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TITLE

The DisCoVeRy trial: multi-centre, adaptive, randomized trial of the safety and efficacy of treatments for COVID-19 in hospitalized adults

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DISCLAIMER

The funder nor the sponsor did not have any role in the design of the trial

COMPETING INTERESTS

François-Xavier Lescure reports fees for development of educational presentations from Gilead, outside the submitted work. Dominique Costagliola reports personal fees from Merck Switzerland, grants and personal fees from MSD France, personal fees from Gilead France, grants and personal fees from Janssen, outside the submitted work. Jean-François Timsit reports grants and personal fees from Merck, grants and personal fees from Pfizer, grants from biomerieux, personal fees from medimune, personal fees from Paratek, personal fees from Gilead, outside the submitted work. Benjamin Hamze reports personal fees from Sanofi, outside the submitted work. Gilles Peytavin has received travel grants, consultancy fees, honoraria, or study grants from various pharmaceutical companies, including Gilead Sciences, Merck, TheraTechnologies and ViiV Healthcare. France Mentre reports grants and personal fees from Sanofi, outside the submitted work.

Other authors declare no competing interests.

DATA SHARING STATEMENT

Systematic data sharing is not intended, but all requests for the trial's data will be considered by the French DisCoVeRy Trial Management Team

ETHICS APPROVAL

Ethical approval was first obtained in France from the institutional review board on March 13, 2020 (Comité de Protection des Personnes Ile de France 3, approval number 20.03.06.51744), and the trial received approval by the French National Agency for Medicines and Health Products (ANSM) on March 9, 2020. The protocol described in this article is the version 7.0 of the DisCoVeRy protocol approved on April 5, 2020. Any substantial amendment made to the protocol by the coordinating investigator is sent to local ethics committee and health authorities in each country for approval, prior to implementation.

INFORMED CONSENT

Prior to any act carried out as part of the research, subjects receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. An emergency consent procedure with the legal guardian or relatives of the patient has been put in place for patients who are unable to consent. The forms have been reviewed by the Ethics committee that authorized the trial.

KEYWORDS

COVID-19; SARS-CoV-2; Randomized clinical trial; Efficacy; Safety; Type 1 interferon; Remdesivir; Lopinavir/ritonavir; Hydroxychloroquine;

Text count: 4777 words

ABSTRACT

Introduction

To find effective and safe treatments for COVID-19, the WHO recommended to systemically evaluate experimental therapeutics in collaborative randomized clinical trials. As COVID-19 was spreading in Europe, the French national institute for Health and Medical Research (Inserm) established a trans-disciplinary team to develop a multi-arm randomized controlled trial named DisCoVeRy. The objective of the trial is to evaluate the clinical efficacy and safety of different investigational repurposed therapeutics relative to Standard of Care (SoC) in patients hospitalized with COVID-19.

Methods and analysis

DisCoVeRy is a phase III, open-label, adaptive, controlled, multicentre clinical trial in which hospitalized patients with COVID-19 in need of oxygen therapy are randomized between 5 arms: (i) a control group managed with SoC and four therapeutic arms with repurposed antiviral agents: *(ii)* remdesivir + SoC, *(iii)* lopinavir/ritonavir + SoC, *(iv)* lopinavir/ritonavir associated with interferon (IFN)-β-1a + SoC and *(v)* hydroxychloroquine + SoC. The primary endpoint is the clinical status at Day 15 on the 7-point ordinal scale of the WHO Master Protocol (version 3.0, March 3, 2020). This trial involves patients hospitalized in conventional departments or intensive care units both from academic or non-academic hospitals throughout Europe. A sample size of 3,100 patients (620 patients per arm) is targeted. This trial has begun on March 22, 2020. Since April 5, 2020, DisCoVeRy has been an add-on trial of the Solidarity consortium of trials conducted by the WHO in Europe and worldwide. On June 8, 2020, 754 patients have been included.

Ethics and dissemination

Inserm is the sponsor of DisCoVeRy. Ethical approval has been obtained from the institutional review board on March 13, 2020 (20.03.06.51744) and from the French National Agency for Medicines and Health Products (ANSM) on March 9, 2020. Results will be submitted for publication in peer-reviewed journals.

Trial registration number

NCT04315948 Eudra-CT 2020-000936-23

ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The DisCoVeRy clinical trial is an adaptive, randomized, open-label clinical trial that aims to evaluate the safety and efficacy of 4 antiviral therapeutic strategies as compared to standard of care in hospitalized adult patients diagnosed with COVID-19.
- Therapeutic strategies can be modified according to new evidence: an arm can become the standard of care if proved superior to others, arms can be discontinued if proved inferior to others and arms can be added if new candidate therapeutic strategies emerge.
- DisCoVeRy is an add-on trial of the Solidarity consortium of trials, conducted under the aegis of the WHO and data on common endpoints are shared with the Solidarity consortium.
- DisCoVeRy is not a placebo-controlled trial and is not double-blind because of the complexity of blinding treatments with different mode of administration (intravenous, sub-cutaneous or oral) and the need to initiate the trial very rapidly.
- DisCoVeRy includes patients who are hospitalized and in need of oxygen therapy and does not target patients at the early phase of the disease.
- DisCoVeRy does not include anti-inflammatory agents that can be used as part of the standard of care in any arm.

INTRODUCTION

Background and scope

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the third coronavirus that has crossed the species barrier to cause deadly pneumonia in humans since the beginning of the 21st century, after SARS-CoV [1,2] and Middle-East respiratory syndrome coronavirus [3] (MERS-CoV) in 2002 and 2012, respectively. The first case of infection with the SARS-CoV-2 was reported in the city of Wuhan, China on December 31, 2019. The associated disease was named “coronavirus disease 2019” (abbreviated “COVID-19”). The emergence and the spread of SARS-CoV-2 is an unprecedented challenge, vividly illustrating the pace at which a viral outbreak can progress among a highly interlinked and susceptible global population. At the beginning of March 2020, when this clinical trial was designed, COVID-19 had spread to more than 100 countries and affected more than 100,000 individuals. Consistently, the World Health Organization (WHO) declared COVID-19 pandemic on March 11, 2020.[4]

Although many drugs have *in vitro* activity against various coronaviruses, no clinical evidence at that time supported the efficacy and safety of any drug against any coronavirus in humans, including SARS-CoV-2. The rapid and simultaneous combination of supportive care and randomized controlled trials (RCT) is the only way to find effective and safe treatments for COVID-19 that could improve patients’ management. WHO thus recommended researchers around the world to systemically evaluate experimental therapeutics in RCT and to gather initiatives in large trials that could provide strong evidence about which treatment are safe and effective.

As COVID-19 was spreading in Europe, the French national institute for Health and Medical Research (Inserm) established a trans-disciplinary team to develop a multi-arm randomized controlled trial to rapidly provide reliable evidence about the efficacy and safety of therapeutics in comparison to a standard of care control arm. The WHO Master Protocol for therapeutics against COVID-19 version 3.0 (March 3, 2020) published by the WHO R&D Blueprint Working Group [5] was used as a template for this clinical trial. Subsequently, the DisCoVeRy trial was launched in France in March 22, 2020. International cooperation being essential in outbreak science and public health, and in actions to prevent trans-frontier disease progression, the DisCoVeRy trial intends to bring together several European countries.

Objective

The objective of the DisCoVeRy trial is to evaluate the clinical efficacy and safety of different investigational therapeutics relative to Standard of Care (SoC) in patients hospitalized with COVID-19.

METHODS AND ANALYSIS

Design and general information

DisCoVeRy is a phase III, open-label, adaptive, randomized, controlled, multicenter clinical trial designed to evaluate the safety and efficacy of repurposed therapeutic interventions in hospitalized adult patients diagnosed with COVID-19. This trial involves patients both from academic or non-academic hospitals throughout Europe, with Inserm as the Sponsor. Study sites can be obtained from the Sponsor's representative. The protocol described in this article is the version 7.0 of the DisCoVeRy protocol approved on April 5.

The DisCoVeRy RCT has 5 arms: (i) a control group managed SoC and four therapeutic arms with repurposed antiviral agents: *(ii)* remdesivir + SoC, *(iii)* lopinavir/ritonavir + SoC, *(iv)* lopinavir/ritonavir associated with interferon (IFN)-β-1a + SoC and *(v)* hydroxychloroquine + SoC (Figure 1). The arms have not been modified between the version 1 and 7 of the protocol. Included participants cannot be treated with antivirals other than the study medications allocated by randomization, but non-antiviral drugs such as steroids, immunomodulatory agents (e.g. anti-interleukin 6 drugs), or antibiotics can be used as part of the standard of care. This is an open-label trial but all investigators are unaware of aggregate outcomes during the study. The design is adaptive upon decision of the DSMB: arms can be discontinued if proved inferior to others, an existing arm can become the standard of care if proved superior and arms can be added if new candidate therapeutic strategies emerge. The trial has been registered at the ClinicalTrials.org registry as NCT04315948 and on the European Clinical Trials Database as 2020-000936-23.

Participants

For the duration of the study, the sponsor has subscribed an insurance policy covering the sponsor's own third-party liability as well as the third-party liability of all the investigators involved in the study.

Inclusion criteria

Patients must fulfil the following criteria prior to trial enrolment:

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 of pulmonary infection (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.

Non-inclusion criteria

Patients with any of the following criteria are not eligible for trial enrolment:

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, piperaquine;
10. Human immunodeficiency virus infection under combination antiretroviral therapy;
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).

Randomisation

Patients are randomly assigned in a 1:1:1:1:1 ratio into one of the five groups. The randomisation list is computer-generated, with blocks of various sizes and stratified by region (according to the administrative definition in each country) and severity of illness at enrolment (severe disease: patients requiring non-invasive ventilation, high flow oxygen devices, invasive mechanical ventilation or ECMO; moderate

disease: patients not requiring non-invasive ventilation, high flow oxygen devices, invasive mechanical ventilation nor ECMO). The randomisation list is implemented in the electronic Case Report Form (eCRF) to ensure appropriate allocation concealment.

Experimental design

Study treatments

The participants are allocated in one of 5 arms (Figure 1).

Patients included in the remdesivir group receive 200 mg intravenous loading dose on Day 1, followed by a 100 mg once-daily intravenous maintenance dose for the duration of the hospitalization and up to a 10 days' total course. Remdesivir is administered through a 30 to 60 minutes IV infusion.

Patients included in the lopinavir/ritonavir group receive 400 mg lopinavir and 100 mg ritonavir 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) is administered as a 5-mL suspension every 12h for 14 days via a nasogastric tube.

Patients included in the lopinavir/ritonavir + interferon ß-1a group receive, in addition to lopinavir/ritonavir as described above, interferon ß-1a 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.

Patients included in the hydroxychloroquine group receive a loading dose of 400 mg twice daily for one day followed by 400 mg once daily for 9 days. The rationale for this loading dose has been published.[6]

Patients included in the control group receive the standard of care of their recruitment center. Investigational drugs were kindly provided by pharmaceutical firms.

Rationale for study treatments

Remdesivir (GS-5734) is a broad-spectrum nucleotide prodrug inhibiting RNA-dependent 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.[7–9] Studies in human airway epithelial cell assays demonstrated that remdesivir inhibits replication of coronaviruses, including MERS-CoV.[10] Remdesivir has shown an *in vitro* activity on SARS-CoV-2[11] and a clinical benefit in rhesus macaques infected with SARS-CoV-2.[12] A large RCT has shown that remdesivir shortened the time to recovery in adults hospitalized with Covid-19 as compared to placebo but the results were not significant for mortality.[13]

Lopinavir/ritonavir is a fixed-dose combination used in HIV infection that has shown an *in vitro* activity against SARS-CoV in several studies.[14] A structure-based study suggested that the spatial structure of the lopinavir/ritonavir binding site was conserved between SARS-CoV and SARS-CoV-2.[15] The results of an open RCT evaluating lopinavir/ritonavir for COVID-19 were published on March 18, 2020.[16] In this trial, adults with confirmed COVID-19 and hypoxemia (SpO_2 < 94 %) were randomized to lopinavir/ritonavir (n=99) or standard of care (n=100). No significant difference between the 2 groups was observed on the time to clinical improvement on a 7-item ordinal scale. (HR of improvement 1.31; CI95% 0.95 - 1.80) but a trend to lower mortality rate was observed (19.0% *vs.* 27.1%) in the 90 patients (45.2% of the total) receiving lopinavir/ritonavir less than 12 days after the beginning of the symptoms.

Interferon (IFN)-ß-1 is a broad-spectrum antiviral drug belonging to the type 1 interferons. Type 1 IFN treatment has shown an activity against MERS-CoV and SARS-CoV in numerous experiments, both *in vitro* and *in vivo*.[17–19] Type 1 interferon is currently being tested for MERS-CoV in the MIRACLE clinical trial.[20] SARS-CoV-2 displays *in vitro* a substantial susceptibility to IFN-α [21] and data regarding the potential activity of type 1 interferons on SARS-CoV-2 has been reviewed recently.[22] A RCT found that COVID-19 patients treated with a triple combination interferon beta-1b, lopinavir-ritonavir, and ribavirin had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 days [IQR 5-11]) than the control group up (12 days [8-15]; hazard ratio 4·37 [95% CI 1·86-10·24], p=0·0010).[23]

The *in vitro* antiviral activity of hydroxychloroquine has been known for a long time [24] and was described on a number of viruses including SARS-CoV.[25][26] Regarding COVID-19, recent publications reported an *in vitro* activity of hydroxychloroquine on SARS-CoV-2 [11][27] and non-randomized observational studies provided conflicting clinical results.[28,29] A RCT on postexposure prophylaxis for COVID-19 found that hydroxychloroquine did not prevent illness compatible with Covid-19 or confirmed infection.[30]

Participant timeline (Figure 2, Table 1)

Clinical evaluations for efficacy and safety are performed at baseline, daily while the patient is hospitalized and at 15 (+/- 2 d) and 29 (+/- 3 d).

Upper (nasopharyngeal swab) and/or lower (endotracheal aspiration) respiratory tract and blood samples for centralized analysis of the SARS-CoV-2 kinetics are collected at baseline and at days 3 (+/- 1 d), 5 (+/- 1 d), 8 (+/- 1 d), 11 (+/- 1 d), 15 (+/- 2 d) and 29 (+/- 3 d). For each sample, the viral load is

measured by a specific SARS-COV-2 real-time (RT)-PCR and normalized according the number of cells in each sample. This method is validated to monitor viral load kinetics over time and expressed in standardized unit log of number of viral copies/10 000 cells.

Blood samples for pharmacokinetic analysis are collected:

- For remdesivir, to measure plasma and intracellular concentrations at days 1, 2, 5, 8 and 11;
- For lopinavir, to measure plasma concentrations at days 1, 3 (+/- 1 d), 6 (+/- 1 d), 8 (+/- 1 d) and 11 (+/- 1 d);
- For IFN ß-1-a, to measure plasma concentrations at days 3 and 6;
- For hydroxychloroquine, to measure plasma concentrations at days 1, 3 (+/- 1 d), 5 (+/- 1 d), 8 (+/- 1 d) and 11 (+/- 1 d).

Thoracic imaging by X-ray or CT scan are performed at baseline, and at days 8 (+/- 1 d), 15 (+/- 2 d) and 29 (+/- 3 d).

Biological evaluations for safety are performed at baseline and at days 3 (+/- 1 d), 5 (+/- 1 d), 8 (+/- 1 d), 11 (+/- 1 d), 15 (+/- 2 d) and 29 (+/- 3 d).

A biobank is constituted for ancillary analyses.

Primary endpoint

The primary endpoint is the clinical status at Day 15 on the 7-point ordinal scale of the WHO Master Protocol (version 3.0, March 3, 2020):

1. Not hospitalized, no limitation 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.

For the scores 1 and 2, limitation of the activities refers to the pre-COVID-19 clinical status, in order to take into account potential pre-existing limitations.

Secondary endpoints

Secondary endpoints are classified as efficacy or safety endpoints.

<u>Efficacy secondary endpoints</u>

1. 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.
2. 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.
3. 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.
4. Mechanical ventilation
   - Ventilator free days in the first 28 days (to Day 29).
   - Incidence and duration of new mechanical ventilation use during the study.
5. Hospitalization
   - Duration of hospitalization (days).
6. Mortality
   - In-hospital mortality
   - 28-day mortality.
   - 90-day mortality

<u>Safety secondary endpoints</u>

1. Cumulative incidence of any grade 3 and 4 adverse events;
2. Cumulative incidence of any serious adverse event;
3. Proportion of patients with a premature discontinuation or temporary suspension of the study drug, for any reason;
4. Grade changes in biological parameters, as measured using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (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.

Exploratory endpoints

1. Qualitative and quantitative PCR for SARS-CoV-2 normalized according to the number of sample cells in nasopharyngeal or lower respiratory tract samples on days 1, 3, 5, 8, 11, 15 and 29;
2. Qualitative and quantitative PCR for SARS-CoV-2 in blood on days 1, 3, 5, 8 and 11;
3. Development of resistance of SARS-CoV-2 in nasopharyngeal or lower respiratory tract samples at days 3, 5, 8, 11, 15 and 29;
4. Whole genome sequencing of participants to identify genetic variants associated with (i) the development of severe clinical disease (ii) the response in terms of safety and efficacy to investigational antiviral drugs;
5. Imagery assessment through chest X-ray or thoracic CT scan on days 1, 8, 15 and 29, depending on availability in centre;
6. Study drugs concentrations, sampled while the participant is hospitalized:
   - For remdesivir, as assessed by plasma concentration after the end of infusion on day 1, trough plasma and intracellular concentrations before the 2nd dose administration on day 2, and trough plasma concentration on days 5 and 8;
   - For lopinavir, peak plasma concentration measured 4 hours after the 1st administration and trough plasma concentrations measured just before the 2nd administration and on days 3, 6, 8 and 11;
   - For IFN ß-1-a, trough plasma concentration on days 3 and 6;
   - For hydroxychloroquine, peak plasma concentration measured 4 hours after the 1st administration and trough plasma concentrations measured just before the 2nd administration and on days 3, 5, 8 and 11.

Data collection

The trial is conducted in accordance with relevant regulations and standard operating procedures, including data protection. The data are collected on an electronic case report form. Clinical site monitoring is conducted to ensure that the rights are protected and confirm the integrity of collected data. The persons responsible for the quality control of the data take all necessary precautions to ensure

the confidentiality of information regarding investigational medicinal products, the trial, trial participants and in particular the identity of the participants and the results obtained.

Safety and adverse events monitoring

All adverse events are collected regardless of their grade of severity. The choice of continuing therapy is at the discretion of the investigator. All adverse events are classified in grades from mild (grade 1) to life threatening (grade 4) following the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (version 2.1 of July 2017) of the National Institute of Health and National Institute of Allergy and Infectious Diseases of the US Department of Health and Human Services.

Statistical considerations

General considerations

Continuous variables will be summarized by the mean, standard deviation, median, interquartile range, minimum and maximum. The change from baseline will be compared using Student's t-test or a Wilcoxon-Man-Whitney test if the normality assumption does not hold.

Categorical data will be summarized with the number and proportion of patients. Data will be compared using odds ratios and a Fisher's exact test.

All statistical tests will be 2-sided with type I error of 0.05. As there are 4 comparisons, each treatment group will be compared to the control group with a two-sided type I error of 0.0125. Subgroup analyses for the primary and secondary endpoints 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.

Sample size computation

A sample size of 3,100 patients (620 patients per arm) is targeted. The sample size was determined assuming the following scenario under standard of care for each item of the ordinal scale: 1: 42%, 2: 38%, 3: 8%, 4: 7%, 5: 2%, 6: 1%, 7: 2%.

There is significant uncertainty with these assumptions given the limited data available. Since a large proportion of patients are moderately ill patients, we power the study for an odds ratio of 1.5 (an odds ratio higher than 1 indicates superiority of the experimental treatment over the control for each ordinal scale category), with 90% power and using an overall one-sided type I error rate of 0.05.[31] 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.) The samples size might evolve whenever any treatment arm is withdrawn or added to the trial.

Definition of analysis sets

The intention-to-treat population is defined as all randomised patients, where patients are analysed in their randomisation group whether they have or not followed the allocated treatment. The modified intention-to-treat population is defined as all randomised patients who did receive at least one dose of the allocated treatment.

The primary and efficacy secondary analysis will be conducted on the intention-to-treat population. Safety analyses will be based on the modified intention-to-treat population.

Adaptive design

This study is intended to allow for adaptations with the ability to add a new experimental arm if one becomes available. The current plan is to evaluate the primary endpoint on day 15. 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 randomized clinical trial.[32]

Interim analyses

Interim analyses will be by the independent statistician of the DSMB. There are no formal stopping rules for efficacy or safety. The DSMB will make recommendations taking into consideration the totality of the evidence from the efficacy and safety outcomes as they accumulate, as well as external evidence.

For efficacy, the statistical analysis will be done on the primary endpoint, the 7-point ordinal scale at 15 days, and be based on the Haybittle Peto rule.[33,34] That is, if any active treatment is superior to control at P<.001 then consideration will 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, i.e. stopping because an active treatment appears ineffective, the statistical analysis will be done with the primary endpoint. 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. All the above is intended for all randomised patients. Analyses will be stratified by baseline severity of disease. For safety, no pre-specify stopping guideline will be defined because there are

various aspects of potential harm that could be studied. However, to allow for some caution, any safety signal on SAE, i.e. active treatment worse than control, requires P<.01 to merit consideration of stopping that treatment arm.

Final analysis of the primary endpoint

The primary outcome uses a 7-point ordinal scale analysed using a 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). Odds ratios are then interpreted as the odds of being "lower" or "higher" on the ordinal scale across the entire range of the scale. 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 validity of the proportionality assumption will be evaluated and tested. To deal with potential missing data, the last observation will be carried forward until the next available value.

Analysis of secondary endpoints

Differences in time-to-event endpoints by treatment will be summarized with Kaplan-Meier curves and 95% confidence interval; and cumulative incidence plots, for time-to-event endpoints with competing risk (e.g. death). Duration of event will be summarized according to median days with quartiles. Incidence data will be summarized as percent with 95% confidence interval. Time-to-event endpoints will be compared using the log-rank test. For time-to-event endpoints with a competing risk Fine and Gray models will be used. All tests will be stratified by the baseline severity.

Committees for the research

A DisCoVeRy European Steering Committee (DSC) has been constituted to serve as the governance organ for the trial. It provides the overall supervision of the trial, including for the relations with European stakeholders, the Steering Committee and the Executive Committee of the Solidarity trial (see below). It ensures that the trial is conducted in accordance with ethical principles and respects participants' safety, take any decision on any changes made to the design of the DisCoVeRy trial, and on the reporting of the trial results, including regarding the publication policy.

An international independent DSMB has been constituted to preserve the interests of trial participants, to monitor the main outcome measures (including safety and efficacy), and to monitor the overall conduct of the trial. Based on interim analyses of the data, it will make recommendations about early study closure or changes to the trial, including adding or removing treatment arms. The DSMB will meet after 100 participants are included into the study, and then every 200 new patients are included, with a maximum of 1 DSMB meeting per week. Other ad hoc reviews will be undertaken if there are 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.

Intertwinement with WHO Solidarity program

Since April 5, 2020, DisCoVeRy has been an add-on trial of the Solidarity program conducted by the WHO in Europe and worldwide. The same treatments are evaluated in DisCoVeRy and in Solidarity. Solidarity has 3 endpoints which are also secondary endpoints of DisCoVeRy: (*i*) mortality during hospitalization (the primary endpoint of Solidarity) (*ii*) length of hospital stay and (*iii*) time to mechanical ventilation or transfer to intensive care. At each DisCoVeRy DSMB meeting, the recommendations will be transmitted to the Data and Safety Monitoring Committee (DSMC) of Solidarity. The Executive Committee of Solidarity will ultimately issue recommendations on the different treatments evaluated, allowing a unique communication on each of the treatments evaluated.

Patient and public involvement

No patients were involved in the design or implementation of this study.

DISCUSSION

Strengths and limitations of the DisCoVeRy trial design

The DisCoVeRy clinical trial is a randomized, open clinical trial that aims to evaluate the safety and efficacy of possible therapeutic agents in hospitalized adult patients diagnosed with COVID-19. The design of DisCoVeRy is adaptive meaning that it can adapt to the ongoing production of evidence and to interim analyses by discontinuing arms that are proved inferior to others, selecting an existing arm as the standard of care if proved superior to others and adding arms if new candidate therapeutic strategies emerge.

As detailed above, DisCoVeRy is an add-on trial of the Solidarity trial, conducted under the aegis of the WHO in Europe and worldwide. Sharing the data from DisCoVeRy relevant to the Solidarity trial

(inclusion data and data related to the Solidarity endpoints) increases the number of participants for whom this data is available and thus leads to a faster conclusion on the effectiveness, deleterious effect or ineffectiveness of the treatments evaluated. Inclusion in a same strategy of hospitalized patients with severe (patients requiring non-invasive ventilation, high flow oxygen devices, invasive mechanical ventilation or ECMO) or moderate disease will allow to evaluate the different drug candidates in different clinical situations. Moreover, by including patients at different times in their clinical history of COVID-19, we will be able to study when is the best time to start an antiviral agent in relation to the delay of symptoms. The collection of samples for pharmacological monitoring, viral kinetics and medical imaging will provide crucial data to analyze the PK/PD of evaluated drugs and the effect of treatment on the virological and radiological evolution. However, DisCoVeRy will not provide data on treatments for COVID-19 at an early phase, before there is a need for hospitalization. As only antiviral agents are evaluated in DisCoVeRy, we will not be able to evaluate the efficacy of immunomodulatory agents, including corticosteroids.

Strengths and limitations of real-time interventional research in the setting of a pandemic

Discovery is not a placebo-controlled trial and is not double-blind because of the complexity of blinding treatments with different mode of administration (intravenous, sub-cutaneous or oral) and the need to initiate the trial very rapidly. Moreover, in a recent meta-epidemiological study, no evidence was found that lack of blinding of patients, healthcare providers, or outcome assessors had an impact on effect estimates in randomised clinical trials.[35]

Integrating clinical trials of experimental therapeutics is an increasingly recognized part of the response during infectious disease outbreaks. Since the Ebola outbreak in West Africa and subsequent outbreaks in the Democratic Republic of Congo, clinical trials of investigative drugs have been fully integrated in the epidemic response.[36–38] Implementing large clinical trial is both direly needed and particularly challenging during a pandemic. Indeed, the pandemic context compels us to organize clinical trials urgently while keeping methodological requirements of the highest level which is the only way to provide reliable answers for clinicians. The selection of the best candidate drugs for a new outbreak is a major challenge and a strength of the DisCoVeRy trial is that its adaptive design allows to add new arms if good evidence emerges while the trial is continuing that some other treatment(s) should also be evaluated. The ever-changing scientific background supporting the use of each candidate treatment

should be clear, detailed and regularly updated. Transparency, consistency and quality of design are more crucial than ever during pandemics to provide relevant and reliable data.

DISSEMINATION

Results will be communicated at scientific meetings and submitted for publication in peer-reviewed journals.

TRIAL STATUS

This trial has begun on March 22, 2020. On June 8, 2020, 754 patients have been included.

579 **Figure 1.** DisCoVeRy trial arms, drugs and dosing schedule

580 **Figure 2.** Schematic representation of the experimental design of the DisCoVeRy clinical trial.

581 **Table 1**. Schedule of enrolment, interventions and assessment in the DisCoVeRy trial

Day +/- Window	**Screening**	**Baseline[1]**	**D1**	**D2-D14[2]**	**D15[2] ± 2**	**D29[2] ± 3**	**D90**
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		X	X	Daily until discharge	X	X	X

Electrocardiogram (EKG)[5]	X			Days 3, 5, 8			
Medication review	X		X	Daily until discharge	X	X	
Adverse event evaluation			X	Daily until discharge	X	X	X
SAFETY LABORATORY							
Safety haematology, chemistry and liver tests	X[3]	X[4]		Days 3, 5, 8, 11 (all ± 1 day)	X	X	
Pregnancy test for females of childbearing potential	X[3]				X	X	
Plasma concentration of lopinavir			X	Days 3, 6, 8, 11 (all ± 1 day)			
Plasma concentration of hydroxychloroquine			X	Days 3, 5, 8, 11(all ± 1 day)			
Plasma and intracellular concentration of remdesivir			X	Days 2, 5, 8 if hospitalized			
Plasma concentration of interferon ß-1a				Days 3, 6 if hospitalized			
RESEARCH LABORATORY							
Blood for serum (serum bank)		X		Days 3, 5, 8, 11 (all ± 1 day)	X	X	
Plasma for PCR SARS-CoV-2		X		Day 3, 5, 8, 11 (all ± 1 day)			
Whole blood for blood bank		X					
Nasopharyngeal swab or lower respiratory tract samples		X		Day 3, 5, 8, 11 (all ± 1 day)	X	X	
Thoracic CT scan or chest x-ray		X		Day 8 (± 1 day)	X	X	
Whole blood for genetic analysis		X					

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

2. *If discharged from the hospital, visits and safety assessments are conducted in the outpatient setting.*
3. *Laboratory tests performed in the 48 hours prior to enrolment are accepted for determination of eligibility.*
4. *Any laboratory tests performed in the 24 hours before randomization can be used for baseline and Day 1*

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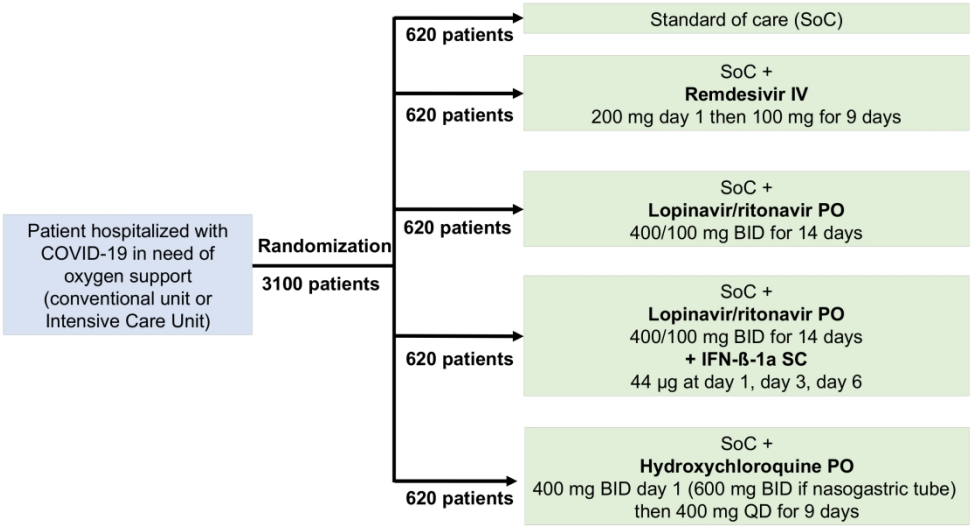

DisCoVeRy trial arms, drugs and dosing schedule

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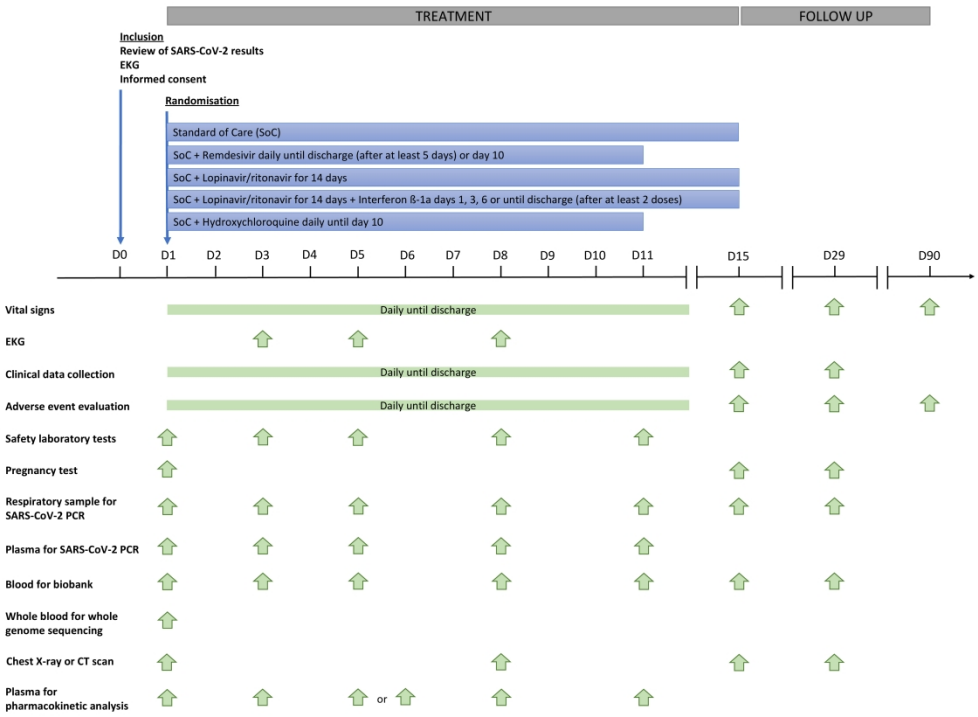

Schematic representation of the experimental design of the DisCoVeRy clinical trial.

419x299mm (300 x 300 DPI)

BMJ Open

Protocol for the DisCoVeRy trial: multi-centre, adaptive, randomized trial of the safety and efficacy of treatments for COVID-19 in hospitalized adults

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TITLE

Protocol for the DisCoVeRy trial: multi-centre, adaptive, randomized trial of the safety and efficacy of treatments for COVID-19 in hospitalized adults

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KEYWORDS

COVID-19; SARS-CoV-2; Randomized clinical trial; Efficacy; Safety; Type 1 interferon; Remdesivir; Lopinavir/ritonavir; Hydroxychloroquine;

Text count: 4777 words

ABSTRACT

Introduction

To find effective and safe treatments for COVID-19, the WHO recommended to systemically evaluate experimental therapeutics in collaborative randomized clinical trials. As COVID-19 was spreading in Europe, the French national institute for Health and Medical Research (Inserm) established a trans-disciplinary team to develop a multi-arm randomized controlled trial named DisCoVeRy. The objective of the trial is to evaluate the clinical efficacy and safety of different investigational repurposed therapeutics relative to Standard of Care (SoC) in patients hospitalized with COVID-19.

Methods and analysis

DisCoVeRy is a phase III, open-label, adaptive, controlled, multicentre clinical trial in which hospitalized patients with COVID-19 in need of oxygen therapy are randomized between 5 arms: (i) a control group

managed with SoC and four therapeutic arms with repurposed antiviral agents: *(ii)* remdesivir + SoC, *(iii)* lopinavir/ritonavir + SoC, *(iv)* lopinavir/ritonavir associated with interferon (IFN)-β-1a + SoC and *(v)* hydroxychloroquine + SoC. The primary endpoint is the clinical status at Day 15 on the 7-point ordinal scale of the WHO Master Protocol (version 3.0, March 3, 2020). This trial involves patients hospitalized in conventional departments or intensive care units both from academic or non-academic hospitals throughout Europe. A sample size of 3,100 patients (620 patients per arm) is targeted. This trial has begun on March 22, 2020. Since April 5, 2020, DisCoVeRy has been an add-on trial of the Solidarity consortium of trials conducted by the WHO in Europe and worldwide. On June 8, 2020, 754 patients have been included.

Ethics and dissemination

Inserm is the sponsor of DisCoVeRy. Ethical approval has been obtained from the institutional review board on March 13, 2020 (20.03.06.51744) and from the French National Agency for Medicines and Health Products (ANSM) on March 9, 2020. Results will be submitted for publication in peer-reviewed journals.

Trial registration number

NCT04315948 Eudra-CT 2020-000936-23

ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The DisCoVeRy clinical trial is an adaptive, randomized, open-label clinical trial that aims to evaluate the safety and efficacy of 4 antiviral therapeutic strategies as compared to standard of care in hospitalized adult patients diagnosed with COVID-19.
- Therapeutic strategies can be modified according to new evidence: an arm can become the standard of care if proved superior to others, arms can be discontinued if proved inferior to others and arms can be added if new candidate therapeutic strategies emerge.
- DisCoVeRy is an add-on trial of the Solidarity consortium of trials, conducted under the aegis of the WHO and data on common endpoints are shared with the Solidarity consortium.
- DisCoVeRy is not a placebo-controlled trial and is not double-blind because of the complexity of blinding treatments with different mode of administration (intravenous, sub-cutaneous or oral) and the need to initiate the trial very rapidly.
- DisCoVeRy includes patients who are hospitalized in need of oxygen therapy, it does not target patients at the early phase of the disease nor include anti-inflammatory agents that can be used as part of the standard of care in any arm.

INTRODUCTION

Background and scope

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the third coronavirus that has crossed the species barrier to cause deadly pneumonia in humans since the beginning of the 21st century, after SARS-CoV [1,2] and Middle-East respiratory syndrome coronavirus [3] (MERS-CoV) in 2002 and 2012, respectively. The first case of infection with the SARS-CoV-2 was reported in the city of Wuhan, China on December 31, 2019. The associated disease was named “coronavirus disease 2019” (abbreviated “COVID-19”). The emergence and the spread of SARS-CoV-2 is an unprecedented challenge, vividly illustrating the pace at which a viral outbreak can progress among a highly interlinked and susceptible global population. At the beginning of March 2020, when this clinical trial was designed, COVID-19 had spread to more than 100 countries and affected more than 100,000 individuals. Consistently, the World Health Organization (WHO) declared COVID-19 pandemic on March 11, 2020.[4]

Although many drugs have *in vitro* activity against various coronaviruses, no clinical evidence at that time supported the efficacy and safety of any drug against any coronavirus in humans, including SARS-CoV-2. The rapid and simultaneous combination of supportive care and randomized controlled trials (RCT) is the only way to find effective and safe treatments for COVID-19 that could improve patients’ management. WHO thus recommended researchers around the world to systemically evaluate experimental therapeutics in RCT and to gather initiatives in large trials that could provide strong evidence about which treatment are safe and effective.

As COVID-19 was spreading in Europe, the French national institute for Health and Medical Research (Inserm) established a trans-disciplinary team to develop a multi-arm randomized controlled trial to rapidly provide reliable evidence about the efficacy and safety of therapeutics in comparison to a standard of care control arm. The WHO Master Protocol for therapeutics against COVID-19 version 3.0 (March 3, 2020) published by the WHO R&D Blueprint Working Group [5] was used as a template for this clinical trial. Subsequently, the DisCoVeRy trial was launched in France in March 22, 2020. International cooperation being essential in outbreak science and public health, and in actions to prevent trans-frontier disease progression, the DisCoVeRy trial intends to bring together several European countries.

Objective

The objective of the DisCoVeRy trial is to evaluate the clinical efficacy and safety of different investigational therapeutics relative to Standard of Care (SoC) in patients hospitalized with COVID-19.

METHODS AND ANALYSIS

Design and general information

DisCoVeRy is a phase III, open-label, adaptive, randomized, controlled, multicenter clinical trial designed to evaluate the safety and efficacy of repurposed therapeutic interventions in hospitalized adult patients diagnosed with COVID-19. This trial involves patients both from academic or non-academic hospitals throughout Europe, with Inserm as the sponsor. Study sites can be obtained from the sponsor's representative (contact: helene.esperou@inserm.fr). The protocol described in this article is the version 7.0 of the DisCoVeRy protocol approved on April 5.

The DisCoVeRy RCT has 5 arms: (i) a control group managed SoC and four therapeutic arms with repurposed antiviral agents: *(ii)* remdesivir + SoC, *(iii)* lopinavir/ritonavir + SoC, *(iv)* lopinavir/ritonavir associated with interferon (IFN)-β-1a + SoC and *(v)* hydroxychloroquine + SoC (Figure 1). The arms have not been modified between the version 1 and 7 of the protocol. Included participants cannot be treated with antivirals other than the study medications allocated by randomization, but non-antiviral drugs such as steroids, immunomodulatory agents (e.g. anti-interleukin 6 drugs), or antibiotics can be used as part of the standard of care. This is an open-label trial but all investigators are unaware of aggregate outcomes during the study. The design is adaptive upon decision of the DSMB: arms can be discontinued if proved inferior to others, an existing arm can become the standard of care if proved superior and arms can be added if new candidate therapeutic strategies emerge. The trial has been registered at the ClinicalTrials.org registry as NCT04315948 and on the European Clinical Trials Database as 2020-000936-23.

Participants

For the duration of the study, the sponsor has subscribed an insurance policy covering the sponsor's own third-party liability as well as the third-party liability of all the investigators involved in the study (EUR 600,000 per participant for bodily injury and property damage combined and EUR 5,000,000 per trial in total. The maximum amount of compensation could vary depending on the country).

Inclusion criteria

Patients must fulfil the following criteria prior to trial enrolment:

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 of pulmonary infection (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.

Non-inclusion criteria

Patients with any of the following criteria are not eligible for trial enrolment:

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, piperaquine;
10. Human immunodeficiency virus infection under combination antiretroviral therapy;
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).

Randomisation

Patients are randomly assigned in a 1:1:1:1:1 ratio into one of the five groups. The randomisation list is computer-generated, with blocks of various sizes and stratified by region (according to the administrative

definition in each country) and severity of illness at enrolment (severe disease: patients requiring non-invasive ventilation, high flow oxygen devices, invasive mechanical ventilation or ECMO; moderate disease: patients not requiring non-invasive ventilation, high flow oxygen devices, invasive mechanical ventilation nor ECMO). The randomisation list is implemented in the electronic Case Report Form (eCRF) to ensure appropriate allocation concealment.

Experimental design

Study treatments

The participants are allocated in one of 5 arms (Figure 1).

Patients included in the remdesivir group receive 200 mg intravenous loading dose on Day 1, followed by a 100 mg once-daily intravenous maintenance dose for the duration of the hospitalization and up to a 10 days' total course. Remdesivir is administered through a 30 to 60 minutes IV infusion.

Patients included in the lopinavir/ritonavir group receive 400 mg lopinavir and 100 mg ritonavir 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) is administered as a 5-mL suspension every 12h for 14 days via a nasogastric tube.

Patients included in the lopinavir/ritonavir + interferon ß-1a group receive, in addition to lopinavir/ritonavir as described above, interferon ß-1a 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.

Patients included in the hydroxychloroquine group receive a loading dose of 400 mg twice daily for one day followed by 400 mg once daily for 9 days. The rationale for this loading dose has been published.[6]

Patients included in the control group receive the standard of care of their recruitment center. Investigational drugs were kindly provided by pharmaceutical firms.

Rationale for study treatments

Remdesivir (GS-5734) is a broad-spectrum nucleotide prodrug inhibiting RNA-dependent 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.[7–9] Studies in human airway epithelial cell assays demonstrated that remdesivir inhibits replication of coronaviruses, including MERS-CoV.[10] Remdesivir has shown an *in vitro* activity on SARS-CoV-2[11] and a clinical benefit in rhesus macaques infected with SARS-CoV-2.[12] A large RCT has shown that remdesivir shortened

the time to recovery in adults hospitalized with Covid-19 as compared to placebo but the results were not significant for mortality.[13]

Lopinavir/ritonavir is a fixed-dose combination used in HIV infection that has shown an *in vitro* activity against SARS-CoV in several studies.[14] A structure-based study suggested that the spatial structure of the lopinavir/ritonavir binding site was conserved between SARS-CoV and SARS-CoV-2.[15] The results of an open RCT evaluating lopinavir/ritonavir for COVID-19 were published on March 18, 2020.[16] In this trial, adults with confirmed COVID-19 and hypoxemia (SpO_2 < 94 %) were randomized to lopinavir/ritonavir (n=99) or standard of care (n=100). No significant difference between the 2 groups was observed on the time to clinical improvement on a 7-item ordinal scale. (HR of improvement 1.31; CI95% 0.95 - 1.80) but a trend to lower mortality rate was observed (19.0% *vs.* 27.1%) in the 90 patients (45.2% of the total) receiving lopinavir/ritonavir less than 12 days after the beginning of the symptoms.

Interferon (IFN)-ß-1 is a broad-spectrum antiviral drug belonging to the type 1 interferons. Type 1 IFN treatment has shown an activity against MERS-CoV and SARS-CoV in numerous experiments, both *in vitro* and *in vivo*.[17–19] Type 1 interferon is currently being tested for MERS-CoV in the MIRACLE clinical trial.[20] SARS-CoV-2 displays *in vitro* a substantial susceptibility to IFN-α [21] and data regarding the potential activity of type 1 interferons on SARS-CoV-2 has been reviewed recently.[22] A RCT found that COVID-19 patients treated with a triple combination interferon beta-1b, lopinavir-ritonavir, and ribavirin had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 days [IQR 5-11]) than the control group up (12 days [8-15]; hazard ratio 4·37 [95% CI 1·86-10·24], p=0·0010).[23]

The *in vitro* antiviral activity of hydroxychloroquine has been known for a long time [24] and was described on a number of viruses including SARS-CoV.[25,26] Regarding COVID-19, recent publications reported an *in vitro* activity of hydroxychloroquine on SARS-CoV-2 [11][27] and non-randomized observational studies provided conflicting clinical results.[28,29] A RCT on postexposure prophylaxis for COVID-19 found that hydroxychloroquine did not prevent illness compatible with Covid-19 or confirmed infection.[30]

Participant timeline

Clinical evaluations for efficacy and safety are performed at baseline, daily while the patient is hospitalized and at 15 (+/- 2 d) and 29 (+/- 3 d) (Table 1, Figure 2).

Upper (nasopharyngeal swab) and/or lower (endotracheal aspiration) respiratory tract and blood samples for centralized analysis of the SARS-CoV-2 kinetics are collected at baseline and at days 3 (+/- 1 d), 5 (+/- 1 d), 8 (+/- 1 d), 11 (+/- 1 d), 15 (+/- 2 d) and 29 (+/- 3 d). RT-PCR methods for SARS-COV-2 detection in participating centers are different but their performances were all validated by French National Reference Center for Viral Respiratory Infections and viral loads are determined using the specific French National Reference Center RT-PCR IP4.[31] For each sample, the viral load is measured by a specific SARS-COV-2 real-time (RT)-PCR and normalized according the number of cells in each sample. This method is validated to monitor viral load kinetics over time and expressed in standardized unit log of number of viral copies/10 000 cells.

Blood samples for pharmacokinetic analysis are collected:

- For remdesivir, to measure plasma and intracellular concentrations at days 1, 2, 5, 8 and 11;
- For lopinavir, to measure plasma concentrations at days 1, 3 (+/- 1 d), 6 (+/- 1 d), 8 (+/- 1 d) and 11 (+/- 1 d);
- For IFN ß-1-a, to measure plasma concentrations at days 3 and 6;
- For hydroxychloroquine, to measure plasma concentrations at days 1, 3 (+/- 1 d), 5 (+/- 1 d), 8 (+/- 1 d) and 11 (+/- 1 d).

Thoracic imaging by X-ray or CT scan are performed at baseline, and at days 8 (+/- 1 d), 15 (+/- 2 d) and 29 (+/- 3 d).

Biological evaluations for safety are performed at baseline and at days 3 (+/- 1 d), 5 (+/- 1 d), 8 (+/- 1 d), 11 (+/- 1 d), 15 (+/- 2 d) and 29 (+/- 3 d).

A sample collection is constituted for each patient (biobank) including whole blood and plasma at baseline and plasma at days 3 (+/- 1 d), 5 (+/- 1 d), 8 (+/- 1 d), 11 (+/- 1 d), 15 (+/- 2 d) and 29 (+/- 3 d). The biobank will be used to conduct ancillary analyses that remain to be determined.

Primary endpoint

The primary endpoint is the clinical status at Day 15 on the 7-point ordinal scale of the WHO Master Protocol (version 3.0, March 3, 2020):

1. Not hospitalized, no limitation 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.

For the scores 1 and 2, limitation of the activities refers to the pre-COVID-19 clinical status, in order to take into account potential pre-existing limitations.

Secondary endpoints

Secondary endpoints are classified as efficacy or safety endpoints.

Efficacy secondary endpoints

1. 7-point ordinal scale
   - Time to an improvement of one category from admission on the ordinal scale.
   - Subject clinical status on the ordinal scale on Days 3, 5, 8, 11, and 29.
   - Mean change in the ranking on the ordinal scale from baseline to Days 3, 5, 8, 11, 15 and 29 from baseline.
2. 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.
3. 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.
4. Mechanical ventilation
   - Ventilator free days in the first 28 days (to Day 29).
   - Incidence and duration of new mechanical ventilation use during the study.
5. Hospitalization
   - Duration of hospitalization (days).
6. Mortality
   - In-hospital mortality
   - 28-day mortality.
   - 90-day mortality

Safety secondary endpoints

1. Cumulative incidence of any grade 3 and 4 adverse events;
2. Cumulative incidence of any serious adverse event;
3. Proportion of patients with a premature discontinuation or temporary suspension of the study drug, for any reason;
4. Grade changes in biological parameters, as measured using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (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.

Exploratory endpoints

1. Qualitative and quantitative PCR for SARS-CoV-2 normalized according to the number of sample cells in nasopharyngeal or lower respiratory tract samples on days 1, 3, 5, 8, 11, 15 and 29;
2. Qualitative and quantitative PCR for SARS-CoV-2 in blood on days 1, 3, 5, 8 and 11;
3. Development of resistance of SARS-CoV-2 in nasopharyngeal or lower respiratory tract samples at days 3, 5, 8, 11, 15 and 29;
4. Whole genome sequencing of participants to identify genetic variants associated with (i) the development of severe clinical disease (ii) the response in terms of safety and efficacy to investigational antiviral drugs;
5. Imagery assessment through chest X-ray or thoracic CT scan on days 1, 8, 15 and 29, depending on availability in centre;
6. Study drugs concentrations, sampled while the participant is hospitalized:
   - For remdesivir, as assessed by plasma concentration after the end of infusion on day 1, trough plasma and intracellular concentrations before the 2nd dose administration on day 2, and trough plasma concentration on days 5 and 8;
   - For lopinavir, peak plasma concentration measured 4 hours after the 1st administration and trough plasma concentrations measured just before the 2nd administration and on days 3, 6, 8 and 11;
   - For IFN ß-1-a, trough plasma concentration on days 3 and 6;
   - For hydroxychloroquine, peak plasma concentration measured 4 hours after the 1st

administration and trough plasma concentrations measured just before the 2nd administration and on days 3, 5, 8 and 11.

Data collection

The trial is conducted in accordance with relevant regulations and standard operating procedures, including data protection. The data are collected on an electronic case report form. Clinical site monitoring is conducted to ensure that the rights are protected and confirm the integrity of collected data. The persons responsible for the quality control of the data take all necessary precautions to ensure the confidentiality of information regarding investigational medicinal products, the trial, trial participants and in particular the identity of the participants and the results obtained.

Safety and adverse events monitoring

All adverse events are collected regardless of their grade of severity. The choice of continuing therapy is at the discretion of the investigator. All adverse events are classified in grades from mild (grade 1) to life threatening (grade 4) following the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (version 2.1 of July 2017) of the National Institute of Health and National Institute of Allergy and Infectious Diseases of the US Department of Health and Human Services.

Statistical considerations

General considerations

Continuous variables will be summarized by the mean, standard deviation, median, interquartile range, minimum and maximum. The change from baseline will be compared using Student's t-test or a Wilcoxon-Man-Whitney test if the normality assumption does not hold.

Categorical data will be summarized with the number and proportion of patients. Data will be compared using odds ratios and a Fisher's exact test.

All statistical tests will be 2-sided with type I error of 0.05. As there are 4 comparisons, each treatment group will be compared to the control group with a two-sided type I error of 0.0125. Subgroup analyses for the primary and secondary endpoints 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.

Sample size computation

A sample size of 3,100 patients (620 patients per arm) is targeted. The sample size was determined assuming the following scenario under standard of care for each item of the ordinal scale: 1: 42%, 2: 38%, 3: 8%, 4: 7%, 5: 2%, 6: 1%, 7: 2%.

There is significant uncertainty with these assumptions given the limited data available. Since a large proportion of patients are moderately ill patients, we power the study for an odds ratio of 1.5 (an odds ratio higher than 1 indicates superiority of the experimental treatment over the control for each ordinal scale category), with 90% power and using an overall one-sided type I error rate of 0.05.[32] 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.) The samples size might evolve whenever any treatment arm is withdrawn or added to the trial.

Definition of analysis sets

The intention-to-treat population is defined as all randomised patients, where patients are analysed in their randomisation group whether they have or not followed the allocated treatment. The modified intention-to-treat population is defined as all randomised patients who did receive at least one dose of the allocated treatment.

The primary and efficacy secondary analysis will be conducted on the intention-to-treat population. Safety analyses will be based on the modified intention-to-treat population.

Adaptive design

This study is intended to allow for adaptations with the ability to add a new experimental arm if one becomes available. The current plan is to evaluate the primary endpoint on day 15. 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 randomized clinical trial.[33]

Interim analyses

Interim analyses will be by the independent statistician of the DSMB. There are no formal stopping rules for efficacy or safety. The DSMB will make recommendations taking into consideration the totality of the evidence from the efficacy and safety outcomes as they accumulate, as well as external evidence.

For efficacy, the statistical analysis will be done on the primary endpoint, the 7-point ordinal scale at 15 days, and be based on the Haybittle Peto rule.[34,35] That is, if any active treatment is superior to

control at P<.001 then consideration will 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, i.e. stopping because an active treatment appears ineffective, the statistical analysis will be done with the primary endpoint. 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. All the above is intended for all randomised patients. Analyses will be stratified by baseline severity of disease. For safety, no pre-specify stopping guideline will be defined because there are various aspects of potential harm that could be studied. However, to allow for some caution, any safety signal on SAE, i.e. active treatment worse than control, requires P<.01 to merit consideration of stopping that treatment arm.

Final analysis of the primary endpoint

The primary outcome uses a 7-point ordinal scale analysed using a 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). Odds ratios are then interpreted as the odds of being “lower” or “higher” on the ordinal scale across the entire range of the scale. 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 validity of the proportionality assumption will be evaluated and tested. To deal with potential missing data, the last observation will be carried forward until the next available value.

Analysis of secondary endpoints

Differences in time-to-event endpoints by treatment will be summarized with Kaplan-Meier curves and 95% confidence interval; and cumulative incidence plots, for time-to-event endpoints with competing risk (e.g. death). Duration of event will be summarized according to median days with quartiles. Incidence data will be summarized as percent with 95% confidence interval. Time-to-event endpoints

will be compared using the log-rank test. For time-to-event endpoints with a competing risk Fine and Gray models will be used. All tests will be stratified by the baseline severity.

Committees for the research

The DisCoVeRy French Trial Management Team (TMT) has developed and implemented the protocol in France (Supplementary file). A DisCoVeRy European Steering Committee (DSC) has been constituted to serve as the governance organ for the trial. It provides the overall supervision of the trial, including for the relations with European stakeholders, the Steering Committee and the Executive Committee of the Solidarity trial (see below). It ensures that the trial is conducted in accordance with ethical principles and respects participants' safety, take any decision on any changes made to the design of the DisCoVeRy trial, and on the reporting of the trial results, including regarding the publication policy. An international independent DSMB has been constituted to preserve the interests of trial participants, to monitor the main outcome measures (including safety and efficacy), and to monitor the overall conduct of the trial. Based on interim analyses of the data, it will make recommendations about early study closure or changes to the trial, including adding or removing treatment arms. The DSMB will meet after 100 participants are included into the study, and then every 200 new patients are included, with a maximum of 1 DSMB meeting per week. Other ad hoc reviews will be undertaken if there are 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.

Intertwinement with WHO Solidarity program

Since April 5, 2020, DisCoVeRy has been an add-on trial of the Solidarity program conducted by the WHO in Europe and worldwide. The same treatments are evaluated in DisCoVeRy and in Solidarity. Solidarity has 3 endpoints which are also secondary endpoints of DisCoVeRy: (*i*) mortality during hospitalization (the primary endpoint of Solidarity) (*ii*) length of hospital stay and (*iii*) time to mechanical ventilation or transfer to intensive care. At each DisCoVeRy DSMB meeting, the recommendations will be transmitted to the Data and Safety Monitoring Committee (DSMC) of Solidarity. The Executive Committee of Solidarity will ultimately issue recommendations on the different treatments evaluated, allowing a unique communication on each of the treatments evaluated.

Patient and public involvement

No patients were involved in the design or implementation of this study.

ETHICS AND DISSEMINATION

Ethics approval

Inserm is the sponsor of DisCoVeRy in Europe. Ethical approval was first obtained in France from the institutional review board on March 13, 2020 (Comité de Protection des Personnes Ile de France 3, approval number 20.03.06.51744), and the trial received approval by the French National Agency for Medicines and Health Products (ANSM) on March 9, 2020. The protocol described in this article is the version 7.0 of the DisCoVeRy protocol approved on April 5, 2020. Any substantial amendment made to the protocol by the coordinating investigator is sent to local ethics committee and health authorities in each country for approval, prior to implementation. The sponsor shall have the right to audit any center participating in the study and may appoint an auditor to carry out such an audit. Such right to audit shall include access all relevant documents and other information relating to the clinical trial. If the sponsor decides to audit the trial, only one audit will be performed

Informed consent

Prior to any act carried out as part of the research, subjects receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. An emergency consent procedure with the legal guardian or relatives of the patient has been put in place for patients who are unable to consent. The informed consent form of the study contains information's about possible data sharing and biological specimens sharing for ancillary studies. Participants are also provided with a link to a website where they can find all information about data sharing. The forms have been reviewed by the Ethics committee that authorized the trial.

Dissemination

Results will be communicated at scientific meetings and submitted for publication in peer-reviewed journals. According to the information sheet, participants will be informed of the overall results at the end of the trial. In addition, participants are informed of the discontinuation of a treatment arm in the trial after validation by the ethics committee.

DISCUSSION

Strengths and limitations of the DisCoVeRy trial design

The DisCoVeRy clinical trial is a randomized, open clinical trial that aims to evaluate the safety and efficacy of possible therapeutic agents in hospitalized adult patients diagnosed with COVID-19. The

design of DisCoVeRy is adaptive meaning that it can adapt to the ongoing production of evidence and to interim analyses by discontinuing arms that are proved inferior to others, selecting an existing arm as the standard of care if proved superior to others and adding arms if new candidate therapeutic strategies emerge.

As detailed above, DisCoVeRy is an add-on trial of the Solidarity trial, conducted under the aegis of the WHO in Europe and worldwide. Sharing the data from DisCoVeRy relevant to the Solidarity trial (inclusion data and data related to the Solidarity endpoints) increases the number of participants for whom this data is available and thus leads to a faster conclusion on the effectiveness, deleterious effect or ineffectiveness of the treatments evaluated. Inclusion in a same strategy of hospitalized patients with severe (patients requiring non-invasive ventilation, high flow oxygen devices, invasive mechanical ventilation or ECMO) or moderate disease will allow to evaluate the different drug candidates in different clinical situations. Moreover, by including patients at different times in their clinical history of COVID-19, we will be able to study when is the best time to start an antiviral agent in relation to the delay of symptoms. The collection of samples for pharmacological monitoring, viral kinetics and medical imaging will provide crucial data to analyze the PK/PD of evaluated drugs and the effect of treatment on the virological and radiological evolution. A biobank has also been planned to conduct further analyses that still remain to be determined. However, DisCoVeRy will not provide data on treatments for COVID-19 at an early phase, before there is a need for hospitalization. As only antiviral agents are evaluated in DisCoVeRy, we will not be able to evaluate the efficacy of immunomodulatory agents, including corticosteroids.

Strengths and limitations of real-time interventional research in the setting of a pandemic

Discovery is not a placebo-controlled trial and is not double-blind because of the complexity of blinding treatments with different mode of administration (intravenous, sub-cutaneous or oral) and the need to initiate the trial very rapidly. Moreover, in a recent meta-epidemiological study, no evidence was found that lack of blinding of patients, healthcare providers, or outcome assessors had an impact on effect estimates in randomised clinical trials.[36]

Integrating clinical trials of experimental therapeutics is an increasingly recognized part of the response during infectious disease outbreaks. Since the Ebola outbreak in West Africa and subsequent outbreaks in the Democratic Republic of Congo, clinical trials of investigative drugs have been fully integrated in

the epidemic response.[37–39] Implementing large clinical trial is both direly needed and particularly challenging during a pandemic. Indeed, the pandemic context compels us to organize clinical trials urgently while keeping methodological requirements of the highest level which is the only way to provide reliable answers for clinicians. The selection of the best candidate drugs for a new outbreak is a major challenge and a strength of the DisCoVeRy trial is that its adaptive design allows to add new arms if good evidence emerges while the trial is continuing that some other treatment(s) should also be evaluated. There have been controversies regarding the candidate treatments that should be selected for COVID-19 clinical trials and notably regarding hydroxychloroquine. Hydroxychloroquine was identified at the beginning of the pandemic as a candidate treatment based on preliminary data and quickly became the most tested treatment in the world for COVID-19.[40,41] However, many of the articles supporting hydroxychloroquine suffered from methodological shortcomings and were in fact non-informative.[42] Hydroxychloroquine has been widely promoted as soon as February 2020 as an effective drug by some scientists and politics[43], leading to difficulties in recruiting patients in randomized clinical trials such as DisCoVeRy.[44] This is why the ever-changing scientific background supporting the use of each candidate treatment should be clear, detailed and regularly updated and pragmatic, adaptive clinical trials should be encouraged. Transparency, consistency and quality of design are more crucial than ever during pandemics to provide relevant and reliable data.

TRIAL STATUS

This trial has begun on March 22, 2020. On July 28, 2020, 801 patients have been included.

DATA SHARING PLAN

Study protocol and statistical analysis plan will be openly available. Systematic individual patient data sharing is not intended, but all requests for the trial's data will be considered by the French DisCoVeRy Trial Management Team.

507 **Figure 1.** DisCoVeRy trial arms, drugs and dosing schedule

508 **Figure 2.** Schematic representation of the experimental design of the DisCoVeRy clinical trial.

509 **Table 1**. Schedule of enrolment, interventions and assessment in the DisCoVeRy trial

Day +/- Window	**Screening**	**Baseline[1]**	**D1**	**D2-D14[2]**	**D15[2] ± 2**	**D29[2] ± 3**	**D90**
ELIGIBILTY							
Informed consent	X						
Demographics & Medical History	X						
EKG	X						
Review SARS-CoV-2 PCR 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		X	X	Daily until discharge	X	X	X

Electrocardiogram (EKG)[3]	X			Days 3, 5, 8			
Medication review	X		X	Daily until discharge	X	X	
Adverse event evaluation			X	Daily until discharge	X	X	X
SAFETY LABORATORY							
Safety haematology, chemistry and liver tests	X[4]	X[5]		Days 3, 5, 8, 11 (all ± 1 day)	X	X	
Pregnancy test for females of childbearing potential	X[4]				X	X	
Plasma concentration of lopinavir			X	Days 3, 6, 8, 11 (all ± 1 day)			
Plasma concentration of hydroxychloroquine			X	Days 3, 5, 8, 11(all ± 1 day)			
Plasma and intracellular concentration of remdesivir			X	Days 2, 5, 8 if hospitalized			
Plasma concentration of interferon ß-1a				Days 3, 6 if hospitalized			
RESEARCH LABORATORY							
Biobank (whole blood and plasma)[6]		X[6]		Days 3, 5, 8, 11 (all ± 1 day)	X	X	
Plasma for PCR SARS-CoV-2[7]		X		Day 3, 5, 8, 11 (all ± 1 day)			
Nasopharyngeal swab or lower respiratory tract samples[7]		X		Day 3, 5, 8, 11 (all ± 1 day)	X	X	
Thoracic CT scan or chest x-ray		X		Day 8 (± 1 day)	X	X	
Whole blood for genetic analysis		X					

1. *Baseline assessments should be performed prior to study drug administration.*
2. *If discharged from the hospital, visits and safety assessments are conducted in the outpatient setting.*

3. *An electrocardiogram (EKG) with calculation of the corrected QT (Fridericia formula) is reviewed at screening and monitored at Day 3, 5, 8 in patients treated with hydroxychloroquine.*
4. *Laboratory tests performed in the 48 hours prior to enrolment are accepted for determination of eligibility.*
5. *Any laboratory tests performed in the 24 hours before randomization can be used for baseline and Day 1.*
6. *For the biobank, whole blood is only collected at baseline.*
7. For each sample, the viral load is measured by a specific SARS-COV-2 real-time (RT)-PCR and normalized according the number of cells in each sample. This method is validated to monitor viral load kinetics over time and expressed in standardized unit log of number of viral copies/10 000 cells.

AUTHOR CONTRIBUTION :

Conceptualization, investigation, supervision, writing - original draft: FA

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COMPETING INTERESTS

François-Xavier Lescure reports fees for development of educational presentations from Gilead, outside the submitted work. Dominique Costagliola reports personal fees from Merck Switzerland, grants and personal fees from MSD France, personal fees from Gilead France, grants and personal fees from Janssen, outside the submitted work. Jean-François Timsit reports grants and personal fees from Merck, grants and personal fees from Pfizer, grants from biomerieux, personal fees from medimune, personal fees from Paratek, personal fees from Gilead, outside the submitted work. Benjamin Hamze reports personal fees from Sanofi, outside the submitted work. Gilles Peytavin has received travel grants, consultancy fees, honoraria, or study grants from various pharmaceutical companies, including Gilead Sciences, Merck, TheraTechnologies and ViiV Healthcare. France Mentre reports grants and personal fees from Sanofi, outside the submitted work.

Other authors declare no competing interests.

DISCLAIMER

The funder nor the sponsor did not have any role in the design of the trial

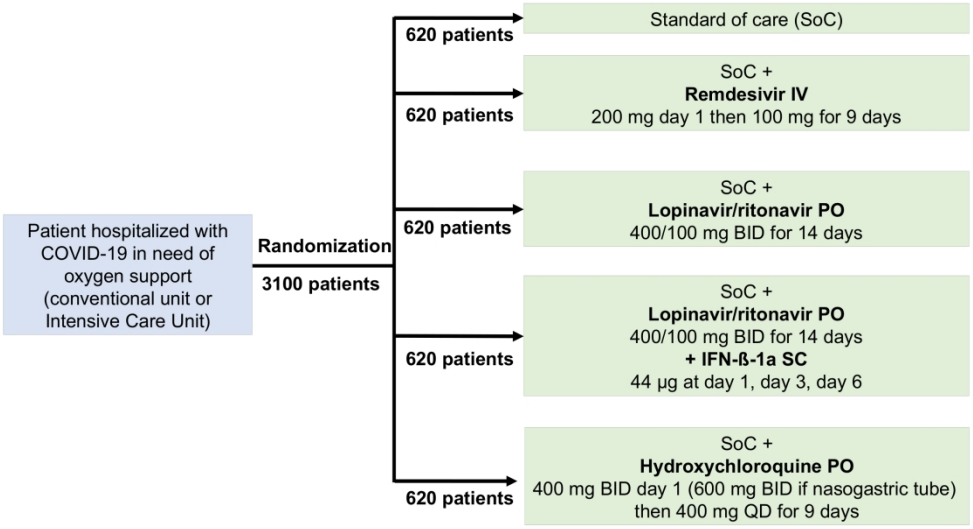

Figure 1. DisCoVeRy trial arms, drugs and dosing schedule

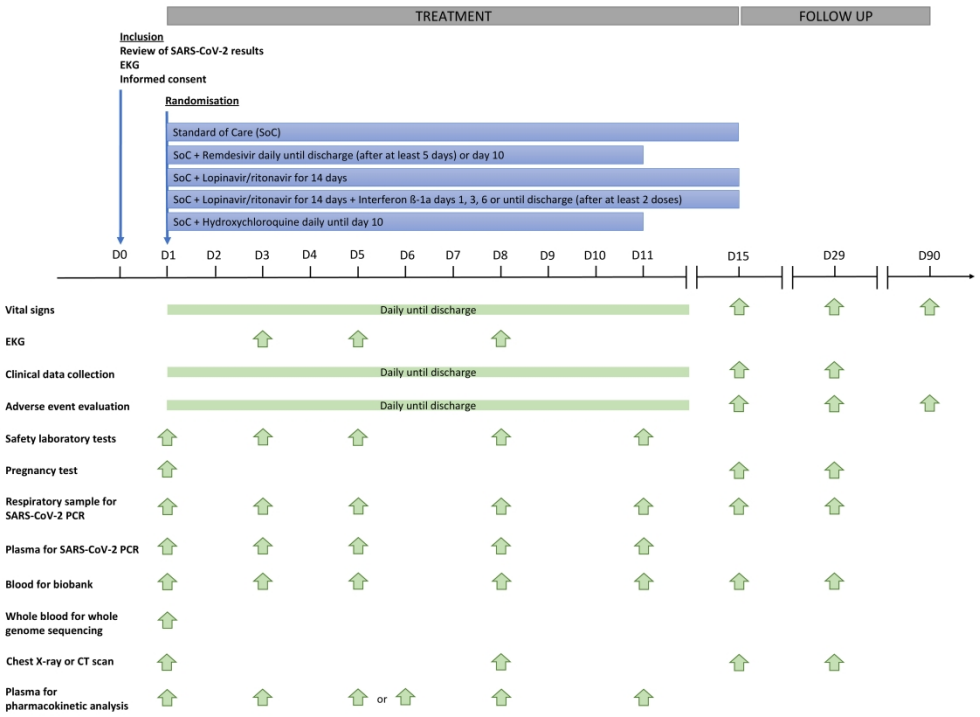

Figure 2. Schematic representation of the experimental design of the DisCoVeRy clinical trial.

419x299mm (300 x 300 DPI)

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2, 5
Protocol version	3	Date and version identifier	15
Funding	4	Sources and types of financial, material, and other support	25
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	23-24 and Supplementary 1
	5b	Name and contact information for the trial sponsor	5, 26
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	26
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14-15

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4, 7-8
	6b	Explanation for choice of comparators	7-8, 16
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5-6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7, 20
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	20
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8-19, 19-20, Figure 2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12-13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6-7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6-7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5, 17
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-12, Table 1
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11-12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11, 13, 15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15-16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15-16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	16
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	26
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15-16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	5
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	23-24
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Table 1

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.