Tissot Dupont H, Riss JM, Arditi-Djiane J, Brouqui P. Treatment of Q fever endocarditis: comparison of 2 regimens containing doxycycline and ofloxacin or hydroxychloroquine. *Arch Intern Med*. 1999;159(2):167-173. doi:10.1001/archinte.159.2.167
51. Rolain JM, Mallet MN, Raoult D. Correlation between serum doxycycline concentrations and serologic evolution in patients with Coxiella burnetii endocarditis. *J Infect Dis*. 2003;188(9):1322-1325. doi:10.1086/379082
52. Elzein FE, Alsherbeeni N, Alnajashi K, et al. Ten-year experience of Q fever endocarditis in a tertiary cardiac center in Saudi Arabia. *Int J Infect Dis*. 2019;88:21-26. doi:10.1016/j.ijid.2019.07.035
53. Lagier J-C, Fenollar F, Lepidi H, Giorgi R, Million M, Raoult D. Treatment of classic Whipple's disease: from in vitro results to clinical outcome. *J Antimicrob Chemother*. 2014;69(1):219-227. doi:10.1093/jac/dkt310
54. Million M, Thuny F, Richet H, Raoult D. Long-term outcome of Q fever endocarditis: a 26-year personal survey. *Lancet Infect Dis*. 2010;10(8):527-535. doi:10.1016/S1473-3099(10)70135-3
55. Stas P, Faes D, Noyens P. Conduction disorder and QT prolongation secondary to long-term treatment with chloroquine. *Int J Cardiol*. 2008;127(2):e80-82. doi:10.1016/j.ijcard.2007.04.055
56. Morgan ND, Patel SV, Dvorkina O. Suspected hydroxychloroquine-associated QT-interval prolongation in a patient with systemic lupus erythematosus. *J Clin Rheumatol*. 2013;19(5):286-288. doi:10.1097/RHU.0b013e31829d5e50
57. Chen C-Y, Wang F-L, Lin C-C. Chronic hydroxychloroquine use associated with QT prolongation and refractory ventricular arrhythmia. *Clin Toxicol (Phila)*. 2006;44(2):173-175. doi:10.1080/15563650500514558
58. Yogasundaram H, Putko BN, Tien J, et al. Hydroxychloroquine-Induced Cardiomyopathy: Case Report, Pathophysiology, Diagnosis, and Treatment. *Canadian Journal of Cardiology*. 2014;30(12):1706-1715. doi:10.1016/j.cjca.2014.08.016
59. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital

settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Circulation*. 2010;121(8):1047-1060. doi:10.1161/CIRCULATIONAHA.109.192704
60. Giudicessi J, Noseworthy P, Friedman P, Ackerman M. Urgent Guidance for Navigating and Circumventing the QTc Prolonging and Torsadogenic Potential of Possible Pharmacotherapies for COVID-19. *Mayo Clinic Proceedings*. March 2020.
61. Vandenberk B, Vandael E, Robyns T, et al. Which QT Correction Formulae to Use for QT Monitoring? *J Am Heart Assoc*. 2016;5(6). doi:10.1161/JAHA.116.003264
62. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac deathThe Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Europace*. 2015;17(11):1601-1687. doi:10.1093/europace/euv319
63. Casado E, Gratacós J, Tolosa C, et al. Antimalarial myopathy: an underdiagnosed complication? Prospective longitudinal study of 119 patients. *Ann Rheum Dis*. 2006;65(3):385-390. doi:10.1136/ard.2004.023200
64. Shalhoub S, Farahat F, Al-Jiffri A, et al. IFN-α2a or IFN-β1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study. *J Antimicrob Chemother*. 2015;70(7):2129-2132. doi:10.1093/jac/dkv085
65. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *International Journal of Antimicrobial Agents*. 2020.