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BMJ Open

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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1
2
3 1 **TITLE**

4
5 2 **The DisCoVeRy trial: multi-centre, adaptive, randomized trial of the safety and efficacy of**
6
7 3 **treatments for COVID-19 in hospitalized adults**

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21
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23 98 **DISCLAIMER**

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26 99 The funder nor the sponsor did not have any role in the design of the trial

27
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29 101 **COMPETING INTERESTS**

30
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50
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52
53 113 Other authors declare no competing interests.

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55 114

56 115 **DATA SHARING STATEMENT**

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3 116 Systematic data sharing is not intended, but all requests for the trial's data will be considered by the
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5 117 French DisCoVeRy Trial Management Team
6

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9 119 **ETHICS APPROVAL**

10 120 Ethical approval was first obtained in France from the institutional review board on March 13, 2020
11
12 121 (Comité de Protection des Personnes Ile de France 3, approval number 20.03.06.51744), and the trial
13
14 122 received approval by the French National Agency for Medicines and Health Products (ANSM) on March
15
16 123 9, 2020. The protocol described in this article is the version 7.0 of the DisCoVeRy protocol approved on
17
18 124 April 5, 2020. Any substantial amendment made to the protocol by the coordinating investigator is sent
19
20 125 to local ethics committee and health authorities in each country for approval, prior to implementation.
21

22 126 **INFORMED CONSENT**

23
24 127 Prior to any act carried out as part of the research, subjects receive a concise and focused presentation
25
26 128 of key information about the clinical trial, verbally and with a written consent form. An emergency consent
27
28 129 procedure with the legal guardian or relatives of the patient has been put in place for patients who are
29
30 130 unable to consent. The forms have been reviewed by the Ethics committee that authorized the trial.
31

32 131 **KEYWORDS**

33 132 COVID-19; SARS-CoV-2; Randomized clinical trial; Efficacy; Safety; Type 1 interferon; Remdesivir;
34
35 133 Lopinavir/ritonavir; Hydroxychloroquine;
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136 ABSTRACT**137 Introduction**

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

144 Methods and analysis

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

156 Ethics and dissemination

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

161 Trial registration number

162 NCT04315948 Eudra-CT 2020-000936-23

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3 163 **ARTICLE SUMMARY**

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5 164 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

6
7 165 . The DisCoVeRy clinical trial is an adaptive, randomized, open-label clinical trial that aims to evaluate
8
9 166 the safety and efficacy of 4 antiviral therapeutic strategies as compared to standard of care in
10
11 167 hospitalized adult patients diagnosed with COVID-19.

12
13 168 . Therapeutic strategies can be modified according to new evidence: an arm can become the
14
15 169 standard of care if proved superior to others, arms can be discontinued if proved inferior to others
16
17 170 and arms can be added if new candidate therapeutic strategies emerge.

18
19 171 . DisCoVeRy is an add-on trial of the Solidarity consortium of trials, conducted under the aegis of the
20
21 172 WHO and data on common endpoints are shared with the Solidarity consortium.

22
23 173 . DisCoVeRy is not a placebo-controlled trial and is not double-blind because of the complexity of
24
25 174 blinding treatments with different mode of administration (intravenous, sub-cutaneous or oral) and
26
27 175 the need to initiate the trial very rapidly.

28
29 176 . DisCoVeRy includes patients who are hospitalized and in need of oxygen therapy and does not
30
31 177 target patients at the early phase of the disease.

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33 178 . DisCoVeRy does not include anti-inflammatory agents that can be used as part of the standard of
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35 179 care in any arm.

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181 INTRODUCTION

182 **Background and scope**

183 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the third coronavirus that has
184 crossed the species barrier to cause deadly pneumonia in humans since the beginning of the 21st
185 century, after SARS-CoV [1,2] and Middle-East respiratory syndrome coronavirus [3] (MERS-CoV) in
186 2002 and 2012, respectively. The first case of infection with the SARS-CoV-2 was reported in the city
187 of Wuhan, China on December 31, 2019. The associated disease was named “coronavirus disease
188 2019” (abbreviated “COVID-19”). The emergence and the spread of SARS-CoV-2 is an unprecedented
189 challenge, vividly illustrating the pace at which a viral outbreak can progress among a highly interlinked
190 and susceptible global population. At the beginning of March 2020, when this clinical trial was designed,
191 COVID-19 had spread to more than 100 countries and affected more than 100,000 individuals.
192 Consistently, the World Health Organization (WHO) declared COVID-19 pandemic on March 11,
193 2020.[4]

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

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

210 **Objective**

1
2
3 211 The objective of the DisCoVeRy trial is to evaluate the clinical efficacy and safety of different
4 212 investigational therapeutics relative to Standard of Care (SoC) in patients hospitalized with COVID-19.

7 213 **METHODS AND ANALYSIS**

9 214 ***Design and general information***

10 215 DisCoVeRy is a phase III, open-label, adaptive, randomized, controlled, multicenter clinical trial
11 216 designed to evaluate the safety and efficacy of repurposed therapeutic interventions in hospitalized adult
12 217 patients diagnosed with COVID-19. This trial involves patients both from academic or non-academic
13 218 hospitals throughout Europe, with Inserm as the Sponsor. Study sites can be obtained from the
14 219 Sponsor's representative. The protocol described in this article is the version 7.0 of the DisCoVeRy
15 220 protocol approved on April 5.

16 221 The DisCoVeRy RCT has 5 arms: (i) a control group managed SoC and four therapeutic arms with
17 222 repurposed antiviral agents: (ii) remdesivir + SoC, (iii) lopinavir/ritonavir + SoC, (iv) lopinavir/ritonavir
18 223 associated with interferon (IFN)- β -1a + SoC and (v) hydroxychloroquine + SoC (Figure 1). The arms
19 224 have not been modified between the version 1 and 7 of the protocol. Included participants cannot be
20 225 treated with antivirals other than the study medications allocated by randomization, but non-antiviral
21 226 drugs such as steroids, immunomodulatory agents (e.g. anti-interleukin 6 drugs), or antibiotics can be
22 227 used as part of the standard of care. This is an open-label trial but all investigators are unaware of
23 228 aggregate outcomes during the study. The design is adaptive upon decision of the DSMB: arms can be
24 229 discontinued if proved inferior to others, an existing arm can become the standard of care if proved
25 230 superior and arms can be added if new candidate therapeutic strategies emerge. The trial has been
26 231 registered at the ClinicalTrials.org registry as NCT04315948 and on the European Clinical Trials
27 232 Database as 2020-000936-23.

28 233 ***Participants***

29 234 For the duration of the study, the sponsor has subscribed an insurance policy covering the sponsor's
30 235 own third-party liability as well as the third-party liability of all the investigators involved in the study.

31 236 Inclusion criteria

32 237 Patients must fulfil the following criteria prior to trial enrolment:

- 33 238 1. Adult ≥ 18 years of age at time of enrolment;
- 34 239 2. Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial
35 240 or public health assay in any specimen < 72 hours prior to randomization;

- 1
2
3 241 3. Hospitalized patients with illness of any duration, and at least one of the following:
4
5 242 – Clinical assessment of pulmonary infection (evidence of rales/crackles on exam) AND SpO₂
6
7 243 ≤ 94% on room air, or
8
9 244 – Acute respiratory failure requiring supplemental oxygen, high flow oxygen devices, non-
10
11 245 invasive ventilation, and/or mechanical ventilation;
12
13 246 4. Women of childbearing potential must agree to use contraception for the duration of the study.

14
15 247 Non-inclusion criteria

16 248 Patients with any of the following criteria are not eligible for trial enrolment:

- 17
18 249 1. Refusal to participate expressed by patient or legally authorized representative if they are
19
20 250 present;
21
22 251 2. Spontaneous blood ALT/AST levels > 5 times the upper limit of normal;
23
24 252 3. Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30 mL/min);
25
26 253 4. Pregnancy or breast-feeding;
27
28 254 5. Anticipated transfer to another hospital, which is not a study site within 72 hours;
29
30 255 6. Patients previously treated with one of the antivirals evaluated in the trial (i.e. remdesivir,
31
32 256 interferon β-1a, lopinavir/ritonavir, hydroxychloroquine) in the past 29 days;
33
34 257 7. Contraindication to any study medication including allergy;
35
36 258 8. Use of medications that are contraindicated with lopinavir/ritonavir i.e. drugs whose metabolism
37
38 259 is highly dependent on the isoform CYP3A with narrow therapeutic range (e.g. amiodarone,
39
40 260 colchicine, simvastatine);
41
42 261 9. Use of medications that are contraindicated with hydroxychloroquine: citalopram, escitalopram,
43
44 262 hydroxyzine, domperidone, piperazine;
45
46 263 10. Human immunodeficiency virus infection under combination antiretroviral therapy;
47
48 264 11. History of severe depression or attempted suicide or current suicidal ideation;
49
50 265 12. Corrected QT interval superior to 500 milliseconds (as calculated with the Fridericia formula).

51 266 **Randomisation**

52
53 267 Patients are randomly assigned in a 1:1:1:1:1 ratio into one of the five groups. The randomisation list is
54
55 268 computer-generated, with blocks of various sizes and stratified by region (according to the administrative
56
57 269 definition in each country) and severity of illness at enrolment (severe disease: patients requiring non-
58
59 270 invasive ventilation, high flow oxygen devices, invasive mechanical ventilation or ECMO; moderate
60

1
2
3 271 disease: patients not requiring non-invasive ventilation, high flow oxygen devices, invasive mechanical
4
5 272 ventilation nor ECMO). The randomisation list is implemented in the electronic Case Report Form
6
7 273 (eCRF) to ensure appropriate allocation concealment.

8 274 ***Experimental design***

9 275 Study treatments

10
11
12 276 The participants are allocated in one of 5 arms (Figure 1).

13
14 277 Patients included in the remdesivir group receive 200 mg intravenous loading dose on Day 1, followed
15
16 278 by a 100 mg once-daily intravenous maintenance dose for the duration of the hospitalization and up to
17
18 279 a 10 days' total course. Remdesivir is administered through a 30 to 60 minutes IV infusion.

19
20 280 Patients included in the lopinavir/ritonavir group receive 400 mg lopinavir and 100 mg ritonavir
21
22 281 administered every 12h for 14 days in tablet form. For patients who are unable to take medications by
23
24 282 mouth, the lopinavir/ritonavir (400 mg lopinavir/100 mg ritonavir) is administered as a 5-mL suspension
25
26 283 every 12h for 14 days via a nasogastric tube.

27
28 284 Patients included in the lopinavir/ritonavir + interferon β -1a group receive, in addition to
29
30 285 lopinavir/ritonavir as described above, interferon β -1a administered subcutaneously at the dose of 44
31
32 286 μ g on Day 1, Day 3, and Day 6 (total of 3 doses). No dosage adjustment is provided for renal or hepatic
33
34 287 impairment for IFN- β -1a.

35
36 288 Patients included in the hydroxychloroquine group receive a loading dose of 400 mg twice daily for one
37
38 289 day followed by 400 mg once daily for 9 days. The rationale for this loading dose has been published.[6]

39
40 290 Patients included in the control group receive the standard of care of their recruitment center.
41
42 291 Investigational drugs were kindly provided by pharmaceutical firms.

43 292 Rationale for study treatments

44
45 293 Remdesivir (GS-5734) is a broad-spectrum nucleotide prodrug inhibiting RNA-dependent polymerase
46
47 294 activity among a diverse group of RNA viruses including filoviruses (e.g. Ebola, Sudan, Marburg),
48
49 295 paramyxoviruses (e.g. RSV, Nipah, Hendra) and pathogenic coronaviruses.[7–9] Studies in human
50
51 296 airway epithelial cell assays demonstrated that remdesivir inhibits replication of coronaviruses, including
52
53 297 MERS-CoV.[10] Remdesivir has shown an *in vitro* activity on SARS-CoV-2[11] and a clinical benefit in
54
55 298 rhesus macaques infected with SARS-CoV-2.[12] A large RCT has shown that remdesivir shortened
56
57 299 the time to recovery in adults hospitalized with Covid-19 as compared to placebo but the results were
58
59 300 not significant for mortality.[13]

1
2
3 301 Lopinavir/ritonavir is a fixed-dose combination used in HIV infection that has shown an *in vitro* activity
4
5 302 against SARS-CoV in several studies.[14] A structure-based study suggested that the spatial structure
6
7 303 of the lopinavir/ritonavir binding site was conserved between SARS-CoV and SARS-CoV-2.[15] The
8
9 304 results of an open RCT evaluating lopinavir/ritonavir for COVID-19 were published on March 18,
10
11 305 2020.[16] In this trial, adults with confirmed COVID-19 and hypoxemia ($SpO_2 < 94\%$) were randomized
12
13 306 to lopinavir/ritonavir (n=99) or standard of care (n=100). No significant difference between the 2 groups
14
15 307 was observed on the time to clinical improvement on a 7-item ordinal scale. (HR of improvement 1.31;
16
17 308 CI95% 0.95 - 1.80) but a trend to lower mortality rate was observed (19.0% vs. 27.1%) in the 90 patients
18
19 309 (45.2% of the total) receiving lopinavir/ritonavir less than 12 days after the beginning of the symptoms.
20
21 310 Interferon (IFN)- β -1 is a broad-spectrum antiviral drug belonging to the type 1 interferons. Type 1 IFN
22
23 311 treatment has shown an activity against MERS-CoV and SARS-CoV in numerous experiments, both *in*
24
25 312 *vitro* and *in vivo*. [17–19] Type 1 interferon is currently being tested for MERS-CoV in the MIRACLE
26
27 313 clinical trial.[20] SARS-CoV-2 displays *in vitro* a substantial susceptibility to IFN- α [21] and data
28
29 314 regarding the potential activity of type 1 interferons on SARS-CoV-2 has been reviewed recently.[22] A
30
31 315 RCT found that COVID-19 patients treated with a triple combination interferon beta-1b, lopinavir-
32
33 316 ritonavir, and ribavirin had a significantly shorter median time from start of study treatment to negative
34
35 317 nasopharyngeal swab (7 days [IQR 5-11]) than the control group up (12 days [8-15]; hazard ratio 4.37
36
37 318 [95% CI 1.86-10.24], $p=0.0010$).[23]
38
39 319 The *in vitro* antiviral activity of hydroxychloroquine has been known for a long time [24] and was
40
41 320 described on a number of viruses including SARS-CoV.[25][26] Regarding COVID-19, recent
42
43 321 publications reported an *in vitro* activity of hydroxychloroquine on SARS-CoV-2 [11][27] and non-
44
45 322 randomized observational studies provided conflicting clinical results.[28,29] A RCT on postexposure
46
47 323 prophylaxis for COVID-19 found that hydroxychloroquine did not prevent illness compatible with Covid-
48
49 324 19 or confirmed infection.[30]

325 **Participant timeline (Figure 2, Table 1)**

50
51 326 Clinical evaluations for efficacy and safety are performed at baseline, daily while the patient is
52
53 327 hospitalized and at 15 (+/- 2 d) and 29 (+/- 3 d).
54
55 328 Upper (nasopharyngeal swab) and/or lower (endotracheal aspiration) respiratory tract and blood
56
57 329 samples for centralized analysis of the SARS-CoV-2 kinetics are collected at baseline and at days 3 (+/-
58
59 330 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
60

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

334 Blood samples for pharmacokinetic analysis are collected:

- 335 – For remdesivir, to measure plasma and intracellular concentrations at days 1, 2, 5, 8 and 11;
- 336 – For lopinavir, to measure plasma concentrations at days 1, 3 (+/- 1 d), 6 (+/- 1 d), 8 (+/- 1 d) and
337 11 (+/- 1 d);
- 338 – For IFN β -1-a, to measure plasma concentrations at days 3 and 6;
- 339 – For hydroxychloroquine, to measure plasma concentrations at days 1, 3 (+/- 1 d), 5 (+/- 1 d), 8
340 (+/- 1 d) and 11 (+/- 1 d).

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

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

345 A biobank is constituted for ancillary analyses.

346 **Primary endpoint**

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

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

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

358 **Secondary endpoints**

359 Secondary endpoints are classified as efficacy or safety endpoints.

360 Efficacy secondary endpoints

- 1
2
3 361 1. Ordinal scale
4
5 362 - Time to an improvement of one category from admission on an ordinal scale.
6
7 363 - Subject clinical status on an ordinal scale on Days 3, 5, 8, 11, and 29.
8
9 364 - Mean change in the ranking on an ordinal scale from baseline to Days 3, 5, 8, 11, 15
10 and 29 from baseline.
11 365
12 366 2. National Early Warning Score (NEWS)
13
14 367 - The time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever
15 occurs first.
16 368
17
18 369 - Change from baseline to Days 3, 5, 8, 11, 15, and 29 in NEWS.
19
20 370 3. Oxygenation
21
22 371 - Oxygenation free days in the first 28 days (to Day 29).
23
24 372 - Incidence and duration of new oxygen use, non-invasive ventilation or high flow oxygen
25 devices during the study.
26 373
27
28 374 4. Mechanical ventilation
29
30 375 - Ventilator free days in the first 28 days (to Day 29).
31
32 376 - Incidence and duration of new mechanical ventilation use during the study.
33
34 377 5. Hospitalization
35
36 378 - Duration of hospitalization (days).
37
38 379 6. Mortality
39
40 380 - In-hospital mortality
41 381 - 28-day mortality.
42
43 382 - 90-day mortality
44

45 383 Safety secondary endpoints

- 47 384 1. Cumulative incidence of any grade 3 and 4 adverse events;
48
49 385 2. Cumulative incidence of any serious adverse event;
50
51 386 3. Proportion of patients with a premature discontinuation or temporary suspension of the study
52 drug, for any reason;
53 387
54 388 4. Grade changes in biological parameters, as measured using the Division of AIDS Table for
55 Grading the Severity of Adult and Pediatric Adverse Events (white cell count, haemoglobin,
56 389 platelets, creatinine, blood electrolytes (including kaliemia), prothrombin time and international
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58 390
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3 391 normalized ratio (INR), glucose, total bilirubin, ALT, and AST) over time.

4
5 392 Exploratory endpoints

- 6
7 393 1. Qualitative and quantitative PCR for SARS-CoV-2 normalized according to the number of
8
9 394 sample cells in nasopharyngeal or lower respiratory tract samples on days 1, 3, 5, 8, 11, 15
10
11 395 and 29;
- 12
13 396 2. Qualitative and quantitative PCR for SARS-CoV-2 in blood on days 1, 3, 5, 8 and 11;
- 14
15 397 3. Development of resistance of SARS-CoV-2 in nasopharyngeal or lower respiratory tract
16
17 398 samples at days 3, 5, 8, 11, 15 and 29;
- 18
19 399 4. Whole genome sequencing of participants to identify genetic variants associated with (i) the
20
21 400 development of severe clinical disease (ii) the response in terms of safety and efficacy to
22
23 401 investigational antiviral drugs;
- 24
25 402 5. Imagery assessment through chest X-ray or thoracic CT scan on days 1, 8, 15 and 29,
26
27 403 depending on availability in centre;
- 28
29 404 6. Study drugs concentrations, sampled while the participant is hospitalized:
- 30 405 – For remdesivir, as assessed by plasma concentration after the end of infusion on day 1,
31
32 406 trough plasma and intracellular concentrations before the 2nd dose administration on day
33
34 407 2, and trough plasma concentration on days 5 and 8;
 - 35
36 408 – For lopinavir, peak plasma concentration measured 4 hours after the 1st administration
37
38 409 and trough plasma concentrations measured just before the 2nd administration and on
39
40 410 days 3, 6, 8 and 11;
 - 41
42 411 – For IFN β -1-a, trough plasma concentration on days 3 and 6;
 - 43
44 412 – For hydroxychloroquine, peak plasma concentration measured 4 hours after the 1st
45
46 413 administration and trough plasma concentrations measured just before the 2nd
47
48 414 administration and on days 3, 5, 8 and 11.

49 415 **Data collection**

50
51 416 The trial is conducted in accordance with relevant regulations and standard operating procedures,
52
53 417 including data protection. The data are collected on an electronic case report form. Clinical site
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55 418 monitoring is conducted to ensure that the rights are protected and confirm the integrity of collected
56
57 419 data. The persons responsible for the quality control of the data take all necessary precautions to ensure
58
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2
3 420 the confidentiality of information regarding investigational medicinal products, the trial, trial participants
4
5 421 and in particular the identity of the participants and the results obtained.

6
7 422 ***Safety and adverse events monitoring***

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9 423 All adverse events are collected regardless of their grade of severity. The choice of continuing therapy
10
11 424 is at the discretion of the investigator. All adverse events are classified in grades from mild (grade 1) to
12
13 425 life threatening (grade 4) following the DAIDS Table for Grading the Severity of Adult and Pediatric
14
15 426 Adverse Events (version 2.1 of July 2017) of the National Institute of Health and National Institute of
16
17 427 Allergy and Infectious Diseases of the US Department of Health and Human Services.

18 428 ***Statistical considerations***

19
20 429 *General considerations*

21
22 430 Continuous variables will be summarized by the mean, standard deviation, median, interquartile range,
23
24 431 minimum and maximum. The change from baseline will be compared using Student's t-test or a
25
26 432 Wilcoxon-Mann-Whitney test if the normality assumption does not hold.

27
28 433 Categorical data will be summarized with the number and proportion of patients. Data will be compared
29
30 434 using odds ratios and a Fisher's exact test.

31
32 435 All statistical tests will be 2-sided with type I error of 0.05. As there are 4 comparisons, each treatment
33
34 436 group will be compared to the control group with a two-sided type I error of 0.0125. Subgroup analyses
35
36 437 for the primary and secondary endpoints will evaluate the treatment effect across the following
37
38 438 subgroups: disease severity at inclusion, geographic region, duration of symptoms prior to enrolment,
39
40 439 age and sex. A forest plot will display confidence intervals across subgroups. Interaction tests will be
41
42 440 conducted to determine whether the effect of treatment varies by subgroup.

43 441 *Sample size computation*

44
45 442 A sample size of 3,100 patients (620 patients per arm) is targeted. The sample size was determined
46
47 443 assuming the following scenario under standard of care for each item of the ordinal scale: 1: 42%, 2:
48
49 444 38%, 3: 8%, 4: 7%, 5: 2%, 6: 1%, 7: 2%.

50
51 445 There is significant uncertainty with these assumptions given the limited data available. Since a large
52
53 446 proportion of patients are moderately ill patients, we power the study for an odds ratio of 1.5 (an odds
54
55 447 ratio higher than 1 indicates superiority of the experimental treatment over the control for each ordinal
56
57 448 scale category), with 90% power and using an overall one-sided type I error rate of 0.05.[31] Adjusting
58
59 449 for multiplicity of 4 pairwise comparisons with the control arm in a 5-arm setting, the (one-sided) false
60

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3 450 positive error rate would be 0.00625, (which requires achieving two-sided $p=0.0125$.) The samples size
4
5 451 might evolve whenever any treatment arm is withdrawn or added to the trial.

6 7 452 Definition of analysis sets

8
9 453 The intention-to-treat population is defined as all randomised patients, where patients are analysed in
10
11 454 their randomisation group whether they have or not followed the allocated treatment. The modified
12
13 455 intention-to-treat population is defined as all randomised patients who did receive at least one dose of
14
15 456 the allocated treatment.

16 457 The primary and efficacy secondary analysis will be conducted on the intention-to-treat population.
17
18 458 Safety analyses will be based on the modified intention-to-treat population.

19 20 459 Adaptive design

21
22 460 This study is intended to allow for adaptations with the ability to add a new experimental arm if one
23
24 461 becomes available. The current plan is to evaluate the primary endpoint on day 15. If additional data
25
26 462 become available to add an experimental therapy, analyses of experimental arms will be performed
27
28 463 comparing concurrently enrolled control subjects. If one treatment crosses an efficacy stopping
29
30 464 boundary, this treatment may become the new control arm for comparisons. This approach was used in
31
32 465 the recent PALM Ebola therapy randomized clinical trial.[32]

33 34 466 Interim analyses

35
36 467 Interim analyses will be by the independent statistician of the DSMB. There are no formal stopping rules
37
38 468 for efficacy or safety. The DSMB will make recommendations taking into consideration the totality of the
39
40 469 evidence from the efficacy and safety outcomes as they accumulate, as well as external evidence.

41 470 For efficacy, the statistical analysis will be done on the primary endpoint, the 7-point ordinal scale at 15
42
43 471 days, and be based on the Haybittle Peto rule.[33,34] That is, if any active treatment is superior to
44
45 472 control at $P<.001$ then consideration will be given to stopping early for efficacy. This would have major
46
47 473 implications; hence the stopping boundary is stringent in the spirit of requiring proof beyond reasonable
48
49 474 doubt.

50
51 475 For futility, i.e. stopping because an active treatment appears ineffective, the statistical analysis will be
52
53 476 done with the primary endpoint. Comparing an active treatment with control, if the upper 95% confidence
54
55 477 limit for the common odds ratio is less than 1.25 then consideration be given to stopping that treatment
56
57 478 for futility. All the above is intended for all randomised patients. Analyses will be stratified by baseline
58
59 479 severity of disease. For safety, no pre-specify stopping guideline will be defined because there are
60

1
2
3 480 various aspects of potential harm that could be studied. However, to allow for some caution, any safety
4
5 481 signal on SAE, i.e. active treatment worse than control, requires $P < .01$ to merit consideration of stopping
6
7 482 that treatment arm.

8 9 483 Final analysis of the primary endpoint

10 484 The primary outcome uses a 7-point ordinal scale analysed using a proportional odds model. This model
11
12 485 assumes that the treatment to control odds ratio of being classified in a given severity category “i” or
13
14 486 better is the same for each category. The null hypothesis being tested is whether the odds of
15
16 487 improvement on the ordinal scale is the same for the control and experimental treatment arms (i.e.,
17
18 488 whether the common odds ratio differs is 1). Odds ratios are then interpreted as the odds of being “lower”
19
20 489 or “higher” on the ordinal scale across the entire range of the scale. The hypothesis test is, for large
21
22 490 sample sizes, nearly the same as the Wilcoxon rank sum test. Therefore, the procedure produces a
23
24 491 valid p-value regardless of whether the proportional odds model is correct. Nonetheless, estimation and
25
26 492 confidence intervals do require the model to be correct. Accordingly, we will evaluate model fit using a
27
28 493 goodness-of-fit likelihood ratio test. The validity of the proportionality assumption will be evaluated and
29
30 494 tested. To deal with potential missing data, the last observation will be carried forward until the next
31
32 495 available value.

33 34 496 Analysis of secondary endpoints

35 497 Differences in time-to-event endpoints by treatment will be summarized with Kaplan-Meier curves and
36
37 498 95% confidence interval; and cumulative incidence plots, for time-to-event endpoints with competing
38
39 499 risk (e.g. death). Duration of event will be summarized according to median days with quartiles.
40
41 500 Incidence data will be summarized as percent with 95% confidence interval. Time-to-event endpoints
42
43 501 will be compared using the log-rank test. For time-to-event endpoints with a competing risk Fine and
44
45 502 Gray models will be used. All tests will be stratified by the baseline severity.

46 47 503 **Committees for the research**

48
49 504 A DisCoVeRy European Steering Committee (DSC) has been constituted to serve as the governance
50
51 505 organ for the trial. It provides the overall supervision of the trial, including for the relations with European
52
53 506 stakeholders, the Steering Committee and the Executive Committee of the Solidarity trial (see below).
54
55 507 It ensures that the trial is conducted in accordance with ethical principles and respects participants’
56
57 508 safety, take any decision on any changes made to the design of the DisCoVeRy trial, and on the
58
59 509 reporting of the trial results, including regarding the publication policy.
60

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3 510 An international independent DSMB has been constituted to preserve the interests of trial participants,
4
5 511 to monitor the main outcome measures (including safety and efficacy), and to monitor the overall
6
7 512 conduct of the trial. Based on interim analyses of the data, it will make recommendations about early
8
9 513 study closure or changes to the trial, including adding or removing treatment arms. The DSMB will meet
10
11 514 after 100 participants are included into the study, and then every 200 new patients are included, with a
12
13 515 maximum of 1 DSMB meeting per week. Other ad hoc reviews will be undertaken if there are specific
14
15 516 safety concerns. The study will not stop enrolment awaiting these DSMB reviews, though the DSMB
16
17 517 may recommend temporary or permanent cessation of enrolment based on their safety reviews.

18 518 ***Intertwinement with WHO Solidarity program***

19
20 519 Since April 5, 2020, DisCoVeRy has been an add-on trial of the Solidarity program conducted by the
21
22 520 WHO in Europe and worldwide. The same treatments are evaluated in DisCoVeRy and in Solidarity.
23
24 521 Solidarity has 3 endpoints which are also secondary endpoints of DisCoVeRy: (i) mortality during
25
26 522 hospitalization (the primary endpoint of Solidarity) (ii) length of hospital stay and (iii) time to mechanical
27
28 523 ventilation or transfer to intensive care. At each DisCoVeRy DSMB meeting, the recommendations will
29
30 524 be transmitted to the Data and Safety Monitoring Committee (DSMC) of Solidarity. The Executive
31
32 525 Committee of Solidarity will ultimately issue recommendations on the different treatments evaluated,
33
34 526 allowing a unique communication on each of the treatments evaluated.

35 527 ***Patient and public involvement***

36
37 528 No patients were involved in the design or implementation of this study.

38
39 529

40 41 530 **DISCUSSION**

42 43 531 ***Strengths and limitations of the DisCoVeRy trial design***

44
45 532 The DisCoVeRy clinical trial is a randomized, open clinical trial that aims to evaluate the safety and
46
47 533 efficacy of possible therapeutic agents in hospitalized adult patients diagnosed with COVID-19. The
48
49 534 design of DisCoVeRy is adaptive meaning that it can adapt to the ongoing production of evidence and
50
51 535 to interim analyses by discontinuing arms that are proved inferior to others, selecting an existing arm as
52
53 536 the standard of care if proved superior to others and adding arms if new candidate therapeutic strategies
54
55 537 emerge.

56
57 538 As detailed above, DisCoVeRy is an add-on trial of the Solidarity trial, conducted under the aegis of the
58
59 539 WHO in Europe and worldwide. Sharing the data from DisCoVeRy relevant to the Solidarity trial
60

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3 540 (inclusion data and data related to the Solidarity endpoints) increases the number of participants for
4
5 541 whom this data is available and thus leads to a faster conclusion on the effectiveness, deleterious effect
6
7 542 or ineffectiveness of the treatments evaluated. Inclusion in a same strategy of hospitalized patients with
8
9 543 severe (patients requiring non-invasive ventilation, high flow oxygen devices, invasive mechanical
10
11 544 ventilation or ECMO) or moderate disease will allow to evaluate the different drug candidates in different
12
13 545 clinical situations. Moreover, by including patients at different times in their clinical history of COVID-19,
14
15 546 we will be able to study when is the best time to start an antiviral agent in relation to the delay of
16
17 547 symptoms. The collection of samples for pharmacological monitoring, viral kinetics and medical imaging
18
19 548 will provide crucial data to analyze the PK/PD of evaluated drugs and the effect of treatment on the
20
21 549 virological and radiological evolution. However, DisCoVeRy will not provide data on treatments for
22
23 550 COVID-19 at an early phase, before there is a need for hospitalization. As only antiviral agents are
24
25 551 evaluated in DisCoVeRy, we will not be able to evaluate the efficacy of immunomodulatory agents,
26
27 552 including corticosteroids.

28 553

30 554 ***Strengths and limitations of real-time interventional research in the setting of a pandemic***

31
32 555 Discovery is not a placebo-controlled trial and is not double-blind because of the complexity of blinding
33
34 556 treatments with different mode of administration (intravenous, sub-cutaneous or oral) and the need to
35
36 557 initiate the trial very rapidly. Moreover, in a recent meta-epidemiological study, no evidence was found
37
38 558 that lack of blinding of patients, healthcare providers, or outcome assessors had an impact on effect
39
40 559 estimates in randomised clinical trials.[35]

41
42 560 Integrating clinical trials of experimental therapeutics is an increasingly recognized part of the response
43
44 561 during infectious disease outbreaks. Since the Ebola outbreak in West Africa and subsequent outbreaks
45
46 562 in the Democratic Republic of Congo, clinical trials of investigative drugs have been fully integrated in
47
48 563 the epidemic response.[36–38] Implementing large clinical trial is both direly needed and particularly
49
50 564 challenging during a pandemic. Indeed, the pandemic context compels us to organize clinical trials
51
52 565 urgently while keeping methodological requirements of the highest level which is the only way to provide
53
54 566 reliable answers for clinicians. The selection of the best candidate drugs for a new outbreak is a major
55
56 567 challenge and a strength of the DisCoVeRy trial is that its adaptive design allows to add new arms if
57
58 568 good evidence emerges while the trial is continuing that some other treatment(s) should also be
59
60 569 evaluated. The ever-changing scientific background supporting the use of each candidate treatment

1
2
3 570 should be clear, detailed and regularly updated. Transparency, consistency and quality of design are
4
5 571 more crucial than ever during pandemics to provide relevant and reliable data.

6
7 572 **DISSEMINATION**

8
9 573 Results will be communicated at scientific meetings and submitted for publication in peer-reviewed
10
11 574 journals.

12
13 575 **TRIAL STATUS**

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15 576 This trial has begun on March 22, 2020. On June 8, 2020, 754 patients have been included.

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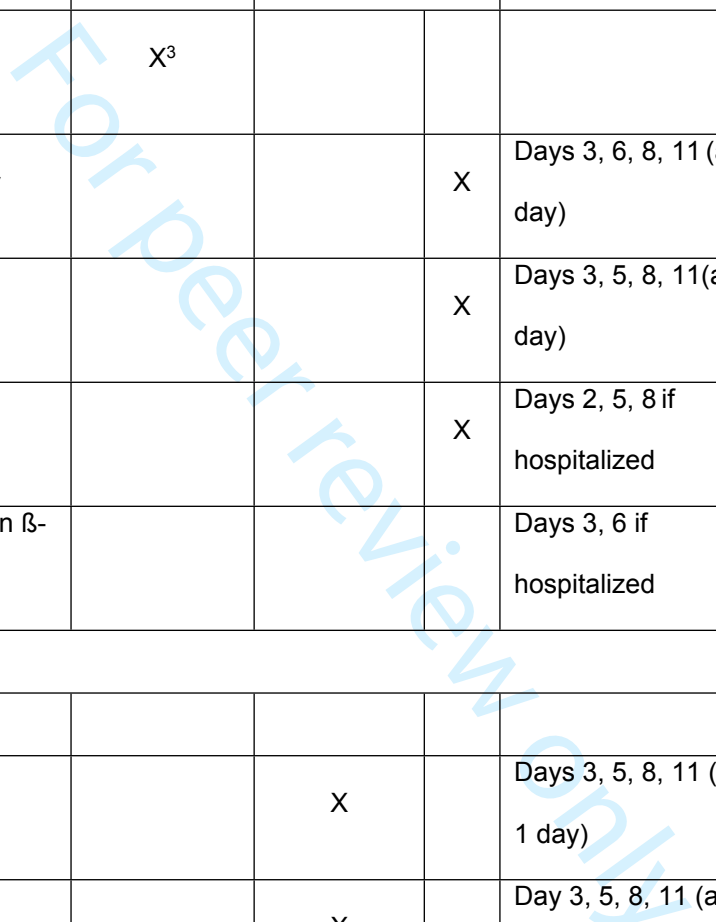
579 **Figure 1.** DisCoVeRy trial arms, drugs and dosing schedule

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
ELIGIBILITY							
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 β1a				Lopinavir/ritonavir for 14 days Interferon β-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

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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 β-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

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- 583 2. *If discharged from the hospital, visits and safety assessments are conducted in the outpatient*
- 584 *setting.*
- 585 3. *Laboratory tests performed in the 48 hours prior to enrolment are accepted for determination of*
- 586 *eligibility.*
- 587 4. *Any laboratory tests performed in the 24 hours before randomization can be used for baseline and*
- 588 *Day 1*
- 589

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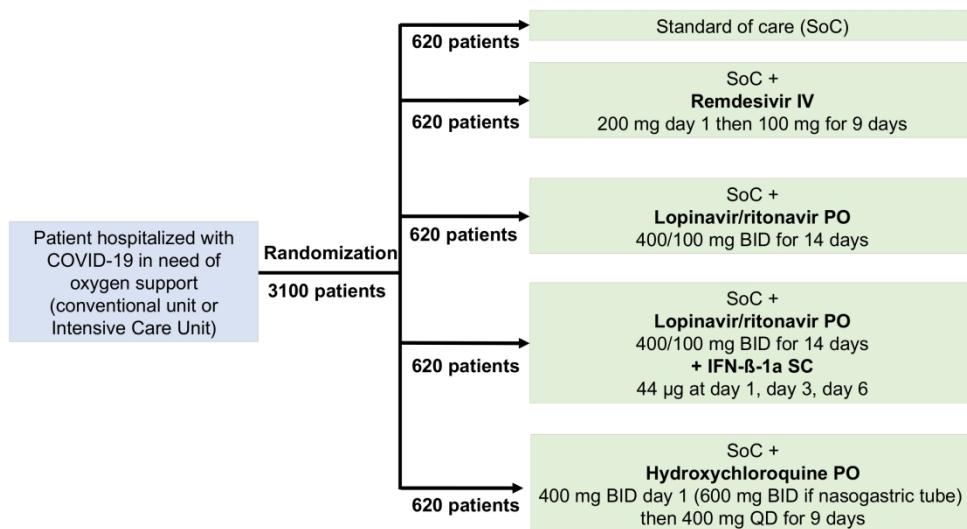
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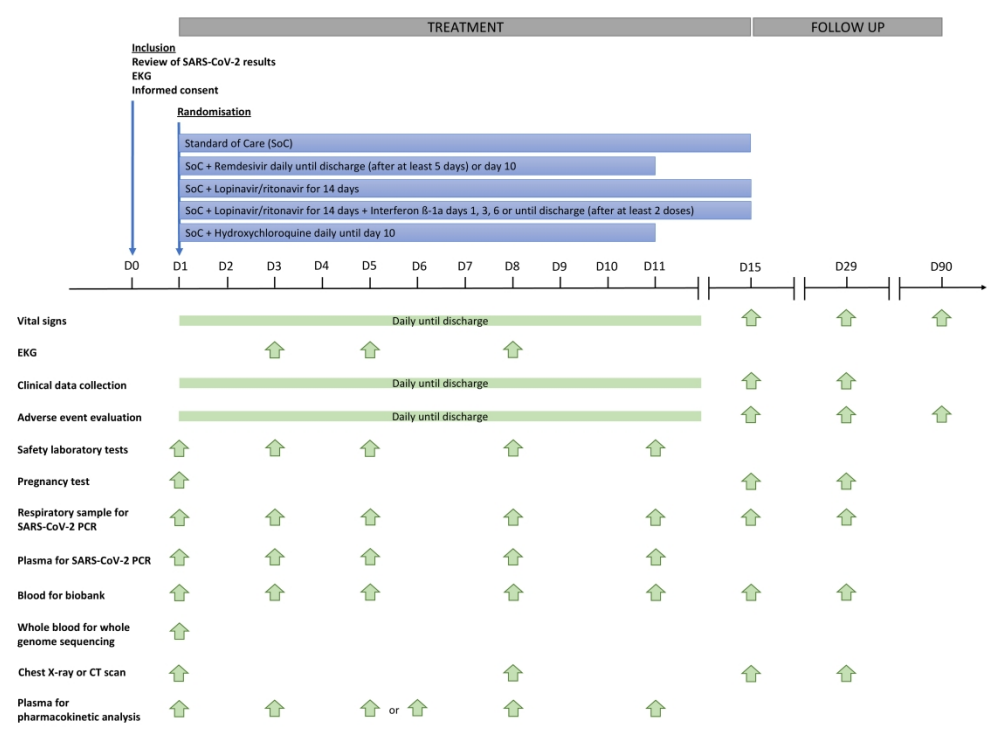
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DisCoVeRy trial arms, drugs and dosing schedule

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

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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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1 TITLE

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

5 AUTHORS

6 **Florence Ader on behalf of The DisCoVeRy French Trial Management Team**

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13 KEYWORDS

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

18 **Text count: 4777 words**

20 ABSTRACT**21 Introduction**

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

28 Methods and analysis

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

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3 31 managed with SoC and four therapeutic arms with repurposed antiviral agents: (ii) remdesivir + SoC,
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5 32 (iii) lopinavir/ritonavir + SoC, (iv) lopinavir/ritonavir associated with interferon (IFN)- β -1a + SoC and (v)
6
7 33 hydroxychloroquine + SoC. The primary endpoint is the clinical status at Day 15 on the 7-point ordinal
8
9 34 scale of the WHO Master Protocol (version 3.0, March 3, 2020). This trial involves patients hospitalized
10
11 35 in conventional departments or intensive care units both from academic or non-academic hospitals
12
13 36 throughout Europe. A sample size of 3,100 patients (620 patients per arm) is targeted. This trial has
14
15 37 begun on March 22, 2020. Since April 5, 2020, DisCoVeRy has been an add-on trial of the Solidarity
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17 38 consortium of trials conducted by the WHO in Europe and worldwide. On June 8, 2020, 754 patients
18
19 39 have been included.

20 40 **Ethics and dissemination**

21
22 41 Inserm is the sponsor of DisCoVeRy. Ethical approval has been obtained from the institutional review
23
24 42 board on March 13, 2020 (20.03.06.51744) and from the French National Agency for Medicines and
25
26 43 Health Products (ANSM) on March 9, 2020. Results will be submitted for publication in peer-reviewed
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28 44 journals.

29 45 **Trial registration number**

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3 47 **ARTICLE SUMMARY**

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5 48 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

6
7 49 . The DisCoVeRy clinical trial is an adaptive, randomized, open-label clinical trial that aims to evaluate
8
9 50 the safety and efficacy of 4 antiviral therapeutic strategies as compared to standard of care in
10
11 51 hospitalized adult patients diagnosed with COVID-19.

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13 52 . Therapeutic strategies can be modified according to new evidence: an arm can become the
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15 53 standard of care if proved superior to others, arms can be discontinued if proved inferior to others
16
17 54 and arms can be added if new candidate therapeutic strategies emerge.

18
19 55 . DisCoVeRy is an add-on trial of the Solidarity consortium of trials, conducted under the aegis of the
20
21 56 WHO and data on common endpoints are shared with the Solidarity consortium.

22
23 57 . DisCoVeRy is not a placebo-controlled trial and is not double-blind because of the complexity of
24
25 58 blinding treatments with different mode of administration (intravenous, sub-cutaneous or oral) and
26
27 59 the need to initiate the trial very rapidly.

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29 60 . DisCoVeRy includes patients who are hospitalized in need of oxygen therapy, it does not target
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31 61 patients at the early phase of the disease nor include anti-inflammatory agents that can be used as
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33 62 part of the standard of care in any arm.

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64 INTRODUCTION

65 **Background and scope**

66 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the third coronavirus that has
67 crossed the species barrier to cause deadly pneumonia in humans since the beginning of the 21st
68 century, after SARS-CoV [1,2] and Middle-East respiratory syndrome coronavirus [3] (MERS-CoV) in
69 2002 and 2012, respectively. The first case of infection with the SARS-CoV-2 was reported in the city
70 of Wuhan, China on December 31, 2019. The associated disease was named “coronavirus disease
71 2019” (abbreviated “COVID-19”). The emergence and the spread of SARS-CoV-2 is an unprecedented
72 challenge, vividly illustrating the pace at which a viral outbreak can progress among a highly interlinked
73 and susceptible global population. At the beginning of March 2020, when this clinical trial was designed,
74 COVID-19 had spread to more than 100 countries and affected more than 100,000 individuals.
75 Consistently, the World Health Organization (WHO) declared COVID-19 pandemic on March 11,
76 2020.[4]

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

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

93 **Objective**

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3 94 The objective of the DisCoVeRy trial is to evaluate the clinical efficacy and safety of different
4
5 95 investigational therapeutics relative to Standard of Care (SoC) in patients hospitalized with COVID-19.

6 7 96 **METHODS AND ANALYSIS**

8 9 97 ***Design and general information***

10
11 98 DisCoVeRy is a phase III, open-label, adaptive, randomized, controlled, multicenter clinical trial
12
13 99 designed to evaluate the safety and efficacy of repurposed therapeutic interventions in hospitalized adult
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15 100 patients diagnosed with COVID-19. This trial involves patients both from academic or non-academic
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17 101 hospitals throughout Europe, with Inserm as the sponsor. Study sites can be obtained from the sponsor's
18
19 102 representative (contact: helene.esperou@inserm.fr). The protocol described in this article is the version
20
21 103 7.0 of the DisCoVeRy protocol approved on April 5.

22
23 104 The DisCoVeRy RCT has 5 arms: (i) a control group managed SoC and four therapeutic arms with
24
25 105 repurposed antiviral agents: (ii) remdesivir + SoC, (iii) lopinavir/ritonavir + SoC, (iv) lopinavir/ritonavir
26
27 106 associated with interferon (IFN)- β -1a + SoC and (v) hydroxychloroquine + SoC (Figure 1). The arms
28
29 107 have not been modified between the version 1 and 7 of the protocol. Included participants cannot be
30
31 108 treated with antivirals other than the study medications allocated by randomization, but non-antiviral
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33 109 drugs such as steroids, immunomodulatory agents (e.g. anti-interleukin 6 drugs), or antibiotics can be
34
35 110 used as part of the standard of care. This is an open-label trial but all investigators are unaware of
36
37 111 aggregate outcomes during the study. The design is adaptive upon decision of the DSMB: arms can be
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39 112 discontinued if proved inferior to others, an existing arm can become the standard of care if proved
40
41 113 superior and arms can be added if new candidate therapeutic strategies emerge. The trial has been
42
43 114 registered at the ClinicalTrials.org registry as NCT04315948 and on the European Clinical Trials
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45 115 Database as 2020-000936-23.

46 47 116 ***Participants***

48
49 117 For the duration of the study, the sponsor has subscribed an insurance policy covering the sponsor's
50
51 118 own third-party liability as well as the third-party liability of all the investigators involved in the study
52
53 119 (EUR 600,000 per participant for bodily injury and property damage combined and EUR 5,000,000 per
54
55 120 trial in total. The maximum amount of compensation could vary depending on the country).

56 57 121 **Inclusion criteria**

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59 122 Patients must fulfil the following criteria prior to trial enrolment:

- 60
123 1. Adult \geq 18 years of age at time of enrolment;

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3 124 2. Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial
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5 125 or public health assay in any specimen < 72 hours prior to randomization;
6
7 126 3. Hospitalized patients with illness of any duration, and at least one of the following:
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9 127 – Clinical assessment of pulmonary infection (evidence of rales/crackles on exam) AND SpO₂
10 128 ≤ 94% on room air, or
11
12 129 – Acute respiratory failure requiring supplemental oxygen, high flow oxygen devices, non-
13
14 130 invasive ventilation, and/or mechanical ventilation;
15
16 131 4. Women of childbearing potential must agree to use contraception for the duration of the study.

18 132 Non-inclusion criteria

20 133 Patients with any of the following criteria are not eligible for trial enrolment:

- 22 134 1. Refusal to participate expressed by patient or legally authorized representative if they are
23 135 present;
24
25 136 2. Spontaneous blood ALT/AST levels > 5 times the upper limit of normal;
26
27 137 3. Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30 mL/min);
28
29 138 4. Pregnancy or breast-feeding;
30
31 139 5. Anticipated transfer to another hospital, which is not a study site within 72 hours;
32
33 140 6. Patients previously treated with one of the antivirals evaluated in the trial (i.e. remdesivir,
34 141 interferon β-1a, lopinavir/ritonavir, hydroxychloroquine) in the past 29 days;
35
36 142 7. Contraindication to any study medication including allergy;
37
38 143 8. Use of medications that are contraindicated with lopinavir/ritonavir i.e. drugs whose metabolism
39 144 is highly dependent on the isoform CYP3A with narrow therapeutic range (e.g. amiodarone,
40 145 colchicine, simvastatine);
41
42 146 9. Use of medications that are contraindicated with hydroxychloroquine: citalopram, escitalopram,
43 147 hydroxyzine, domperidone, piperazine;
44
45 148 10. Human immunodeficiency virus infection under combination antiretroviral therapy;
46
47 149 11. History of severe depression or attempted suicide or current suicidal ideation;
48
49 150 12. Corrected QT interval superior to 500 milliseconds (as calculated with the Fridericia formula).

54 151 **Randomisation**

56 152 Patients are randomly assigned in a 1:1:1:1:1 ratio into one of the five groups. The randomisation list is
57
58 153 computer-generated, with blocks of various sizes and stratified by region (according to the administrative
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60

1
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3 154 definition in each country) and severity of illness at enrolment (severe disease: patients requiring non-
4
5 155 invasive ventilation, high flow oxygen devices, invasive mechanical ventilation or ECMO; moderate
6
7 156 disease: patients not requiring non-invasive ventilation, high flow oxygen devices, invasive mechanical
8
9 157 ventilation nor ECMO). The randomisation list is implemented in the electronic Case Report Form
10
11 158 (eCRF) to ensure appropriate allocation concealment.

12 159 ***Experimental design***

13 160 Study treatments

14 161 The participants are allocated in one of 5 arms (Figure 1).

15 162 Patients included in the remdesivir group receive 200 mg intravenous loading dose on Day 1, followed
16 163 by a 100 mg once-daily intravenous maintenance dose for the duration of the hospitalization and up to
17 164 a 10 days' total course. Remdesivir is administered through a 30 to 60 minutes IV infusion.

18 165 Patients included in the lopinavir/ritonavir group receive 400 mg lopinavir and 100 mg ritonavir
19 166 administered every 12h for 14 days in tablet form. For patients who are unable to take medications by
20 167 mouth, the lopinavir/ritonavir (400 mg lopinavir/100 mg ritonavir) is administered as a 5-mL suspension
21 168 every 12h for 14 days via a nasogastric tube.

22 169 Patients included in the lopinavir/ritonavir + interferon β -1a group receive, in addition to
23 170 lopinavir/ritonavir as described above, interferon β -1a administered subcutaneously at the dose of 44
24 171 μ g on Day 1, Day 3, and Day 6 (total of 3 doses). No dosage adjustment is provided for renal or hepatic
25 172 impairment for IFN- β -1a.

26 173 Patients included in the hydroxychloroquine group receive a loading dose of 400 mg twice daily for one
27 174 day followed by 400 mg once daily for 9 days. The rationale for this loading dose has been published.[6]

28 175 Patients included in the control group receive the standard of care of their recruitment center.
29 176 Investigational drugs were kindly provided by pharmaceutical firms.

30 177 Rationale for study treatments

31 178 Remdesivir (GS-5734) is a broad-spectrum nucleotide prodrug inhibiting RNA-dependent polymerase
32 179 activity among a diverse group of RNA viruses including filoviruses (e.g. Ebola, Sudan, Marburg),
33 180 paramyxoviruses (e.g. RSV, Nipah, Hendra) and pathogenic coronaviruses.[7–9] Studies in human
34 181 airway epithelial cell assays demonstrated that remdesivir inhibits replication of coronaviruses, including
35 182 MERS-CoV.[10] Remdesivir has shown an *in vitro* activity on SARS-CoV-2[11] and a clinical benefit in
36 183 rhesus macaques infected with SARS-CoV-2.[12] A large RCT has shown that remdesivir shortened
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184 the time to recovery in adults hospitalized with Covid-19 as compared to placebo but the results were
185 not significant for mortality.[13]

186 Lopinavir/ritonavir is a fixed-dose combination used in HIV infection that has shown an *in vitro* activity
187 against SARS-CoV in several studies.[14] A structure-based study suggested that the spatial structure
188 of the lopinavir/ritonavir binding site was conserved between SARS-CoV and SARS-CoV-2.[15] The
189 results of an open RCT evaluating lopinavir/ritonavir for COVID-19 were published on March 18,
190 2020.[16] In this trial, adults with confirmed COVID-19 and hypoxemia ($SpO_2 < 94\%$) were randomized
191 to lopinavir/ritonavir (n=99) or standard of care (n=100). No significant difference between the 2 groups
192 was observed on the time to clinical improvement on a 7-item ordinal scale. (HR of improvement 1.31;
193 CI95% 0.95 - 1.80) but a trend to lower mortality rate was observed (19.0% vs. 27.1%) in the 90 patients
194 (45.2% of the total) receiving lopinavir/ritonavir less than 12 days after the beginning of the symptoms.

195 Interferon (IFN)- β -1 is a broad-spectrum antiviral drug belonging to the type 1 interferons. Type 1 IFN
196 treatment has shown an activity against MERS-CoV and SARS-CoV in numerous experiments, both *in*
197 *vitro* and *in vivo*.[17–19] Type 1 interferon is currently being tested for MERS-CoV in the MIRACLE
198 clinical trial.[20] SARS-CoV-2 displays *in vitro* a substantial susceptibility to IFN- α [21] and data
199 regarding the potential activity of type 1 interferons on SARS-CoV-2 has been reviewed recently.[22] A
200 RCT found that COVID-19 patients treated with a triple combination interferon beta-1b, lopinavir-
201 ritonavir, and ribavirin had a significantly shorter median time from start of study treatment to negative
202 nasopharyngeal swab (7 days [IQR 5-11]) than the control group up (12 days [8-15]; hazard ratio 4.37
203 [95% CI 1.86-10.24], $p=0.0010$).[23]

204 The *in vitro* antiviral activity of hydroxychloroquine has been known for a long time [24] and was
205 described on a number of viruses including SARS-CoV.[25,26] Regarding COVID-19, recent
206 publications reported an *in vitro* activity of hydroxychloroquine on SARS-CoV-2 [11][27] and non-
207 randomized observational studies provided conflicting clinical results.[28,29] A RCT on postexposure
208 prophylaxis for COVID-19 found that hydroxychloroquine did not prevent illness compatible with Covid-
209 19 or confirmed infection.[30]

210 **Participant timeline**

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

1
2
3 213 Upper (nasopharyngeal swab) and/or lower (endotracheal aspiration) respiratory tract and blood
4
5 214 samples for centralized analysis of the SARS-CoV-2 kinetics are collected at baseline and at days 3 (+/
6
7 215 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
8
9 216 detection in participating centers are different but their performances were all validated by French
10
11 217 National Reference Center for Viral Respiratory Infections and viral loads are determined using the
12
13 218 specific French National Reference Center RT-PCR IP4.[31] For each sample, the viral load is
14
15 219 measured by a specific SARS-COV-2 real-time (RT)-PCR and normalized according the number of cells
16
17 220 in each sample. This method is validated to monitor viral load kinetics over time and expressed in
18
19 221 standardized unit log of number of viral copies/10 000 cells.

20 222 Blood samples for pharmacokinetic analysis are collected:

- 21 223 – For remdesivir, to measure plasma and intracellular concentrations at days 1, 2, 5, 8 and 11;
- 22 224 – For lopinavir, to measure plasma concentrations at days 1, 3 (+/- 1 d), 6 (+/- 1 d), 8 (+/- 1 d) and
23 225 11 (+/- 1 d);
- 24 226 – For IFN β -1-a, to measure plasma concentrations at days 3 and 6;
- 25 227 – For hydroxychloroquine, to measure plasma concentrations at days 1, 3 (+/- 1 d), 5 (+/- 1 d), 8
26 228 (+/- 1 d) and 11 (+/- 1 d).

27
28
29
30
31
32
33 229 Thoracic imaging by X-ray or CT scan are performed at baseline, and at days 8 (+/- 1 d), 15 (+/- 2 d)
34
35 230 and 29 (+/- 3 d).

36
37 231 Biological evaluations for safety are performed at baseline and at days 3 (+/- 1 d), 5 (+/- 1 d), 8 (+/- 1
38
39 232 d), 11 (+/- 1 d), 15 (+/- 2 d) and 29 (+/- 3 d).

40
41 233 A sample collection is constituted for each patient (biobank) including whole blood and plasma at
42
43 234 baseline and plasma at days 3 (+/- 1 d), 5 (+/- 1 d), 8 (+/- 1 d), 11 (+/- 1 d), 15 (+/- 2 d) and 29 (+/- 3 d).

44
45 235 The biobank will be used to conduct ancillary analyses that remain to be determined.

46 47 236 **Primary endpoint**

48
49 237 The primary endpoint is the clinical status at Day 15 on the 7-point ordinal scale of the WHO Master
50
51 238 Protocol (version 3.0, March 3, 2020):

- 52 239 1. Not hospitalized, no limitation on activities;
 - 53 240 2. Not hospitalized, limitation on activities;
 - 54 241 3. Hospitalized, not requiring supplemental oxygen;
 - 55 242 4. Hospitalized, requiring supplemental oxygen;
- 56
57
58
59
60

- 1
2
3 243 5. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
4
5 244 6. Hospitalized, on invasive mechanical ventilation or ECMO;
6
7 245 7. Death.

8
9 246 For the scores 1 and 2, limitation of the activities refers to the pre-COVID-19 clinical status, in order to
10
11 247 take into account potential pre-existing limitations.

12
13 248 **Secondary endpoints**

14
15 249 Secondary endpoints are classified as efficacy or safety endpoints.

16
17 250 Efficacy secondary endpoints

18
19 251 1. 7-point ordinal scale

- 20 252 - Time to an improvement of one category from admission on the ordinal scale.
21
22 253 - Subject clinical status on the ordinal scale on Days 3, 5, 8, 11, and 29.
23
24 254 - Mean change in the ranking on the ordinal scale from baseline to Days 3, 5, 8, 11, 15
25
26 255 and 29 from baseline.

27
28 256 2. National Early Warning Score (NEWS)

- 29
30 257 - The time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever
31
32 258 occurs first.
33
34 259 - Change from baseline to Days 3, 5, 8, 11, 15, and 29 in NEWS.

35
36 260 3. Oxygenation

- 37 261 - Oxygenation free days in the first 28 days (to Day 29).
38
39 262 - Incidence and duration of new oxygen use, non-invasive ventilation or high flow oxygen
40
41 263 devices during the study.

42
43 264 4. Mechanical ventilation

- 44
45 265 - Ventilator free days in the first 28 days (to Day 29).
46
47 266 - Incidence and duration of new mechanical ventilation use during the study.

48
49 267 5. Hospitalization

- 50
51 268 - Duration of hospitalization (days).

52
53 269 6. Mortality

- 54
55 270 - In-hospital mortality
56
57 271 - 28-day mortality.
58
59 272 - 90-day mortality
60

1
2
3 273 Safety secondary endpoints
4

- 5 274 1. Cumulative incidence of any grade 3 and 4 adverse events;
6
7 275 2. Cumulative incidence of any serious adverse event;
8
9 276 3. Proportion of patients with a premature discontinuation or temporary suspension of the study
10 drug, for any reason;
11 277
12 278 4. Grade changes in biological parameters, as measured using the Division of AIDS Table for
13 Grading the Severity of Adult and Pediatric Adverse Events (white cell count, haemoglobin,
14 279 platelets, creatinine, blood electrolytes (including kaliemia), prothrombin time and international
15 280 normalized ratio (INR), glucose, total bilirubin, ALT, and AST) over time.
16 281

17
18
19
20 282 Exploratory endpoints
21

- 22 283 1. Qualitative and quantitative PCR for SARS-CoV-2 normalized according to the number of
23 sample cells in nasopharyngeal or lower respiratory tract samples on days 1, 3, 5, 8, 11, 15
24 284 and 29;
25 285
26 286 2. Qualitative and quantitative PCR for SARS-CoV-2 in blood on days 1, 3, 5, 8 and 11;
27
28 287 3. Development of resistance of SARS-CoV-2 in nasopharyngeal or lower respiratory tract
29 samples at days 3, 5, 8, 11, 15 and 29;
30 288
31 289 4. Whole genome sequencing of participants to identify genetic variants associated with (i) the
32 development of severe clinical disease (ii) the response in terms of safety and efficacy to
33 investigational antiviral drugs;
34 290
35 291 5. Imagery assessment through chest X-ray or thoracic CT scan on days 1, 8, 15 and 29,
36 depending on availability in centre;
37 292
38 293 6. Study drugs concentrations, sampled while the participant is hospitalized:
39
40 294
41 295 - For remdesivir, as assessed by plasma concentration after the end of infusion on day 1,
42 trough plasma and intracellular concentrations before the 2nd dose administration on day
43 296 2, and trough plasma concentration on days 5 and 8;
44 297
45 298 - For lopinavir, peak plasma concentration measured 4 hours after the 1st administration
46 and trough plasma concentrations measured just before the 2nd administration and on
47 299 days 3, 6, 8 and 11;
48 300
49 301 - For IFN β -1-a, trough plasma concentration on days 3 and 6;
50
51 302 - For hydroxychloroquine, peak plasma concentration measured 4 hours after the 1st
52
53
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55
56
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1
2
3 303 administration and trough plasma concentrations measured just before the 2nd
4
5 304 administration and on days 3, 5, 8 and 11.

6
7 305 ***Data collection***

8
9 306 The trial is conducted in accordance with relevant regulations and standard operating procedures,
10
11 307 including data protection. The data are collected on an electronic case report form. Clinical site
12
13 308 monitoring is conducted to ensure that the rights are protected and confirm the integrity of collected
14
15 309 data. The persons responsible for the quality control of the data take all necessary precautions to ensure
16
17 310 the confidentiality of information regarding investigational medicinal products, the trial, trial participants
18
19 311 and in particular the identity of the participants and the results obtained.

20 312 ***Safety and adverse events monitoring***

21
22 313 All adverse events are collected regardless of their grade of severity. The choice of continuing therapy
23
24 314 is at the discretion of the investigator. All adverse events are classified in grades from mild (grade 1) to
25
26 315 life threatening (grade 4) following the DAIDS Table for Grading the Severity of Adult and Pediatric
27
28 316 Adverse Events (version 2.1 of July 2017) of the National Institute of Health and National Institute of
29
30 317 Allergy and Infectious Diseases of the US Department of Health and Human Services.

31
32 318 ***Statistical considerations***

33
34 319 *General considerations*

35
36 320 Continuous variables will be summarized by the mean, standard deviation, median, interquartile range,
37
38 321 minimum and maximum. The change from baseline will be compared using Student's t-test or a
39
40 322 Wilcoxon-Mann-Whitney test if the normality assumption does not hold.

41
42 323 Categorical data will be summarized with the number and proportion of patients. Data will be compared
43
44 324 using odds ratios and a Fisher's exact test.

45
46 325 All statistical tests will be 2-sided with type I error of 0.05. As there are 4 comparisons, each treatment
47
48 326 group will be compared to the control group with a two-sided type I error of 0.0125. Subgroup analyses
49
50 327 for the primary and secondary endpoints will evaluate the treatment effect across the following
51
52 328 subgroups: disease severity at inclusion, geographic region, duration of symptoms prior to enrolment,
53
54 329 age and sex. A forest plot will display confidence intervals across subgroups. Interaction tests will be
55
56 330 conducted to determine whether the effect of treatment varies by subgroup.

57 331 *Sample size computation*

1
2
3 332 A sample size of 3,100 patients (620 patients per arm) is targeted. The sample size was determined
4
5 333 assuming the following scenario under standard of care for each item of the ordinal scale: 1: 42%, 2:
6
7 334 38%, 3: 8%, 4: 7%, 5: 2%, 6: 1%, 7: 2%.

8
9 335 There is significant uncertainty with these assumptions given the limited data available. Since a large
10
11 336 proportion of patients are moderately ill patients, we power the study for an odds ratio of 1.5 (an odds
12
13 337 ratio higher than 1 indicates superiority of the experimental treatment over the control for each ordinal
14
15 338 scale category), with 90% power and using an overall one-sided type I error rate of 0.05.[32] Adjusting
16
17 339 for multiplicity of 4 pairwise comparisons with the control arm in a 5-arm setting, the (one-sided) false
18
19 340 positive error rate would be 0.00625, (which requires achieving two-sided $p=0.0125$.) The samples size
20
21 341 might evolve whenever any treatment arm is withdrawn or added to the trial.

22 342 Definition of analysis sets

23
24 343 The intention-to-treat population is defined as all randomised patients, where patients are analysed in
25
26 344 their randomisation group whether they have or not followed the allocated treatment. The modified
27
28 345 intention-to-treat population is defined as all randomised patients who did receive at least one dose of
29
30 346 the allocated treatment.

31
32 347 The primary and efficacy secondary analysis will be conducted on the intention-to-treat population.
33
34 348 Safety analyses will be based on the modified intention-to-treat population.

35 349 Adaptive design

36
37 350 This study is intended to allow for adaptations with the ability to add a new experimental arm if one
38
39 351 becomes available. The current plan is to evaluate the primary endpoint on day 15. If additional data
40
41 352 become available to add an experimental therapy, analyses of experimental arms will be performed
42
43 353 comparing concurrently enrolled control subjects. If one treatment crosses an efficacy stopping
44
45 354 boundary, this treatment may become the new control arm for comparisons. This approach was used in
46
47 355 the recent PALM Ebola therapy randomized clinical trial.[33]

48 49 356 Interim analyses

50
51 357 Interim analyses will be by the independent statistician of the DSMB. There are no formal stopping rules
52
53 358 for efficacy or safety. The DSMB will make recommendations taking into consideration the totality of the
54
55 359 evidence from the efficacy and safety outcomes as they accumulate, as well as external evidence.

56
57 360 For efficacy, the statistical analysis will be done on the primary endpoint, the 7-point ordinal scale at 15
58
59 361 days, and be based on the Haybittle Peto rule.[34,35] That is, if any active treatment is superior to
60

1
2
3 362 control at $P < .001$ then consideration will be given to stopping early for efficacy. This would have major
4
5 363 implications; hence the stopping boundary is stringent in the spirit of requiring proof beyond reasonable
6
7 364 doubt.

8
9 365 For futility, i.e. stopping because an active treatment appears ineffective, the statistical analysis will be
10
11 366 done with the primary endpoint. Comparing an active treatment with control, if the upper 95% confidence
12
13 367 limit for the common odds ratio is less than 1.25 then consideration be given to stopping that treatment
14
15 368 for futility. All the above is intended for all randomised patients. Analyses will be stratified by baseline
16
17 369 severity of disease. For safety, no pre-specify stopping guideline will be defined because there are
18
19 370 various aspects of potential harm that could be studied. However, to allow for some caution, any safety
20
21 371 signal on SAE, i.e. active treatment worse than control, requires $P < .01$ to merit consideration of stopping
22
23 372 that treatment arm.

24 373 Final analysis of the primary endpoint

25
26 374 The primary outcome uses a 7-point ordinal scale analysed using a proportional odds model. This model
27
28 375 assumes that the treatment to control odds ratio of being classified in a given severity category “i” or
29
30 376 better is the same for each category. The null hypothesis being tested is whether the odds of
31
32 377 improvement on the ordinal scale is the same for the control and experimental treatment arms (i.e.,
33
34 378 whether the common odds ratio differs is 1). Odds ratios are then interpreted as the odds of being “lower”
35
36 379 or “higher” on the ordinal scale across the entire range of the scale. The hypothesis test is, for large
37
38 380 sample sizes, nearly the same as the Wilcoxon rank sum test. Therefore, the procedure produces a
39
40 381 valid p-value regardless of whether the proportional odds model is correct. Nonetheless, estimation and
41
42 382 confidence intervals do require the model to be correct. Accordingly, we will evaluate model fit using a
43
44 383 goodness-of-fit likelihood ratio test. The validity of the proportionality assumption will be evaluated and
45
46 384 tested. To deal with potential missing data, the last observation will be carried forward until the next
47
48 385 available value.

49 386 Analysis of secondary endpoints

50
51 387 Differences in time-to-event endpoints by treatment will be summarized with Kaplan-Meier curves and
52
53 388 95% confidence interval; and cumulative incidence plots, for time-to-event endpoints with competing
54
55 389 risk (e.g. death). Duration of event will be summarized according to median days with quartiles.
56
57 390 Incidence data will be summarized as percent with 95% confidence interval. Time-to-event endpoints
58
59
60

1
2
3 391 will be compared using the log-rank test. For time-to-event endpoints with a competing risk Fine and
4
5 392 Gray models will be used. All tests will be stratified by the baseline severity.

6 7 393 **Committees for the research**

8
9 394 The DisCoVeRy French Trial Management Team (TMT) has developed and implemented the protocol
10
11 395 in France (Supplementary file). A DisCoVeRy European Steering Committee (DSC) has been
12
13 396 constituted to serve as the governance organ for the trial. It provides the overall supervision of the trial,
14
15 397 including for the relations with European stakeholders, the Steering Committee and the Executive
16
17 398 Committee of the Solidarity trial (see below). It ensures that the trial is conducted in accordance with
18
19 399 ethical principles and respects participants' safety, take any decision on any changes made to the design
20
21 400 of the DisCoVeRy trial, and on the reporting of the trial results, including regarding the publication policy.
22
23 401 An international independent DSMB has been constituted to preserve the interests of trial participants,
24
25 402 to monitor the main outcome measures (including safety and efficacy), and to monitor the overall
26
27 403 conduct of the trial. Based on interim analyses of the data, it will make recommendations about early
28
29 404 study closure or changes to the trial, including adding or removing treatment arms. The DSMB will meet
30
31 405 after 100 participants are included into the study, and then every 200 new patients are included, with a
32
33 406 maximum of 1 DSMB meeting per week. Other ad hoc reviews will be undertaken if there are specific
34
35 407 safety concerns. The study will not stop enrolment awaiting these DSMB reviews, though the DSMB
36
37 408 may recommend temporary or permanent cessation of enrolment based on their safety reviews.

37 38 409 **Intertwinement with WHO Solidarity program**

39
40 410 Since April 5, 2020, DisCoVeRy has been an add-on trial of the Solidarity program conducted by the
41
42 411 WHO in Europe and worldwide. The same treatments are evaluated in DisCoVeRy and in Solidarity.
43
44 412 Solidarity has 3 endpoints which are also secondary endpoints of DisCoVeRy: (i) mortality during
45
46 413 hospitalization (the primary endpoint of Solidarity) (ii) length of hospital stay and (iii) time to mechanical
47
48 414 ventilation or transfer to intensive care. At each DisCoVeRy DSMB meeting, the recommendations will
49
50 415 be transmitted to the Data and Safety Monitoring Committee (DSMC) of Solidarity. The Executive
51
52 416 Committee of Solidarity will ultimately issue recommendations on the different treatments evaluated,
53
54 417 allowing a unique communication on each of the treatments evaluated.

54 55 418 **Patient and public involvement**

56
57 419 No patients were involved in the design or implementation of this study.

58
59 420
60

421 **ETHICS AND DISSEMINATION**

422 **Ethics approval**

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

433 **Informed consent**

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

441 **Dissemination**

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

446

447 **DISCUSSION**

448 ***Strengths and limitations of the DisCoVeRy trial design***

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

1
2
3 451 design of DisCoVeRy is adaptive meaning that it can adapt to the ongoing production of evidence and
4
5 452 to interim analyses by discontinuing arms that are proved inferior to others, selecting an existing arm as
6
7 453 the standard of care if proved superior to others and adding arms if new candidate therapeutic strategies
8
9 454 emerge.

10 455 As detailed above, DisCoVeRy is an add-on trial of the Solidarity trial, conducted under the aegis of the
11
12 456 WHO in Europe and worldwide. Sharing the data from DisCoVeRy relevant to the Solidarity trial
13
14 457 (inclusion data and data related to the Solidarity endpoints) increases the number of participants for
15
16 458 whom this data is available and thus leads to a faster conclusion on the effectiveness, deleterious effect
17
18 459 or ineffectiveness of the treatments evaluated. Inclusion in a same strategy of hospitalized patients with
19
20 460 severe (patients requiring non-invasive ventilation, high flow oxygen devices, invasive mechanical
21
22 461 ventilation or ECMO) or moderate disease will allow to evaluate the different drug candidates in different
23
24 462 clinical situations. Moreover, by including patients at different times in their clinical history of COVID-19,
25
26 463 we will be able to study when is the best time to start an antiviral agent in relation to the delay of
27
28 464 symptoms. The collection of samples for pharmacological monitoring, viral kinetics and medical imaging
29
30 465 will provide crucial data to analyze the PK/PD of evaluated drugs and the effect of treatment on the
31
32 466 virological and radiological evolution. A biobank has also been planned to conduct further analyses that
33
34 467 still remain to be determined. However, DisCoVeRy will not provide data on treatments for COVID-19
35
36 468 at an early phase, before there is a need for hospitalization. As only antiviral agents are evaluated in
37
38 469 DisCoVeRy, we will not be able to evaluate the efficacy of immunomodulatory agents, including
39
40 470 corticosteroids.

41 471

42 43 472 ***Strengths and limitations of real-time interventional research in the setting of a pandemic***

44
45 473 Discovery is not a placebo-controlled trial and is not double-blind because of the complexity of blinding
46
47 474 treatments with different mode of administration (intravenous, sub-cutaneous or oral) and the need to
48
49 475 initiate the trial very rapidly. Moreover, in a recent meta-epidemiological study, no evidence was found
50
51 476 that lack of blinding of patients, healthcare providers, or outcome assessors had an impact on effect
52
53 477 estimates in randomised clinical trials.[36]

54
55 478 Integrating clinical trials of experimental therapeutics is an increasingly recognized part of the response
56
57 479 during infectious disease outbreaks. Since the Ebola outbreak in West Africa and subsequent outbreaks
58
59 480 in the Democratic Republic of Congo, clinical trials of investigative drugs have been fully integrated in
60

1
2
3 481 the epidemic response.[37–39] Implementing large clinical trial is both direly needed and particularly
4
5 482 challenging during a pandemic. Indeed, the pandemic context compels us to organize clinical trials
6
7 483 urgently while keeping methodological requirements of the highest level which is the only way to provide
8
9 484 reliable answers for clinicians. The selection of the best candidate drugs for a new outbreak is a major
10
11 485 challenge and a strength of the DisCoVeRy trial is that its adaptive design allows to add new arms if
12
13 486 good evidence emerges while the trial is continuing that some other treatment(s) should also be
14
15 487 evaluated. There have been controversies regarding the candidate treatments that should be selected
16
17 488 for COVID-19 clinical trials and notably regarding hydroxychloroquine. Hydroxychloroquine was
18
19 489 identified at the beginning of the pandemic as a candidate treatment based on preliminary data and
20
21 490 quickly became the most tested treatment in the world for COVID-19.[40,41] However, many of the
22
23 491 articles supporting hydroxychloroquine suffered from methodological shortcomings and were in fact non-
24
25 492 informative.[42] Hydroxychloroquine has been widely promoted as soon as February 2020 as an
26
27 493 effective drug by some scientists and politics[43], leading to difficulties in recruiting patients in
28
29 494 randomized clinical trials such as DisCoVeRy.[44] This is why the ever-changing scientific background
30
31 495 supporting the use of each candidate treatment should be clear, detailed and regularly updated and
32
33 496 pragmatic, adaptive clinical trials should be encouraged. Transparency, consistency and quality of
34
35 497 design are more crucial than ever during pandemics to provide relevant and reliable data.

36 498

37 499 **TRIAL STATUS**

39 500 This trial has begun on March 22, 2020. On July 28, 2020, 801 patients have been included.

41 501

43 502 **DATA SHARING PLAN**

45 503 Study protocol and statistical analysis plan will be openly available. Systematic individual patient data
46
47 504 sharing is not intended, but all requests for the trial's data will be considered by the French DisCoVeRy
48
49 505 Trial Management Team.

51 506

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
ELIGIBILITY							
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 β1a				Lopinavir/ritonavir for 14 days Interferon β-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

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

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

511 2. If discharged from the hospital, visits and safety assessments are conducted in the outpatient

512 setting.

- 1
2
3 513 3. *An electrocardiogram (EKG) with calculation of the corrected QT (Fridericia formula) is reviewed*
4
5 514 *at screening and monitored at Day 3, 5, 8 in patients treated with hydroxychloroquine.*
6
7 515 4. *Laboratory tests performed in the 48 hours prior to enrolment are accepted for determination of*
8
9 516 *eligibility.*
10
11 517 5. *Any laboratory tests performed in the 24 hours before randomization can be used for baseline and*
12
13 518 *Day 1.*
14
15 519 6. *For the biobank, whole blood is only collected at baseline.*
16
17 520 7. For each sample, the viral load is measured by a specific SARS-COV-2 real-time (RT)-PCR and
18
19 521 normalized according the number of cells in each sample. This method is validated to monitor viral
20
21 522 load kinetics over time and expressed in standardized unit log of number of viral copies/10 000 cells.
22
23 523

524

525 **AUTHOR CONTRIBUTION :**526 **Conceptualization, investigation, supervision, writing - original draft: FA**

527

528 **REFERENCES**

529

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22 708 **COMPETING INTERESTS**

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25
26 710 François-Xavier Lescure reports fees for development of educational presentations from Gilead, outside
27
28 711 the submitted work. Dominique Costagliola reports personal fees from Merck Switzerland, grants and
29
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31
32 713 Janssen, outside the submitted work. Jean-François Timsit reports grants and personal fees from
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44 719 personal fees from Sanofi, outside the submitted work.

45 720 Other authors declare no competing interests.

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47 721

48
49 722 **DISCLAIMER**

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51 723 The funder nor the sponsor did not have any role in the design of the trial
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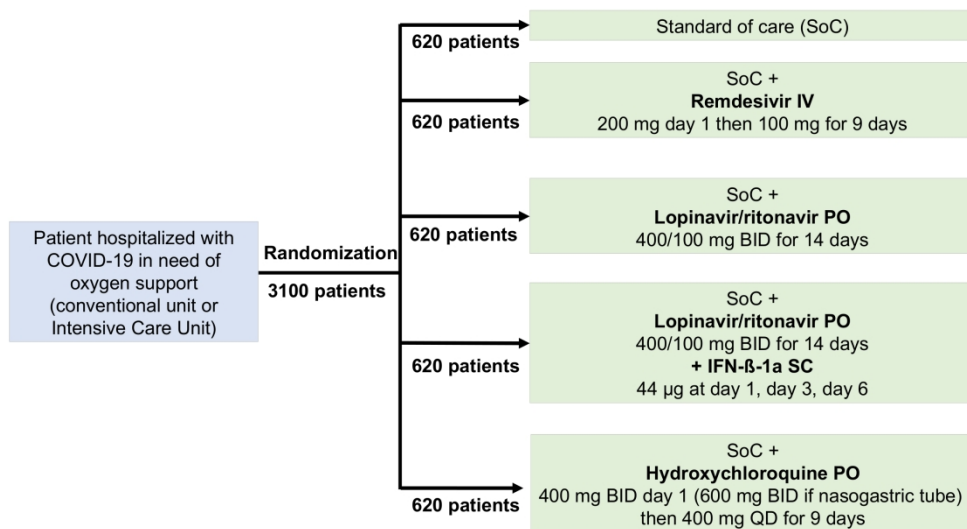


Figure 1. DisCoVeRy trial arms, drugs and dosing schedule

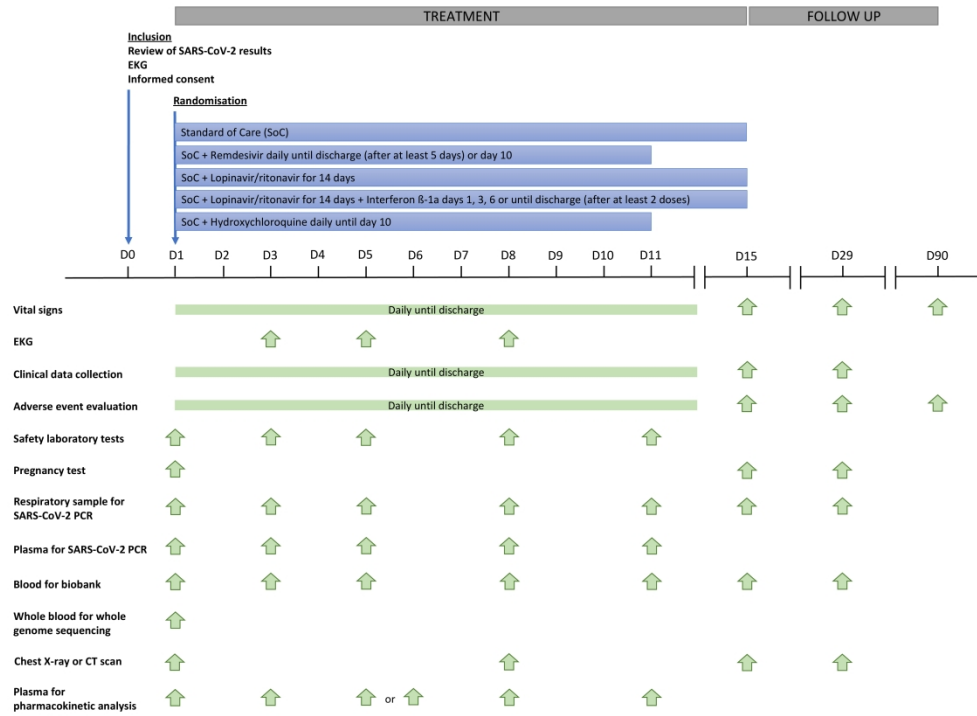


Figure 2. Schematic representation of the experimental design of the DisCoVeRy clinical trial.

419x299mm (300 x 300 DPI)

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For peer review only



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 _____

1	Introduction			
2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	4, 7-8_____
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	7-8, 16_____
7				
8	Objectives	7	Specific objectives or hypotheses	5_____
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	5_____
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	5-6_____
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	5-6_____
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	7, 20_____
23			administered	
24				
25		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	13_____
26			change in response to harms, participant request, or improving/worsening disease)	
27				
28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	20_____
29			(eg, drug tablet return, laboratory tests)	
30				
31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5_____
32				
33	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	9-11_____
34			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
35			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
36			efficacy and harm outcomes is strongly recommended	
37				
38	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	8-19, 19-20, Figure
39			participants. A schematic diagram is highly recommended (see Figure)	2_____
40				
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1	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_____
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15_____
5				

6 **Methods: Assignment of interventions (for controlled trials)**

7 Allocation:

8				
9				
10	Sequence	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_____
11	generation			
12				
13				
14				
15				
16	Allocation	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_____
17	concealment			
18	mechanism			
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6-7_____
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5, 17
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a_____
28				
29				
30				

31 **Methods: Data collection, management, and analysis**

32				
33	Data collection	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__
34	methods			
35				
36				
37				
38		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_____
39				
40				
41				
42				

1	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_____
2				
3				
4				
5	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
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14_____
9				
10		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_____
11				
12				
13				
14	Methods: Monitoring			
15				
16	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
17				
18				
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22		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
23				
24				
25	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_____
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_16_____
29				
30				
31				
32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15-16
35				
36				
37	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_____
38				
39				
40				
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42				

1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16_____
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	16_____
5				
6				
7	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_____
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	26_____
11				
12				
13	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
14				
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_____
17				
18				
19				
20	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_____
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	23-24_____
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18_____
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a_____
32				
33				
34	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
35				
36				

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