

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Efficacy of pragmatic same-day ring prophylaxis for adult individuals exposed to SARS-CoV-2 in Switzerland (COPEP): protocol of an open-label cluster randomized trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-040110
Article Type:	Protocol
Date Submitted by the Author:	07-May-2020
Complete List of Authors:	<p>Smit, Mikaela; Geneva University Hospitals, HIV Unit; University of Geneva, Faculty of Medicine</p> <p>Marinosci, Annalisa; Hopitaux Universitaires de Geneve, HIV Unit</p> <p>Nicoletti, Giovanni; Swiss Tropical and Public Health Institute, Department of Medicine</p> <p>Perneger, Thomas; Hopitaux Universitaires de Geneve, Division of clinical epidemiology; University of Geneva, Faculty of Medicine</p> <p>Ragozzino, Silvio; University of Basel, Department of Infectious Diseases and Hospital Epidemiology</p> <p>Andrey, Diego; Hopitaux Universitaires de Geneve, HIV Unit; University of Geneva, Faculty of Medicine</p> <p>Stoeckle, Marcel; University of Basel, Department of Infectious Diseases and Hospital Epidemiology</p> <p>Jacquierioz, Frederique; Hopitaux Universitaires de Geneve, Department of Primary Care</p> <p>Lebowitz, Dan; Hopitaux Universitaires de Geneve, Infection Control Programme; Republique et Canton de Geneve, Direction Geneale de la Sante</p> <p>Agoritsas, Thomas; Hopitaux Universitaires de Geneve, Faculty of Medicine; University of Geneva, Departement of Medicine</p> <p>Meyer, Benjamin; University of Geneva, Department of Pathology and Immunology,</p> <p>Spechbach, Herve; Hopitaux Universitaires de Geneve, Department of Primary Care</p> <p>Salamun, Julien; Hopitaux Universitaires de Geneve, Department of Primary Care</p> <p>Back, Moritz; Canton of Basel City, Gesundheitsdepartement</p> <p>Schaubhut, Carla; Canton of Basel City, Gesundheitsdepartement</p> <p>Fuchs, Simon; Canton of Basel City, Gesundheitsdepartement</p> <p>Decosterd, Laurent; University of Lausanne, Laboratory of Clinical Pharmacology</p> <p>Battegay, Manuel; University of Basel, Department of Infectious Diseases and Hospital Epidemiology</p> <p>Guessous, Idris; Hopitaux Universitaires de Geneve, Department of Primary Care</p> <p>Chappuis, François; Hopitaux Universitaires de Geneve, Department of Primary Care</p> <p>Kaiser, Laurent; Hopitaux Universitaires de Geneve, Division of Infectious Diseases; Hopitaux Universitaires de Geneve, Geneva Centre</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

	for Emerging Viral Diseases Geneva Labhardt, Niklaus; Swiss Tropical and Public Health Institute, Department of Medicine, ; University of Basel, Department of Infectious Diseases and Hospital Epidemiology Calmy, Alexandra; Hopitaux Universitaires de Geneve, HIV Unit; University of Geneva, Faculty of Medicine
Keywords:	INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES, PREVENTIVE MEDICINE, Clinical trials < THERAPEUTICS





I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 1 **Efficacy of pragmatic same-day ring prophylaxis for adult individuals exposed to**
4
5 2 **SARS-CoV-2 in Switzerland (COPEP): protocol of an open-label cluster randomized**
6
7 3 **trial**
8
9 4

10
11 5 Mikaela SMIT^{1,2,3}, Annalisa MARINOSCI¹, Giovanni Jacopo NICOLETTI⁴, Thomas
12
13 6 PERNEGER^{2,5}, Silvio RAGOZZINO⁶, Diego O ANDREY^{1,2,7}, Marcel P STOECKLE⁶,
14
15 7 Frédérique JACQUERIOZ⁸, Dan LEBOWITZ^{9,10}, Thomas AGORITSAS^{2,11,12}, Benjamin
16
17 8 MEYER¹³, Hervé SPECHBACH⁸, Julien SALAMUN⁸, Moritz BACK¹⁴, Carla SCHAUBHUT¹⁴,
18
19 9 Simon FUCHS¹⁴, Laurent DECOSTERD¹⁵, Manuel BATTEGAY⁶, Idris GUESSOUS⁸,
20
21 10 Francois CHAPPUIS⁸, Laurent KAISER^{16,17}, Niklaus D LABHARDT^{4,6}, Alexandra CALMY^{1,2}
22
23
24 11

25
26 12 From: ¹HIV Unit, Geneva University Hospitals, Switzerland; ²Faculty of Medicine, University
27
28 13 of Geneva, Switzerland; ³Department of Infectious Disease Epidemiology, Imperial College,
29
30 14 Faculty of Medicine, London, UK; ⁴Department of Medicine, Swiss Tropical and Public
31
32 15 Health Institute, Switzerland; ⁵Division of Clinical Epidemiology, Geneva University
33
34 16 Hospitals, Switzerland; ⁶Department of Infectious Diseases and Hospital Epidemiology,
35
36 17 University Hospital of Basel, Switzerland; ⁷Division of Laboratory Medicine, Diagnostic
37
38 18 Department, Geneva University Hospitals, Switzerland; ⁸Department of Primary Care,
39
40 19 Geneva University Hospitals, Switzerland; ⁹Infection Control Programme, Geneva University
41
42 20 Hospitals, Switzerland; ¹⁰Direction Générale de la Santé, Canton de Genève, Switzerland;
43
44 21 ¹¹Département de Médecine, Geneva University Hospitals, Switzerland; ¹²Département of
45
46 22 Health Research Methods, Evidence, and Impact, Hamilton, Ontario, Canada; ¹³Centre for
47
48 23 Vaccinology, Department of Pathology and Immunology, University of Geneva, Switzerland,
49
50 24 ¹⁴Gesundheitsdepartement des Kantons Basel-Stadt; ¹⁵Laboratory of Clinical Pharmacology,
51
52 25 Lausanne University Hospital, Switzerland; ¹⁶Division of Infectious Diseases, Geneva
53
54 26 University Hospitals, Switzerland; ¹⁷Geneva Centre for Emerging Viral Diseases Geneva
55
56 27 University Hospitals, Switzerland.
57
58
59
60 28

1
2
3 29 **Keywords:** COVID-19; SARS-CoV-2, prophylaxis; cluster randomized trial;
4
5 30 hydroxychloroquine; lopinavir
6

7 31

8
9 32 **Running title:** COPEP trial
10

11 33

12
13 34 **Word count:** 2,621
14

15 35 **Corresponding author:**

16
17 36 Dr Mikaela Smit, ¹HIV Unit, Geneva University Hospitals, Switzerland.
18

19
20 37 Email: Mikaela.smit@hcuge.ch
21

22 38

23
24 39 **40 Word Summary:**

25
26 40 COPEP is a three-arm cluster randomized open-label clinical trial to test the efficacy of
27

28 41 hydroxychloroquine and of lopinavir/ritonavir versus the standard of care as post-exposure
29

30 42 ring prophylaxis for adults exposed to SARS-CoV-2.
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **43 Abstract**

4
5 **44 Introduction**

6
7 45 Hydroxychloroquine (HCQ) and lopinavir/ritonavir (LPV/r) have both been proposed as
8
9 46 repurposed for pre- and post-exposure prophylaxis as well as therapy of Coronavirus
10
11 47 Disease (COVID-19). COPEP trial aims at assessing their efficacy as post-exposure ring-
12
13 48 prophylaxis among adults exposed to severe acute respiratory syndrome coronavirus 2
14
15 49 (SARS-CoV-2).

16
17
18 **50 Methods and Analysis**

19
20 51 COPEP is a three-arm open-label cluster-randomized trial conducted in two cantons of
21
22 52 Switzerland. Asymptomatic adult (≥ 18 years) contacts of individuals diagnosed with COVID-
23
24 53 19 will be randomized (1:1:1) to: a single-dose hydroxychloroquine (HCQ) 800mg,
25
26 54 lopinavir/ritonavir (LPV/r) (400mg/100mg twice daily) for 5 days, or a standard of care arm
27
28 55 (no treatment). Contacts living in the single household will form a cluster and will be
29
30 56 randomized into the same arm. All participants will be followed-up for 21 days and undergo
31
32 57 daily monitoring for COVID-19 symptoms. The primary endpoint is 21-day incidence of
33
34 58 COVID-19, analyzed in an intention-to-treat (ITT) analysis. The secondary endpoints include
35
36 59 the 21-day incidence of COVID-19 as well as SARS-CoV-2 infection in a modified ITT
37
38 60 analysis, excluding participants who had a positive SARS-CoV-2 RT-PCR (polymerase
39
40 61 chain reaction) from oropharyngeal swab and/or a positive SARS-CoV-2 IgG serology at
41
42 62 baseline. Assuming a 21-day incidence for COVID-19 of 20% among contacts without post-
43
44 63 exposure chemoprophylaxis, to detect a relative risk reduction of 60% (i.e. translating in an
45
46 64 absolute reduction from 20% to 8%), with a power of 80%, an alpha of 5%. Accounting for
47
48 65 design effect of cluster design of circa 1.1, we plan to enroll 140 participants per arm, 420
49
50 66 participants in total.

51
52
53 **67 Ethics and Dissemination** Ethics approval has been granted by the Commission cantonale
54
55 68 d'éthique de la recherche and Ethikkommission Nordwest- und Zentralschweiz (ref 2020-
56
57 69 00864) and Swissmedic (2020DR3056). Results from this trial will be disseminated via
58
59 70 journal articles and presentations at national and international conferences.

1
2
3 71
4

5 72 **Trial registration:** Clinicaltrials.gov (NCT04364022); Swiss National Clinical Trial Portal

6
7 73 (SNCTP 000003732)
8

9 74 **Registered Report Identifier:** CCER 2020-0864

10
11 75
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3 76 **Strengths and Limitations:**
4

- 5 77 - Amongst the first clinical trials to study two prophylactic candidates for COVID-19 in
6
7 78 the general population as well as health care workers.
8
9 79 - The trial will test pragmatic ring prophylactic strategies that can be prescribed the
10
11 80 same day with minimal clinical and laboratory assessment
12
13
14 81 - Recruitment may be slowed down by the evolution of the epidemic.
15

16 82
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

83 Introduction

84 Since the beginning of the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2)
85 outbreak in December 2019, the medical and scientific community has scrambled to identify
86 effective pharmacological candidates for its prevention and treatment. Coronavirus Disease-
87 19 (COVID-19, which is the clinical manifestation of SARS-CoV-2 infection) has caused
88 unprecedented pressure on modern health systems across the world. The sudden and
89 uncontrolled influx of severe COVID-19 cases has caused critical shortage of hospital-based
90 resources and forced many countries into lockdown in early 2020.

91 Containing the COVID-19 pandemic may necessitate a multi-pronged strategy,
92 including immunization, treatment, and prophylaxis. The latter would facilitate the containment
93 of future outbreaks of the disease in non-immunized populations. This current pandemic wave
94 will likely be followed by subsequent outbreaks and authorities will need to consider less strict
95 isolation measures when apprising multiple economic impacts (including on health-related
96 outcome) over a prolonged period of time.

97 Two drugs have been identified as possible prophylactic candidates;
98 hydroxychloroquine (HCQ), an anti-malarial drug¹ and the protease inhibitors
99 lopinavir/ritonavir (LPV/r) used for the treatment of HIV.^{2,3} HCQ acts as an endosomal
100 acidification fusion inhibitor and thus may blocks, at least *in vitro*, viral entry into the host cell.⁴
101 Protease inhibitors work by preventing viral replication and LPV/r has been shown to bind to
102 active site of the SARS-CoV protease *in vitro*, with studies confirming that the spatial structure
103 of the binding site was conserved between SARS-CoV and SARS-CoV-2.⁵⁻⁷ Both drugs are
104 licensed in most countries, are part of the World Health Organization essential list, and are
105 available globally and at low cost.⁸

106 However, to date there are no published randomized studies assessing the efficacy of
107 HCQ or LPV/r as prophylaxis for COVID-19. COPEP is a Swiss three-arm open-label cluster
108 randomized trial that will assess the efficacy, safety and acceptability of same-day HCQ-and
109 LPV/r-based prophylaxis, compared to standard of care alone (no treatment) for asymptomatic
110 individuals exposed to SARS-CoV-2.

111 **Methods**

112 COPEP is an open-label three-arm (1:1:1) cluster randomized superiority trial to assess
113 efficacy, safety and acceptability of same-day HCQ-prophylaxis and same-day LPV/r-
114 prophylaxis versus standard of care (no treatment) for asymptomatic adult individuals exposed
115 to SARS-CoV-2. The study will be performed at two sites in Switzerland, Geneva and Basel,
116 and seeks to recruit 420 participants over four to six months. The main objective of COPEP is
117 to assess prevention of COVID-19, with secondary objectives including preventing of SARS-
118 COV-2 infection, and attenuation of COVID-19 severity.

120 **Participants**

121 This trial enrolls adult individuals (≥ 18 years) who have come into close contact with a
122 confirmed case of SARS-CoV-2 infection. A close contact is defined as a person who spent
123 >15 minutes in < 2 meter distance or shared closed space with a confirmed case for a
124 prolonged period (e.g. more than 2 hours) in the period extending from 48 hours before onset
125 of symptoms (or before date of testing in absence of symptoms), or a person who had direct
126 contact with the body fluids or laboratory specimens of a case without recommended personal
127 protective equipment (PPE) or in case of failure of PPE.

128 Recruitment of participants to this study will be performed through two routes; i) the
129 Public Health Authorities in Geneva and Basel, who, as the standard of care, contact all
130 individuals tested positive for SARS-CoV-2 to provide them with instructions on isolating
131 procedures and self-monitoring, and ii) health care workers will be recruited via social media
132 platforms and internal hospital-based platforms. All close contacts of confirmed SARS-CoV-2
133 positive index case will be screened for eligibility (Table 1).

134

135

136

137

138

139 **Table 1.** Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion criteria
<ol style="list-style-type: none"> 1. Documented close contact with a PCR-confirmed SARS-CoV-2 positive individual within the last 48 hours; 2. ≥ 18 years of age; 3. Informed consent documented by signature; 	<ol style="list-style-type: none"> 1. Fever (temperature $>38.0^{\circ}$) and/or respiratory symptoms (cough, dyspnoea) and/or new anosmia/ageusia; 2. Individuals with previous confirmed SARS-CoV-2 infection; 3. Known impairment of liver function; 4. Haemolytic anaemia, porphyria, haemophilia and G6PD deficit; known retinopathy, epilepsy or visual field impairment; 5. Individuals with known severe renal impairment (creatinine clearance $<30\text{mL/min}$) or undergoing dialysis; 6. Known hypersensitivity to any of the study medications; 7. Known <i>long</i> QT syndrome (LQTS) 8. Use of QT interval prolonging medications (https://crediblemeds.org), anti-arrhythmic drugs, or any other medications that are contraindicated with LPV/r and HCQ using the website www.covid19-druginteractions.org 9. Individuals on either HCQ or a boosted protease inhibitor as part of an antiretroviral therapy 10. <i>Inability to be followed-up for the trial period</i>

140 *Abbreviations: G6PD - glucose-6-phosphate dehydrogenase; HCQ – hydroxychloroquine;*
 141 *LPV/r – lopinavir/ritonavir; LQTS – long QT syndrome; SARS-CoV-2 - severe acute respiratory*
 142 *syndrome coronavirus 2*

144 **Intervention**

145 Participants will be randomized in household clusters, 1:1:1, to receive either a single dose of
 146 800 mg of HCQ (4 x 200mg pills); LPV/r, 400mg/100mg (2x 200mg/50mg pills) twice daily for
 147 5 days; or surveillance. The dose of HCQ and the first dose of LPV/r will be taken during the
 148 baseline visit, as directly observed therapy.

149

150

151

1
2
3 152 **Outcomes**

4
5 153 Primary Endpoint

6
7 154 The primary endpoint is the 21-day incidence of COVID-19 in individuals exposed to SARS-
8
9 155 CoV-2 who are asymptomatic at baseline. The primary analysis includes all individuals
10
11 156 enrolled, irrespective of their baseline oropharyngeal swab results or the baseline SARS-CoV-
12
13 157 2 serology (intent-to-treat (ITT) analysis).
14
15

16 158

17
18 159 Secondary endpoints

- 19
20 160 - 21-day incidence of COVID-19 in individuals exposed to SARS-CoV-2 who are
21
22 161 asymptomatic, and have negative SARS-CoV-2 PCR and serology at baseline (modified
23
24 162 ITT),
25
26 163 - 21-day incidence of SARS-CoV-2 infection in individuals exposed to SARS-CoV-2 who
27
28 164 are asymptomatic, and have negative SARS-CoV-2 PCR and serology at baseline
29
30 165 (modified ITT)
31
32 166 - Severity of clinical COVID-19 on a 7-point ordinal scale
33
34 167 - Incidence of serious adverse events.
35
36

37 168

38
39 169 Explorative endpoints include;

- 40
41 170 i) acceptability of a prophylaxis for COVID-19,
42
43 171 ii) reported adherence to LPV/r for participants on the LPV/r arm and HCQ and LPV/r drug
44
45 172 levels on day 5 amongst all individuals.
46
47

48 173

49
50 174

51
52 175 **Measurements**

53
54 176 The following clinical definitions will be used. COVID-19 is defined as ≥ 1 symptom compatible
55
56 177 with COVID-19 and either

- 57
58 178 i) a positive PCR for SARS-CoV-2 in oropharyngeal swab and/or
59
60

1
2
3 179 ii) a seroconversion of IgG only or IgG and IgA for SARS-CoV-2 at day 21 in individuals with
4
5 180 negative serology at baseline. In case of seroconversion of IgA only, seroconversion of IgG
6
7 181 using more sensitive spike-based recombination immunofluorescence assay (S-rIFA) will be
8
9 182 assessed.

10
11 183

12
13 184 New SARS-CoV-2 infection is defined as

14
15 185 i) a positive PCR for SARS-CoV-2 (oropharyngeal swab) amongst those with a negative PCR
16
17 186 at baseline and/or

18
19 187 ii) a seroconversion of IgG only or IgG and IgA for SARS-CoV-2 at day 21 in individuals with
20
21 188 negative serology at baseline. In case of seroconversion of IgA only, seroconversion of IgG
22
23 189 using more sensitive S-rIFA will be used.

24
25 190

26
27 191 Seroconversion for SARS-CoV-2 is defined as negative results for IgG in ELISA at baseline
28
29 192 and either

30
31 193 i) positive result for IgG in ELISA and confirmation by S-rIFA at day 21 or

32
33 194 ii) doubtful result for IgG in ELISA at day 21 and confirmation by S-rIFA. In case of negative
34
35 195 result for IgG in ELISA at day 21 seroconversion can alternatively be defined as follows:

36
37 196 Negative result of IgA in ELISA at baseline and i) positive or doubtful result for IgA in ELISA
38
39 197 at day 21 and ii) positive result for IgG in S-rIFA at day 21.

40
41 198

42 43 199 **Procedures**

44
45 200 All participants will be followed-up for 21 days (Fig 1 and Table 2). Participants will undergo
46
47 201 an oropharyngeal swab for SARS-CoV-2 PCR and a SARS-CoV-2 serology at baseline and
48
49 202 on Day 21. In addition, all participants will be asked to provide on day 5 a capillary puncture
50
51 203 on dried blood spot (DBS) to assess blood levels of HCQ and LPV/r. Participants will be given
52
53 204 the option of “self-test”, or of a home-visit for this DBS procedure.

54
55 205

56
57
58
59
60

1
2
3 206 During follow-up, individuals will be asked to complete a daily online COVID-19 symptoms
4
5 207 questionnaire. The online questionnaire generates alerts when individuals report a symptom
6
7 208 associated with COVID-19 and if participants do not complete the questionnaire for 2
8
9 209 consecutive days. The online questionnaire also serves as a reminder for those on the LPV/r
10
11 210 arm, to take their daily medication up to Day 5. Paper questionnaires will be made available
12
13 211 for those without access to internet. All questionnaires are available in several languages.
14
15

16 212

17
18 213 The team will contact the participant in case an alert is triggered and do a first clinical
19
20 214 assessment by phone. Participants who report COVID-related symptoms (e.g. dyspnoea,
21
22 215 cough, fever (>38.0C), anosmia) will be asked to come on site for an extra visit and undergo
23
24 216 clinical assessment and an oropharyngeal swab to confirm/exclude SARS-CoV-2 infection. If
25
26 217 found positive, participants will be provided with appropriate care, as per local protocol. A
27
28 218 follow-up visit 14 days after a positive diagnosis will be conducted, in order to establish the
29
30 219 worst clinical manifestation of disease.
31

32 220

33
34
35 221 On Day 21, participants will further complete a questionnaire on adverse events and
36
37 222 acceptability of the treatment.
38

39 223

40 41 224 **Sample size**

42
43 225 The sample size for the primary endpoint assumes that without treatment 20% of close
44
45 226 contacts will develop COVID-19, based on the clinical observations made by the team. To
46
47 227 detect a relative risk reduction of 60% (i.e. translating in an absolute reduction from 20% to
48
49 228 8%), with a power of 80%, an alpha of 5% and accounting for design effect of cluster design
50
51 229 of circa 1.1 (based on $= (n - 1)\rho + 1$, where $n=3$ denotes the average cluster size, and
52
53 230 $\rho=0.05$ is the assumed intraclass correlation coefficient). A sample size of 140 participants in
54
55 231 each per arm, 420 in total will thus be needed.
56

57 232

58
59
60

1
2
3 233 For the first of the secondary endpoint (occurrence of new SARS-CoV-2 infection) we assume
4
5 234 40% of close contact without prophylaxis will become infected and 16% with prophylaxis; but
6
7 235 we also expect a baseline prevalence of positive PCR of 30% (these participants will be
8
9 236 excluded from this analysis in a modified ITT). With an effective sample size of 98 individuals
10
11 237 per arm (140×0.7) the power will be 95% for this endpoint.
12

13
14 238

15 239 **Randomization and blinding**

16
17
18 240 Randomization will be done in variable-sized blocks (sizes 6 or 9) in random sequence,
19
20 241 stratified by site (Geneva and Basel). Randomization will be done by cluster, that is where
21
22 242 close contacts reside in the same household (for example the family or friends of the index
23
24 243 case that live together). The randomization procedure will consist of sealed envelopes, one
25
26 244 for each household cluster, prepared by individuals who are not associated with the
27
28 245 recruitment for the trial. Treatment will be identical within households because of the risk of
29
30 246 cross-contamination and to simplify treatment administration to individuals in the same
31
32 247 household. This is an open-label trial.
33

34
35 248

36 249 **Statistical analysis**

37
38
39 250 For the analysis of the primary endpoint, 21-day incidence of COVID-19, we will perform an
40
41 251 intention to treat analysis (ITT), including all individuals who were randomized (including those
42
43 252 who will retrospectively be found to be PCR-confirmed SARS-CoV-2 positive at baseline as
44
45 253 well as individuals retrospectively found SARS-CoV-2 seropositive by serology).
46

47
48 254

49
50 255 Both intervention arms, HCQ and LPV/r, will be compared to the surveillance arm, using
51
52 256 separate indicator variables for the active treatment arms. Because the hypotheses about
53
54 257 treatment efficacy are unrelated and independent, and because we will focus on estimation
55
56 258 and confidence intervals rather than on statistical tests, no adjustment will be done for
57
58 259 multiplicity. Since individual observations will be clustered within households (randomization
59
60 260 units), themselves nested within index cases, we will use mixed complementary log-log

1
2
3 261 regression models for the main analysis (complementary log-log regression is similar to
4
5 262 logistic regression, but yields relative hazards, rather than odds ratios; relative hazards are
6
7 263 more readily interpretable in the context of disease incidence). The outcome variable will be
8
9 264 the occurrence of COVID-19 by day 21. A random intercept will be defined by each household,
10
11 265 nested within the index case. The main fixed effect will be treatment (separate indicators for
12
13 266 HCQ versus surveillance, and LPV/r versus surveillance). The main statistical model will be
14
15 267 adjusted for potential confounding variables, guided by the most up to date evidence. We
16
17 268 foresee that for the incidence of COVID-19, adjustment variables are: age, presence of
18
19 269 comorbidities (specifically cardiac, liver or pulmonary disease), treatment of the index case,
20
21 270 occupational versus non-occupational exposure, and/or positive serology.
22
23
24 271

25
26 272 In a modified intent to treat analysis we will evaluate the secondary endpoints; i) 21-day
27
28 273 incidence of COVID-19 in individuals exposed to SARS-CoV-2 who are asymptomatic, PCR-
29
30 274 confirmed SARS-CoV-2 negative and have negative SARS-CoV-2 serology at baseline
31
32 275 (modified ITT), ii) 21-day incidence of SARS-CoV-2 infection in individuals exposed to SARS-
33
34 276 CoV-2 who are asymptomatic, PCR-confirmed SARS-CoV-2 negative and have negative
35
36 277 SARS-CoV-2 serology at baseline (modified ITT)
37
38

39 278
40
41 279 To ensure that the adjustment model is identical for the two treatment effects, we will run a
42
43 280 single model including all participants, with separate indicators for treatments. The output will
44
45 281 be an adjusted relative hazard of each treatment effect versus surveillance, with a 95%
46
47 282 confidence interval.
48

49 283
50
51 284 For the secondary outcome "severity of disease", rated on a 7-point scale, we will use a Mann-
52
53 285 Whitney test to compare this ordinal outcome variable between intervention arms and
54
55 286 surveillance. For the analysis of individual-reported adverse events, the population will include
56
57 287 all randomized participants, and the comparisons will be by cross-tabulations and chi-square
58
59 288 tests, since the probability of experiencing adverse events will likely not be affected by

289 clustering. For the analysis of acceptability/compliance, only the 2 intervention arms will be
 290 compared. We will use R software version 1.2.5019 and Stata software version 16 for the
 291 analysis.

292

293 **Data collection and management**

294 Any data collected during the course of this study will be protected under secure password,
 295 or kept under lock and key in the research office. No records bearing patient identification will
 296 be provided to anyone outside of the institution except regulatory agencies. Patients will not
 297 be identifiable as individuals in any publication or presentation of this study. Data will be
 298 recorded in RedCap and analysed as described above. The trial will follow all standard
 299 procedures, including reporting of adverse events. The protocol was written in accordance
 300 with SPIRIT checklist (Appendix 1)

301

302 **Patient and public involvement**

303 No patient or patient advisor was involved with study design, recruitment or conduct.

304

305 **Table 2.** SPIRIT table.

	Screening	Baseline: Day 0	Day 1-21 (Daily self- assessment) Participant's home	Day 5 ⁹	Day 21
	Phone	On-site			On-site
Informed consent procedure	X ¹	X ³			
Eligibility check; inclusion and exclusion criteria	X ²	X ⁴			
Oropharyngeal swab		X	Prompted by COVID-19 compatible symptoms ⁵		X
Laboratory-based serology		X			X
Randomization		X			
Administration of prophylaxis⁶		X	X ⁷		

Daily Self-assessment			X		
Questionnaire on adherence of intervention^{7,8}			X ^{7,8}		
Questionnaire on adverse events				X	X
Dried blood spot collection for blood drug concentration				X	
Questionnaire on acceptability					X
Participants who report COVID-19 symptoms on or prior to day 21; will have on-site visit as soon as possible. An oropharyngeal swab will be performed, and if SARS-CoV-2 is PCR confirmed, participants will undergo a follow-up visit 14 days after symptoms onset. ⁵					

306

307 ¹ Study information will be provided to participants by phone308 ² Eligibility criteria will be checked with participant by phone309 ³ Informed consent will be signed by participant and medical investigator on site310 ⁴ Eligibility criteria will be confirmed311 ⁵ Participants with a positive SARS-CoV-2 swab during follow-up will be provided with appropriate care, as per local protocol312 ⁶ Only for participants randomized to HCQ or LPV/r, as directly observed therapy313 ⁷ Only for participants randomized to LPV/r314 ⁸ Only between baseline and Day 5315 ⁹Participants will be given the option of either a self-test DBS, or home visit by a team member

316

317

318

319

320 **Ethics and Dissemination**

321

322 The study has been approved by the following boards: Commission cantonale d'éthique de la
 323 recherche, Geneva, Switzerland (2020-00864), Ethikkommission Nordwest- und
 324 Zentralschweiz, Swissmedic (Swiss Agency for Therapeutic Products).

325

326 All participants will be asked for written informed consent with a dedicated member of the
 327 research team. This trial will be conducted in accordance to Good Clinical Practice and the
 328 Helsinki Declaration. The WHO Trial Registration Data Set is in online supplementary
 329 appendix 2.

330

331 The COPEP-trial will establish whether either or both HCQ and LPV/r are effective as post-
 332 exposure chemoprophylaxis against clinical COVID-19 and / or SARS-CoV-2 infection
 333 compared to surveillance amongst asymptomatic individuals with recent contact to a person
 334 infected with SARS-CoV-2. Furthermore, this trial will aim to investigate whether HCQ and /

1
2
3 332 or LPV/r reduces the severity of clinical COVID-19 over surveillance alone, and whether these
4
5 333 prophylaxes are safe and acceptable for post-exposure prophylaxis of SARS-CoV-2 and
6
7 334 COVID-19.

9 335 If effective, such a pragmatic approach with prescription the same day and without waiting
10
11 336 for laboratory results, will provide a feasible and relatively low-cost strategy to contain local
12
13 337 COVID-19 outbreaks in future. All results will be disseminated in peer-reviewed journals and
14
15 338 national and international conferences.

17
18 339

19
20 340 **Fig 1.** CONSORT Flow Diagram.

21
22 341

23
24 342 **Funding:** Fondation privée des HUG, SNF grant submitted

25
26 343

27
28 344 **Role of funding source:** The sponsor of the study had no role in study design, data
29
30 345 collection, data analysis, data interpretation, or writing of the report. The corresponding
31
32 346 author had full access to all the data in the study and had final responsibility for the decision
33
34 347 to submit for publication.

35
36 348

37
38 349 **Author Contributions:**

39
40 350 AC and NL conceived the overall trial, including the overall design and therapeutic
41
42 351 candidates and are the PI and Co-PI. AC, NL, MS, TP, MPS, and AM designed the trial,
43
44 352 including decision on intervention dosage and administration, study endpoints and
45
46 353 procedures. MS and TP developed all statistical aspects of the trial design. DL and SF
47
48 354 contributed to the formulation of recruitment via the cantonal health authorities. AM and DA
49
50 355 developed the patient and laboratory pathways. BM, LK, and LD helped with all laboratory
51
52 356 aspects of the trial design. MS wrote the first draft of this manuscript. All authors contributed
53
54 357 to the re-drafting of the manuscript and in the process of approving the final draft.

55
56 358

57
58 359 **Conflicts of interest:** We declare that we have no conflicts of interests.

360

361 **Acknowledgements:** The authors thank the funders for supporting this work.

362

363 **References**

364 1. Organización Mundial de la Salud. *Guidelines for the treatment of malaria*. (World Health
365 Organization, 2015).

366 2. European AIDS Clinical Society. *Guidelines*.

367 http://www.europeanaidsclinicalsociety.org/index.php?option=com_content&view=article
368 &id=59&Itemid=41 (2019).

369 3. World Health Organization. WHO | Antiretroviral therapy for HIV infection in adults and
370 adolescents. <http://www.who.int/hiv/pub/arv/adult/en/index.html>.

371 4. Cortegiani, A., Ingoglia, G., Ippolito, M., Giarratano, A. & Einav, S. A systematic review
372 on the efficacy and safety of chloroquine for the treatment of COVID-19. *J Crit Care*
373 (2020) doi:10.1016/j.jcrc.2020.03.005.

374 5. Anand, K. *et al.* Structure of coronavirus main proteinase reveals combination of a
375 chymotrypsin fold with an extra α -helical domain. *The EMBO Journal* **21**, 3213–3224
376 (2002).

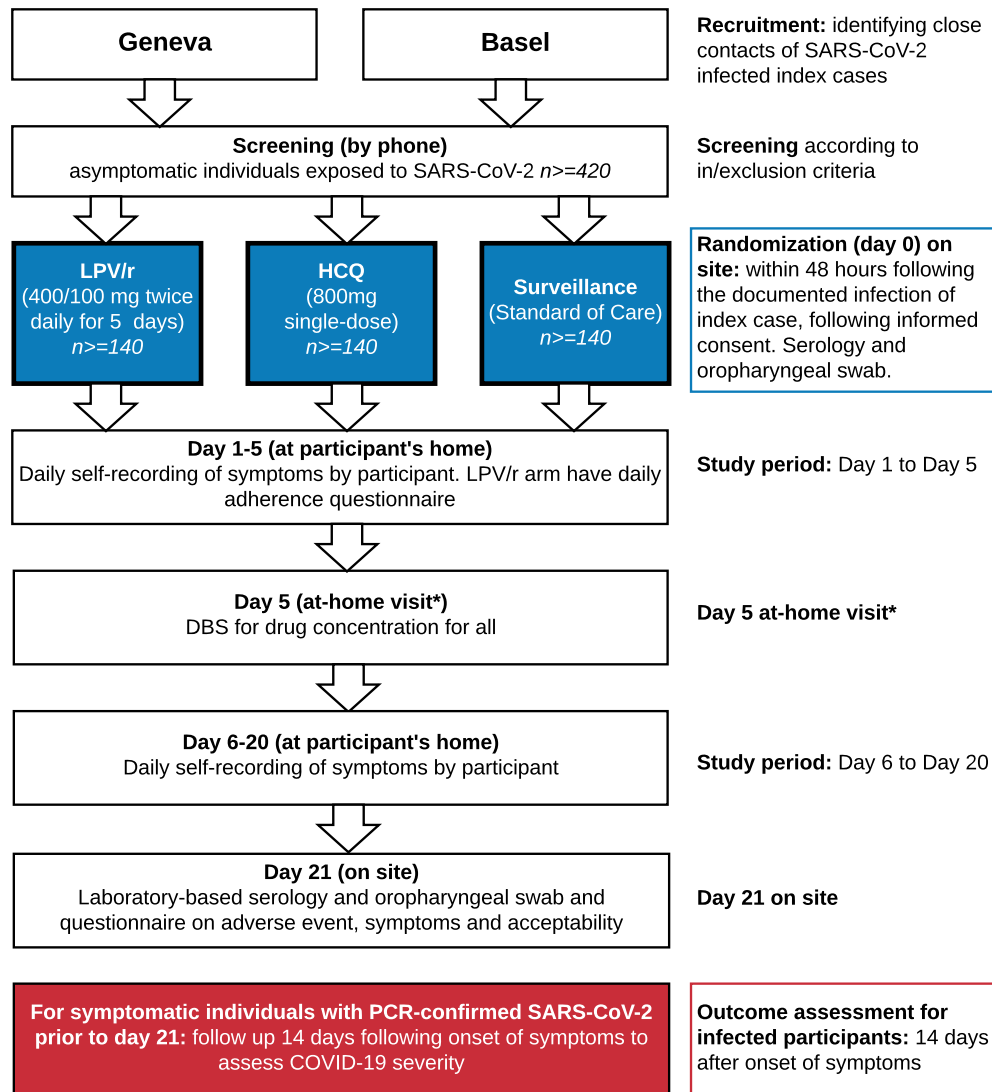
377 6. Lin, C.-W. *et al.* Characterization of trans- and cis-cleavage activity of the SARS
378 coronavirus 3CL_{pro} protease: basis for the in vitro screening of anti-SARS drugs. *FEBS*
379 *Letters* **574**, 131–137 (2004).

380 7. Harrison, C. Coronavirus puts drug repurposing on the fast track. *Nature Biotechnology*
381 (2020) doi:10.1038/d41587-020-00003-1.

382 8. World Health Organization. WHO | WHO Model Lists of Essential Medicines. *WHO*
383 <http://www.who.int/medicines/publications/essentialmedicines/en/>.

384

Fig 1. CONSORT Flow Diagram.



*Day 5 visit: participants will be given the option of self-testing or of a home-visit to take the DBS samples.

Abbreviations: COVID-19 -coronavirus disease 19; HCQ – hydroxychloroquine; LPV/r – lopinavir/ritonavir; PCR – polymerase chain reaction; SARS-CoV-2 - severe acute respiratory syndrome coronavirus 2

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	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, 4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	15
Protocol version	#3	Date and version identifier	15
Funding	#4	Sources and types of financial, material, and other support	16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,16

1	Roles and	#5b	Name and contact information for the trial sponsor	16
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	16
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate authority	
12			over any of these activities	
13				
14				
15				
16	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	NA
17	responsibilities:		centre, steering committee, endpoint adjudication committee,	
18	committees		data management team, and other individuals or groups	
19			overseeing the trial, if applicable (see Item 21a for data	
20			monitoring committee)	
21				
22				
23				
24	Introduction			
25				
26				
27	Background and	#6a	Description of research question and justification for undertaking	6
28	rationale		the trial, including summary of relevant studies (published and	
29			unpublished) examining benefits and harms for each intervention	
30				
31				
32	Background and	#6b	Explanation for choice of comparators	6
33	rationale: choice of			
34	comparators			
35				
36				
37	Objectives	#7	Specific objectives or hypotheses	6
38				
39				
40	Trial design	#8	Description of trial design including type of trial (eg, parallel	6
41			group, crossover, factorial, single group), allocation ratio, and	
42			framework (eg, superiority, equivalence, non-inferiority,	
43			exploratory)	
44				
45				
46	Methods:			
47	Participants,			
48	interventions, and			
49	outcomes			
50				
51				
52				
53	Study setting	#9	Description of study settings (eg, community clinic, academic	7
54			hospital) and list of countries where data will be collected.	
55			Reference to where list of study sites can be obtained	
56				
57				
58				
59				
60				

1	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
2				
3				
4				
5				
6	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
7	description			
8				
9				
10	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	NA
11	modifications			
12				
13				
14				
15	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10-11
16	adherence			
17				
18				
19				
20	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
21	concomitant care			
22				
23				
24	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
25				
26				
27				
28				
29				
30				
31				
32				
33				
34	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10-11
35				
36				
37				
38				
39				
40	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	11
41				
42				
43				
44				
45	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10-11
46				
47				
48				
49	Methods: Assignment			
50	of interventions (for			
51	controlled trials)			
52				
53				
54	Allocation: 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	12
55	generation			
56				
57				
58				
59				
60				

provided in a separate document that is unavailable to those who enrol participants or assign interventions

1			
2			
3			
4	Allocation	#16b	Mechanism of implementing the allocation sequence (eg, central
5	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
6			describing any steps to conceal the sequence until interventions
7	mechanism		are assigned
8			
9			
10			
11	Allocation:	#16c	Who will generate the allocation sequence, who will enrol
12	implementation		participants, and who will assign participants to interventions
13			
14			
15	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial
16			participants, care providers, outcome assessors, data analysts),
17			and how
18			
19			
20	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible,
21	emergency unblinding		and procedure for revealing a participant's allocated intervention
22			during the trial
23			
24			
25	Methods: Data		
26	collection,		
27	management, and		
28	analysis		
29			
30			
31			
32	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and
33			other trial data, including any related processes to promote data
34			quality (eg, duplicate measurements, training of assessors) and a
35			description of study instruments (eg, questionnaires, laboratory
36			tests) along with their reliability and validity, if known.
37			Reference to where data collection forms can be found, if not in
38			the protocol
39			
40			
41			
42			
43	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up,
44	retention		including list of any outcome data to be collected for participants
45			who discontinue or deviate from intervention protocols
46			
47			
48			
49	Data management	#19	Plans for data entry, coding, security, and storage, including any
50			related processes to promote data quality (eg, double data entry;
51			range checks for data values). Reference to where details of data
52			management procedures can be found, if not in the protocol
53			
54			
55	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary
56			outcomes. Reference to where other details of the statistical
57			analysis plan can be found, if not in the protocol
58			
59			
60			

1	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted	13-14
2	analyses		analyses)	
3				
4	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	13-14
5	population and missing		adherence (eg, as randomised analysis), and any statistical	
6	data		methods to handle missing data (eg, multiple imputation)	
7				
8				
9				
10	Methods: Monitoring			
11				
12	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary of	NA
13	formal committee		its role and reporting structure; statement of whether it is	
14			independent from the sponsor and competing interests; and	
15			reference to where further details about its charter can be found,	
16			if not in the protocol. Alternatively, an explanation of why a	
17			DMC is not needed	
18				
19				
20				
21				
22	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	NA
23	interim analysis		including who will have access to these interim results and make	
24			the final decision to terminate the trial	
25				
26				
27	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited	14
28			and spontaneously reported adverse events and other unintended	
29			effects of trial interventions or trial conduct	
30				
31				
32				
33	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and	NA
34			whether the process will be independent from investigators and	
35			the sponsor	
36				
37				
38	Ethics and			
39	dissemination			
40				
41				
42	Research ethics	#24	Plans for seeking research ethics committee / institutional review	15
43	approval		board (REC / IRB) approval	
44				
45				
46	Protocol amendments	#25	Plans for communicating important protocol modifications (eg,	NA
47			changes to eligibility criteria, outcomes, analyses) to relevant	
48			parties (eg, investigators, REC / IRBs, trial participants, trial	
49			registries, journals, regulators)	
50				
51				
52				
53	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial	15
54			participants or authorised surrogates, and how (see Item 32)	
55				
56				
57				
58				
59				
60				

1	Consent or assent:	#26b	Additional consent provisions for collection and use of	NA
2	ancillary studies		participant data and biological specimens in ancillary studies, if	
3			applicable	
4				
5				
6	Confidentiality	#27	How personal information about potential and enrolled	14
7			participants will be collected, shared, and maintained in order to	
8			protect confidentiality before, during, and after the trial	
9				
10				
11	Declaration of interests	#28	Financial and other competing interests for principal investigators	16
12			for the overall trial and each study site	
13				
14				
15	Data access	#29	Statement of who will have access to the final trial dataset, and	14
16			disclosure of contractual agreements that limit such access for	
17			investigators	
18				
19				
20	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care, and for	NA
21	care		compensation to those who suffer harm from trial participation	
22				
23				
24	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial results	16
25	trial results		to participants, healthcare professionals, the public, and other	
26			relevant groups (eg, via publication, reporting in results	
27			databases, or other data sharing arrangements), including any	
28			publication restrictions	
29				
30				
31				
32				
33	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	NA
34	authorship		professional writers	
35				
36				
37	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	NA
38	reproducible research		participant-level dataset, and statistical code	
39				
40				
41	Appendices			
42				
43	Informed consent	#32	Model consent form and other related documentation given to	NA
44	materials		participants and authorised surrogates	
45				
46				
47	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	NA
48			biological specimens for genetic or molecular analysis in the	
49			current trial and for future use in ancillary studies, if applicable	
50				
51				

The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist was completed on 05. May 2020 using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)

Supplementary material

Supplement 2. The World Health Organization Trial Registration Data Set for the COPEP trial

1. Primary Registry and Trial Identifying Number

Swiss National Clinical Trial Portal (SNCTP 000003732)

2. Date of Registration in Primary Registry

17.04.2020

3. Secondary Identifying Numbers

Clinicaltrials.gov (NCT04364022);

4. Source of Monetary or Material Support

Fondation privée des HUG

5. Primary Sponsor

Fondation privée des HUG

6. Secondary Sponsor(s)

SNF grant submitted

7. Contact for Public Queries

Professeur Alexandra Calmy

Hôpitaux Universitaires de Genève (HUG)

Rue Gabrielle-Perret-Gentil 4, 1205 Genève, Switzerland

Email : alexandra.calmy@hcuge.ch

8. Contact for Scientific Queries

Dr Mikaela Smit

Hôpitaux Universitaires de Genève (HUG)

Rue Gabrielle-Perret-Gentil 4, 1205 Genève, Switzerland

Email : mikaela.smit@hcuge.ch

9. Public Title

Médecin adjointe agréée

Director of the HIV Unite

10. Scientific Title

Chef de Clinique Scientifique

Epidemiologist

11. Countries of Recruitment

Switzerland

12. Health Conditions(s) or Problem(s) Studied

COVID-19

13. Intervention(s)

Supplementary material

BMJ Open

Participants will be randomized in household clusters, 1:1:1, to receive either a single dose of 800 mg of HCQ (4 x 200mg pills); LPV/r, 400mg/100mg (2x 200mg/50mg pills) twice daily for 5 days; or surveillance. The dose of HCQ and the first dose of LPV/r will be taken during the baseline visit, as directly observed therapy.

14. Key Inclusion and Exclusion Criteria

Inclusion Criteria

1. Documented close contact with a PCR-confirmed SARS-CoV-2 positive individual within the last 48 hours;
2. ≥ 18 years of age;
3. Informed consent documented by signature;

Exclusion Criteria

1. Fever (temperature $>38.0^{\circ}$) and/or respiratory symptoms (cough, dyspnoea) and/or new anosmia/ageusia;
2. Individuals with previous confirmed SARS-CoV-2 infection;
3. Known impairment of liver function;
4. Haemolytic anaemia, porphyria, haemophilia and G6PD deficit; known retinopathy, epilepsy or visual field impairment;
5. Individuals with known severe renal impairment (creatinine clearance $<30\text{mL/min}$) or undergoing dialysis;
6. Known hypersensitivity to any of the study medications;
7. Known *long* QT syndrome (LQTS)
8. Use of QT interval prolonging medications (<https://crediblemeds.org>), anti-arrhythmic drugs, or any other medications that are contraindicated with LPV/r and HCQ using the website www.covid19-druginteractions.org
9. Individuals on either HCQ or a boosted protease inhibitor as part of an antiretroviral therapy
10. Inability to be followed-up for the trial period

15. Study type:

Study type: interventional

Method of allocation: randomized

Masking: open

16. Date of First Enrollment

23/04/20

17. Sample Size

420

18. Recruitment Status

Recruiting

19. Primary outcomes:

Outcome: incidence of COVID-19

Supplementary material

BMJ Open

Measurement: ≥ 1 symptom compatible with COVID-19 and either
i) a positive PCR for SARS-CoV-2 in oropharyngeal swab and/or
ii) a seroconversion of IgG only or IgG and IgA for SARS-CoV-2 at day 21 in individuals with negative serology at baseline. In case of seroconversion of IgA only, seroconversion of IgG using more sensitive spike-based recombination immunofluorescence assay (S-rIFA) will be assessed.

Timepoint: 21 days

20. Key Secondary Outcomes

Outcome: incidence of COVID-19

Measurement: modified ITT (negative SARS-CoV-2 PCR and serology at baseline)

Timepoint: 21 days

Outcome: incidence of SARS-CoV-2

Measurement: i) a positive PCR for SARS-CoV-2 (oropharyngeal swab) amongst those with a negative PCR at baseline and/or

ii) a seroconversion of IgG only or IgG and IgA for SARS-CoV-2 at day 21 in individuals with negative serology at baseline. In case of seroconversion of IgA only, seroconversion of IgG using more sensitive S-rIFA will be used.

Timepoint: 21 days

Outcome: severity of COVID-19

Measurement: 7-point ordinal scale

Timepoint: 14 days post onset of disease, end of hospitalization where applicable

21. Ethics review

The study has been approved by the following boards: Commission cantonale d'éthique de la recherche, Geneva, Switzerland (2020-00864), Ethikkommission Nordwest- und Zentralschweiz, Swissmedic (Swiss Agency for Therapeutic Products).

All participants will be asked for written informed consent. This trial will be conducted in accordance to Good Clinical Practice and the Helsinki Declaration.

22. Completion data

N/A

23. Summary Results:

N/A

24. IPD sharing statement:

Plan to share IPD: the IPD for this trial will not be made available

Plan description: study protocol

BMJ Open

Efficacy of pragmatic same-day ring prophylaxis for adult individuals exposed to SARS-CoV-2 in Switzerland (COPEP): protocol of an open-label cluster randomized trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-040110.R1
Article Type:	Protocol
Date Submitted by the Author:	07-Oct-2020
Complete List of Authors:	<p>Smit, Mikaela; Geneva University Hospitals, HIV Unit; University of Geneva, Faculty of Medicine</p> <p>Marinosci, Annalisa; Hopitaux Universitaires de Geneve, HIV Unit</p> <p>Nicoletti, Giovanni; Swiss Tropical and Public Health Institute, Department of Medicine</p> <p>Perneger, Thomas; Hopitaux Universitaires de Geneve, Division of clinical epidemiology; University of Geneva, Faculty of Medicine</p> <p>Ragozzino, Silvio; University of Basel, Department of Infectious Diseases and Hospital Epidemiology</p> <p>Andrey, Diego; Hopitaux Universitaires de Geneve, HIV Unit; University of Geneva, Faculty of Medicine</p> <p>Stoeckle, Marcel; University of Basel, Department of Infectious Diseases and Hospital Epidemiology</p> <p>Jacquierioz, Frederique; Hopitaux Universitaires de Geneve, Department of Primary Care</p> <p>Lebowitz, Dan; Hopitaux Universitaires de Geneve, Infection Control Programme; Republique et Canton de Geneve, Direction Geneale de la Sante</p> <p>Agoritsas, Thomas; Hopitaux Universitaires de Geneve, Faculty of Medicine; University of Geneva, Departement of Medicine</p> <p>Meyer, Benjamin; University of Geneva, Department of Pathology and Immunology,</p> <p>Spechbach, Herve; Hopitaux Universitaires de Geneve, Department of Primary Care</p> <p>Salamun, Julien; Hopitaux Universitaires de Geneve, Department of Primary Care</p> <p>Back, Moritz; Canton of Basel City, Gesundheitsdepartement</p> <p>Schaubhut, Carla; Canton of Basel City, Gesundheitsdepartement</p> <p>Fuchs, Simon; Canton of Basel City, Gesundheitsdepartement</p> <p>Decosterd, Laurent; University of Lausanne, Laboratory of Clinical Pharmacology</p> <p>Battegay, Manuel; University of Basel, Department of Infectious Diseases and Hospital Epidemiology</p> <p>Guessous, Idris; Hopitaux Universitaires de Geneve, Department of Primary Care</p> <p>Chappuis, François; Hopitaux Universitaires de Geneve, Department of Primary Care</p> <p>Kaiser, Laurent; Hopitaux Universitaires de Geneve, Division of Infectious Diseases; Hopitaux Universitaires de Geneve, Geneva Centre</p>

	for Emerging Viral Diseases Geneva Labhardt, Niklaus; Swiss Tropical and Public Health Institute, Department of Medicine, ; University of Basel, Department of Infectious Diseases and Hospital Epidemiology Calmy, Alexandra; Hopitaux Universitaires de Geneve, HIV Unit; University of Geneva, Faculty of Medicine
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Infectious diseases
Keywords:	INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES, PREVENTIVE MEDICINE, Clinical trials < THERAPEUTICS, COVID-19

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 1 **Efficacy of pragmatic same-day ring prophylaxis for adult individuals exposed to**
4
5 2 **SARS-CoV-2 in Switzerland (COPEP): protocol of an open-label cluster randomized**
6
7 3 **trial**
8
9 4

10
11 5 Mikaela SMIT^{1,2,3}, Annalisa MARINOSCI¹, Giovanni Jacopo NICOLETTI⁴, Thomas
12
13 6 PERNEGER^{2,5}, Silvio RAGOZZINO⁶, Diego O ANDREY^{1,2,7}, Marcel P STOECKLE⁶,
14
15 7 Frédérique JACQUERIOZ⁸, Dan LEBOWITZ^{9,10}, Thomas AGORITSAS^{2,11,12}, Benjamin
16
17 8 MEYER¹³, Hervé SPECHBACH⁸, Julien SALAMUN⁸, Moritz BACK¹⁴, Carla SCHAUBHUT¹⁴,
18
19 9 Simon FUCHS¹⁴, Laurent DECOSTERD¹⁵, Manuel BATTEGAY⁶, Idris GUESSOUS⁸,
20
21 10 Francois CHAPPUIS⁸, Laurent KAISER^{16,17}, Niklaus D LABHARDT^{3,6}, Alexandra CALMY^{1,2}
22
23
24 11

25
26 12 From: ¹HIV Unit, Geneva University Hospitals, Switzerland; ²Faculty of Medicine, University
27
28 13 of Geneva, Switzerland; ³Department of Infectious Disease Epidemiology, Imperial College,
29
30 14 Faculty of Medicine, London, UK; ⁴Department of Medicine, Swiss Tropical and Public
31
32 15 Health Institute, Switzerland; ⁵Division of Clinical Epidemiology, Geneva University
33
34 16 Hospitals, Switzerland; ⁶Department of Infectious Diseases and Hospital Epidemiology,
35
36 17 University Hospital of Basel, Switzerland; ⁷Division of Laboratory Medicine, Diagnostic
37
38 18 Department, Geneva University Hospitals, Switzerland; ⁸Department of Primary Care,
39
40 19 Geneva University Hospitals, Switzerland; ⁹Infection Control Programme, Geneva University
41
42 20 Hospitals, Switzerland; ¹⁰Direction Générale de la Santé, Canton de Genève, Switzerland;
43
44 21 ¹¹Departement of Medicine, Geneva University Hospitals, Switzerland; ¹²Departement of
45
46 22 Health Research Methods, Evidence, and Impact, Hamilton, Ontario, Canada; ¹³Centre for
47
48 23 Vaccinology, Department of Pathology and Immunology, University of Geneva, Switzerland,
49
50 24 ¹⁴Gesundheitsdepartement des Kantons Basel-Stadt; ¹⁵Laboratory of Clinical Pharmacology,
51
52 25 Lausanne University Hospital, Switzerland; ¹⁶Division of Infectious Diseases, Geneva
53
54 26 University Hospitals, Switzerland; ¹⁷Geneva Centre for Emerging Viral Diseases Geneva
55
56 27 University Hospitals, Switzerland.
57
58
59
60 28

1
2
3 29 **Keywords:** COVID-19; SARS-CoV-2, prophylaxis; cluster randomized trial; lopinavir
4
5
6

7
8
9 30

10
11 31 **Running title:** COPEP (Coronavirus post-exposure prophylaxis) trial
12
13

14
15 32

16 33 **Word count:** 2,621
17

18 34 **Corresponding author:**

19 35 Dr Mikaela Smit, ¹HIV Unit, Geneva University Hospitals, Switzerland.
20

21 36 Email: Mikaela.smit@hcuge.ch
22

23 37

24 38 **40 Word Summary:**

25 39 COPEP is a two-arm cluster randomized open-label clinical trial to test the efficacy of

26 40 lopinavir/ritonavir versus the standard of care as post-exposure ring prophylaxis for adults

27 41 exposed to SARS-CoV-2.
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Abstract**Introduction**

Lopinavir/ritonavir (LPV/r) has been proposed as repurposed drugs for pre- and post-exposure prophylaxis as well as therapy of Coronavirus Disease (COVID-19). COPEP (Coronavirus post-exposure prophylaxis) trial aims at assessing their efficacy as post-exposure ring-prophylaxis among adults exposed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Methods and Analysis

COPEP is a two-arm open-label cluster-randomized trial conducted in three cantons of Switzerland. Asymptomatic contacts (≥ 16 years) of individuals diagnosed with COVID-19 will be randomized (2:1) to either lopinavir/ritonavir (LPV/r) (400mg/100mg twice daily) for 5 days, or a standard of care arm (no treatment). Asymptomatic individuals may be either SARS-CoV-2 positive or negative. Contacts living in the single household will form a cluster and will be randomized into the same arm. All participants will be followed-up for 21 days and undergo daily monitoring for COVID-19 symptoms. The primary endpoint is 21-day incidence of laboratory-confirmed COVID-19 with ≥ 1 compatible symptom, analyzed in an intention-to-treat (ITT) analysis. The secondary endpoints include the 21-day incidence of COVID-19 as well as SARS-CoV-2 infection in a modified ITT analysis, excluding participants who had a positive SARS-CoV-2 RT-PCR (polymerase chain reaction) from oropharyngeal swab and/or a positive SARS-CoV-2 IgG serology at baseline. Assuming a 21-day incidence for COVID-19 of 20% among contacts without post-exposure chemoprophylaxis, to detect a relative risk reduction of 60% (i.e. translating in an absolute reduction from 20% to 8%), with a power of 80%, an alpha of 5%. Accounting for design effect of cluster design of circa 1.1, we plan to enroll 200 participants to the LPV/r arm and 100 to the standard of care arm, 300 participants in total.

Ethics and Dissemination Ethics approval has been granted by the Commission Cantonale d’Ethique de la Recherche, Ethikkommission Nordwest- und Zentralschweiz and Comitato Etico Cantonale (ref 2020-00864) and Swissmedic (2020DR3056). Results from this trial will

1
2
3 70 be disseminated via journal articles and presentations at national and international
4
5 71 conferences.
6

7
8 72

9 73 **Trial registration:** Clinicaltrials.gov (NCT04364022); Swiss National Clinical Trial Portal
10
11 74 (SNCTP 000003732)
12

13 75 **Registered Report Identifier:** CCER 2020-0864
14
15

16 76
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3 77 **Strengths and Limitations:**
4

- 5 78 - Amongst the first clinical trials to study two prophylactic candidates for COVID-19 in
6
7 79 the general population as well as health care workers.
8
9 80 - The trial will test pragmatic ring prophylactic strategies that can be prescribed the
10
11 81 same day with minimal clinical and laboratory assessment
12
13
14 82 - Recruitment may be slowed down by the evolution of the epidemic.
15
16 83 - This is an unblinded trial
17
18
19 84

85 Introduction

86 Since the beginning of the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2)
87 outbreak in December 2019, the medical and scientific community has scrambled to identify
88 effective pharmacological candidates for its prevention and treatment. Coronavirus Disease-
89 19 (COVID-19, which is the clinical manifestation of SARS-CoV-2 infection) has caused
90 unprecedented pressure on modern health systems across the world. The sudden and
91 uncontrolled influx of severe COVID-19 cases has caused critical shortage of hospital-based
92 resources and forced many countries into lockdown in early 2020.

93 Containing the COVID-19 pandemic may necessitate a multi-pronged strategy,
94 including immunization, treatment, and prophylaxis. The latter would facilitate the containment
95 of future outbreaks of the disease in non-immunized populations. This current pandemic wave
96 will likely be followed by subsequent outbreaks and authorities will need to consider less strict
97 isolation measures when apprising multiple economic impacts (including on health-related
98 outcome) over a prolonged period of time.

99 Several drugs have been identified as possible prophylactic candidates. These include
100 the protease inhibitors lopinavir/ritonavir (LPV/r) used for the treatment of HIV.^{1,2} Protease
101 inhibitors work by preventing viral replication and LPV/r has been shown to bind to active site
102 of the SARS-CoV protease *in vitro*, with studies confirming that the spatial structure of the
103 binding site was conserved between SARS-CoV and SARS-CoV-2.³⁻⁵ LPV/r is licensed in
104 most countries, are part of the World Health Organization essential list, and are available
105 globally and at low cost.⁶

106 However, to date there are no published randomized studies assessing the efficacy of
107 LPV/r as prophylaxis for COVID-19. COPEP (coronavirus post-exposure prophylaxis) is a
108 Swiss two-arm open-label cluster randomized trial that will assess the efficacy, safety and
109 acceptability of same-day LPV/r-based prophylaxis, compared to standard of care alone (no
110 treatment) for asymptomatic individuals exposed to SARS-CoV-2.

111
112

113 **Methods**

114 COPEP is an open-label two-arm (2:1) cluster randomized superiority trial to assess efficacy,
115 safety and acceptability of same-day same-day LPV/r-prophylaxis versus standard of care (no
116 treatment) for asymptomatic adult individuals exposed to SARS-CoV-2. Asymptomatic
117 individuals may be either SARS-CoV-2 positive or negative. The study will be performed at
118 three sites in Switzerland, Geneva, Basel and Lugano, and seeks to recruit 300 participants
119 over eight to nine months. The main objective of COPEP is to assess prevention of laboratory-
120 confirmed COVID-19 with ≥ 1 compatible symptom, with secondary objectives including
121 preventing of SARS-CoV-2 infection, and attenuation of COVID-19 severity.

123 **Participants**

124 This trial enrolls individuals (≥ 16 years) who have come into close contact with a confirmed
125 case of SARS-CoV-2 infection. Individuals are eligible to be enrolled if the contact occurred
126 within the last 7 days but no more than 72 hours after the index case was diagnosed. A close
127 contact is defined, as per the Swiss Federal Office of Public Health, as a person who spent
128 >15 minutes in < 2 meter distance or shared closed space with a confirmed case for a
129 prolonged period (e.g. more than 2 hours) in the period extending from 48 hours before onset
130 of symptoms (or before date of testing in absence of symptoms), or a person who had direct
131 contact with the body fluids or laboratory specimens of a case without recommended personal
132 protective equipment (PPE) or in case of failure of PPE.

133 Recruitment of participants to this study will be performed through two routes; i) the
134 Public Health Authorities in Geneva, Basel and Lugano, who, as the standard of care, contact
135 all individuals tested positive for SARS-CoV-2 to provide them with instructions on isolating
136 procedures and self-monitoring, and ii) health care workers will be recruited via social media
137 platforms and internal hospital-based platforms. All close contacts of confirmed SARS-CoV-2
138 positive index case will be screened for eligibility (Table 1).

139

140

141 **Table 1.** Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion criteria
1. Documented close contact with a PCR-confirmed SARS-CoV-2 positive individual; 2. ≥ 16 years of age; 3. Informed consent documented by signature (including parent's or legal guardian's signature if the participant is 16 and 18 y.o.);	1. Fever (temperature $>38.0^{\circ}$) and/or respiratory symptoms (cough, dyspnoea) and/or new anosmia/ageusia; 2. Individuals with previous confirmed SARS-CoV-2 infection within the last six months; 3. Known impairment of liver function; 4. Known hypersensitivity to any of the study medications; 5. Use of any medications that are contraindicated with LPV/r using the website www.hiv-druginteractions.org/checker 6. Individuals on boosted protease inhibitor as part of an antiretroviral therapy 7. Inability to be followed-up for the trial period

142 *Abbreviations: LPV/r – lopinavir/ritonavir; SARS-CoV-2 - severe acute respiratory syndrome*
 143 *coronavirus 2*

145 **Intervention**

146 Participants will be randomized in household clusters, 2:1, to receive either LPV/r,
 147 400mg/100mg (2x 200mg/50mg pills) twice daily for 5 days; or standard of care (no treatment).
 148 The first dose of LPV/r will be taken during the baseline visit, as directly observed therapy.

150 **Outcomes**

151 *Primary Endpoint*

152 The primary endpoint is the 21-day incidence of laboratory-confirmed COVID-19 with ≥ 1
 153 compatible symptom in individuals exposed to SARS-CoV-2 who are asymptomatic (either
 154 SARS_CoV-2 positive or negative) at baseline. The primary analysis includes all individuals
 155 enrolled, irrespective of their baseline oropharyngeal swab results or the baseline SARS-CoV-
 156 2 serology (intent-to-treat (ITT) analysis).

1
2
3 159 *Secondary endpoints*
4

- 5 160 - 21-day incidence of COVID-19 in individuals exposed to SARS-CoV-2 who are
6
7 161 asymptomatic, and have negative SARS-CoV-2 PCR and serology at baseline (modified
8
9 162 ITT),
10
11 163 - 21-day incidence of SARS-CoV-2 infection in individuals exposed to SARS-CoV-2 who
12
13 164 are asymptomatic, and have negative SARS-CoV-2 PCR and serology at baseline
14
15 165 (modified ITT)
16
17 166 - Severity of clinical COVID-19 on a 7-point ordinal scale
18
19 167 - Incidence of serious adverse events.
20
21
22
23

24 168

25 169 Explorative endpoints include;

- 26
27 170 i) acceptability of a prophylaxis for COVID-19,
28
29 171 ii) reported adherence to LPV/r for participants on the LPV/r arm and HCQ and LPV/r drug
30
31 172 levels on day 5 amongst all individuals.
32

33 173

34 174

35
36
37 175 **Measurements**
38

39 176 The following clinical definitions will be used. COVID-19 is defined as ≥ 1 symptom compatible
40
41 177 with COVID-19 (cough, dyspnea, anosmia, ageusia, elevated temperature ($>38^\circ$)) and either
42

43 178 i) a positive PCR for SARS-CoV-2 in oropharyngeal swab and/or

44
45 179 ii) a seroconversion of IgG only or IgG and IgA for SARS-CoV-2 at day 21 in individuals with
46
47 180 negative serology at baseline. In case of seroconversion of IgA only, seroconversion of IgG
48
49 181 using more sensitive spike-based recombination immunofluorescence assay (S-rIFA) will be
50
51 182 assessed.
52
53

54 183

55
56 184 New SARS-CoV-2 infection is defined as
57
58
59
60

- 1
2
3 185 i) a positive PCR for SARS-CoV-2 (oropharyngeal swab) amongst those with a negative PCR
4
5 186 at baseline and/or
6
7 187 ii) a seroconversion of IgG only or IgG and IgA for SARS-CoV-2 at day 21 in individuals with
8
9 188 negative serology at baseline. In case of seroconversion of IgA only, seroconversion of IgG
10
11 189 using more sensitive S-rIFA will be used.
12

13
14 190

15
16 191 Seroconversion for SARS-CoV-2 is defined as negative results for IgG in ELISA at baseline
17
18 192 and either

19
20 193 i) positive result for IgG in ELISA and confirmation by S-rIFA at day 21 or

21
22 194 ii) doubtful result for IgG in ELISA at day 21 and confirmation by S-rIFA. In case of negative
23
24 195 result for IgG in ELISA at day 21 seroconversion can alternatively be defined as follows:
25
26 196 Negative result of IgA in ELISA at baseline and i) positive or doubtful result for IgA in ELISA
27
28 197 at day 21 and ii) positive result for IgG in S-rIFA at day 21.
29

30
31 198

32 199 **Procedures**

33
34 200 All participants will be followed-up for 21 days (Fig 1 and Table 2). Participants will undergo
35
36 201 an oropharyngeal swab for SARS-CoV-2 PCR and a SARS-CoV-2 serology at baseline and
37
38 202 on Day 21. In addition, participants will be asked to provide on day 5 a capillary puncture on
39
40 203 dried blood spot (DBS) to assess blood levels of LPV/r. Participants will be given the option of
41
42 204 “self-test”, or of a home-visit for this DBS procedure.
43
44 205

45
46 206

47 206 During follow-up, individuals will be asked to complete a daily online COVID-19 symptoms
48
49 207 questionnaire. The online questionnaire generates alerts when individuals report a symptom
50
51 208 associated with COVID-19 and if participants do not complete the questionnaire for 2
52
53 209 consecutive days. The online questionnaire also serves as a reminder for those on the LPV/r
54
55 210 arm, to take their daily medication up to Day 5. Paper questionnaires will be made available
56
57 211 for those without access to internet. All questionnaires are available in several languages.
58
59 212

60

1
2
3 213 The team will contact the participant in case an alert is triggered and do a first clinical
4
5 214 assessment by phone. Participants who report COVID-related symptoms (e.g. dyspnoea,
6
7 215 cough, fever (>38.0C), anosmia) will be asked to come on site for an extra visit and undergo
8
9 216 clinical assessment and an oropharyngeal swab to confirm/exclude SARS-CoV-2 infection. If
10
11 217 found positive, participants will be provided with appropriate care, as per local protocol. A
12
13 218 follow-up visit 14 days after a positive diagnosis will be conducted, in order to establish the
14
15 219 level of clinical manifestation of disease.
16

17
18 220
19
20 221 On Day 21, participants will further complete a questionnaire on adverse events and
21
22 222 acceptability of the treatment. Participants on the LPV/r arm are asked to bring the vials which
23
24 223 contained the medication to the Day 21 visit, so that the study team can record the number of
25
26 224 returned pills, as per Good Clinical Practice standard.
27

28 225

29 226 **Sample size**

30
31
32 227 The sample size for the primary endpoint assumes that without treatment 20% of close
33
34 228 contacts will develop COVID-19, based on the clinical observations made by the team. To
35
36 229 detect a relative risk reduction of 60% (i.e. translating in an absolute reduction from 20% to
37
38 230 8%), with a power of 80%, an alpha of 5% and accounting for design effect of cluster design
39
40 231 of circa 1.1 (based on $= (n - 1)\rho + 1$, where $n=3$ denotes the average cluster size, and
41
42 232 $\rho=0.05$ is the assumed intraclass correlation coefficient). A sample size of 200 participants on
43
44 233 LPV/r and 100 on standard of care arm, or 300 in total will thus be needed.
45

46 234

47
48
49 235 For the first of the secondary endpoint (occurrence of new SARS-CoV-2 infection) we assume
50
51 236 40% of close contact without prophylaxis will become infected and 16% with prophylaxis; but
52
53 237 we also expect a baseline prevalence of positive PCR of 30% (these participants will be
54
55 238 excluded from this analysis in a modified ITT). With an effective sample size of 140 individuals
56
57 239 on the LPV/r arm (200×0.7) and 70 on the standard of care arm (100×0.7) the power will be
58
59 240 95% for this endpoint.
60

241 **Randomization and blinding**

242 Randomization will be done in variable-sized blocks (sizes 6 or 9) in random sequence,
243 stratified by site (Geneva, Basel, and Lugano). Randomization will be done by cluster, that is
244 where close contacts reside in the same household (for example the family or friends of the
245 index case that live together). The randomization procedure will consist of sealed envelopes,
246 one for each household cluster, prepared by individuals who are not associated with the
247 recruitment for the trial. Treatment will be identical within households because of the risk of
248 cross-contamination and to simplify treatment administration to individuals in the same
249 household. This is an open-label trial.

250

251 **Statistical analysis**

252 For the analysis of the primary endpoint, 21-day incidence of COVID-19, we will perform an
253 intention to treat analysis (ITT), including all individuals who were randomized (including those
254 who will retrospectively be found to be PCR-confirmed SARS-CoV-2 positive at baseline as
255 well as individuals retrospectively found SARS-CoV-2 seropositive by serology).

256

257 The intervention arm, LPV/r, will be compared to the surveillance arm, using separate indicator
258 variables for the active treatment arms. Because the hypotheses about treatment efficacy are
259 unrelated and independent, and because we will focus on estimation and confidence intervals
260 rather than on statistical tests, no adjustment will be done for multiplicity. Since individual
261 observations will be clustered within households (randomization units), themselves nested
262 within index cases, we will use mixed complementary log-log regression models for the main
263 analysis (complementary log-log regression is similar to logistic regression, but yields relative
264 hazards, rather than odds ratios; relative hazards are more readily interpretable in the context
265 of disease incidence). The outcome variable will be the occurrence of COVID-19 by day 21.
266 A random intercept will be defined by each household, nested within the index case. The main
267 fixed effect will be treatment. The main statistical model will be adjusted for potential
268 confounding variables, guided by the most up to date evidence. We foresee that for the

1
2
3 269 incidence of COVID-19, adjustment variables are: age, presence of comorbidities (specifically
4
5 270 cardiac, liver or pulmonary disease), treatment of the index case, occupational versus non-
6
7 271 occupational exposure, and/or positive serology.
8

9 272

10
11 273 In a modified intent to treat analysis we will evaluate the secondary endpoints; i) 21-day
12
13 274 incidence of COVID-19 in individuals exposed to SARS-CoV-2 who are asymptomatic, PCR-
14
15 275 confirmed SARS-CoV-2 negative and have negative SARS-CoV-2 serology at baseline
16
17 276 (modified ITT), ii) 21-day incidence of SARS-CoV-2 infection in individuals exposed to SARS-
18
19 277 CoV-2 who are asymptomatic, PCR-confirmed SARS-CoV-2 negative and have negative
20
21 278 SARS-CoV-2 serology at baseline (modified ITT). The output will be an adjusted relative
22
23 279 hazard of the treatment effect versus surveillance, with a 95% confidence interval.
24
25

26 280

27
28 281 For the secondary outcome “severity of disease”, rated on a 7-point scale, we will use a Mann-
29
30 282 Whitney test to compare this ordinal outcome variable between intervention arm and
31
32 283 surveillance. For the analysis of individual-reported adverse events, the population will include
33
34 284 all randomized participants, and the comparisons will be by cross-tabulations and chi-square
35
36 285 tests, since the probability of experiencing adverse events will likely not be affected by
37
38 286 clustering. For the analysis of acceptability/compliance, only the intervention arm will be
39
40 287 evaluated. We will use R software version 1.2.5019 and Stata software version 16 for the
41
42 288 analysis.
43
44

45 289

46 47 290 **Data collection and management**

48
49 291 Any data collected during the course of this study will be protected under secure password,
50
51 292 or kept under lock and key in the research office. No records bearing patient identification will
52
53 293 be provided to anyone outside of the institution except regulatory agencies. Patients will not
54
55 294 be identifiable as individuals in any publication or presentation of this study. Data will be
56
57 295 recorded in RedCap and analysed as described above. The trial will follow all standard
58
59
60

296 procedures, including reporting of adverse events. The protocol was written in accordance
297 with SPIRIT checklist (Appendix 1)

298

299

300 Patient and public involvement

301 No patient or patient advisor was involved with study design, recruitment or conduct.

302

303 **Table 2.** SPIRIT table.

	Screening	Baseline: Day 0	Day 1-21 (Daily self- assessment) Participant's home	Day 5 ⁹	Day 21 On-site
	Phone	On-site			
Informed consent procedure	X ¹	X ³			
Eligibility check; inclusion and exclusion criteria	X ²	X ⁴			
Oropharyngeal swab		X	Prompted by COVID-19 compatible symptoms ⁵		X
Laboratory-based serology		X			X
Randomization		X			
Administration of prophylaxis⁶		X	X ⁷		
Daily Self-assessment			X		
Questionnaire on adherence of intervention^{7,8}			X ^{7,8}		
Questionnaire on adverse events				X	X
Dried blood spot collection for blood drug concentration				X	
Questionnaire on acceptability					X
Participants who report COVID-19 symptoms on or prior to day 21; will have on-site visit as soon as possible. An oropharyngeal swab will be performed, and if SARS-CoV-2 is PCR confirmed, participants will undergo a follow-up visit 14 days after symptoms onset. ⁵					

304

305 ¹ Study information will be provided to participants by phone

306 ² Eligibility criteria will be checked with participant by phone

1
2
3 307 ³ Informed consent will be signed by participant and medical investigator on site
4 308 ⁴ Eligibility criteria will be confirmed
5 309 ⁵ Participants with a positive SARS-CoV-2 swab during follow-up will be provided with
6 310 appropriate care, as per local protocol
7 311 ⁶ Only for participants randomized to LPV/r, as directly observed therapy for first dose
8 312 ⁷ Only for participants randomized to LPV/r
9 313 ⁸ Only between baseline and Day 5
10 314 ⁹Participants will be given the option of either a self-test DBS, or home visit by a team
11 315 member
12 316

14
15 317

16 318 **Ethics and Dissemination**

17 319 The study (protocol v3 09.06.2020) has been approved by the following boards: Commission
18
19 320 Cantonale d'éthique de la Recherche, Geneva, Switzerland (2020-00864), Ethikkommission
20
21 321 Nordwest- und Zentralschweiz, Comitato Etico Cantonale and Swissmedic (Swiss Agency for
22
23 322 Therapeutic Products).

24
25 323 All participants will be asked for written informed consent with a dedicated member of the
26
27 324 research team. This trial will be conducted in accordance to Good Clinical Practice and the
28
29 325 Helsinki Declaration. The WHO Trial Registration Data Set is in online supplementary
30
31 326 appendix 2.

32
33
34 327 The COPEP-trial will establish whether LPV/r is effective as post-exposure
35
36 328 chemoprophylaxis against clinical COVID-19 and / or SARS-CoV-2 infection compared to
37
38 329 surveillance amongst asymptomatic individuals with recent contact to a person infected with
39
40 330 SARS-CoV-2. Furthermore, this trial will aim to investigate whether LPV/r reduces the severity
41
42 331 of clinical COVID-19 over surveillance alone, and whether these prophylaxes are safe and
43
44 332 acceptable for post-exposure prophylaxis of SARS-CoV-2 and COVID-19.

45
46 333 If effective, such a pragmatic approach with prescription the same day and without waiting
47
48 334 for laboratory results, will provide a feasible and relatively low-cost strategy to contain local
49
50 335 COVID-19 outbreaks in future. All results will be disseminated in peer-reviewed journals and
51
52 336 national and international conferences.

53
54
55 337

56
57
58
59 338 **Fig 1. CONSORT Flow Diagram.**

1
2
3 339

4
5 340 **Funding:** Fondation privée des HUG (no grant number), Swiss National Fund (project
6
7 341 number: 33IC30_166819)

8
9 342

10
11 343 **Role of funding source:** The sponsor of the study had no role in study design, data
12
13 344 collection, data analysis, data interpretation, or writing of the report. The corresponding
14
15 345 author had full access to all the data in the study and had final responsibility for the decision
16
17 346 to submit for publication.

18
19
20 347

21
22 348 **Author Contributions:**

23
24 349 AC and NL conceived the overall trial, including the overall design and therapeutic
25
26 350 candidates and are the PI and Co-PI. AC, NL, MS, TP, MPS, and AM designed the trial,
27
28 351 including decision on intervention dosage and administration, study endpoints and
29
30 352 procedures. MS and TP developed all statistical aspects of the trial design. MS will perform
31
32 353 the analysing the trial data, with the support of TP. DL and SF contributed to the formulation
33
34 354 of recruitment via the cantonal health authorities, together with MB and CS. AM and DA
35
36 355 developed the patient and laboratory pathways. BM, LK, and LD helped with all laboratory
37
38 356 aspects of the trial design. MS wrote the first draft of this manuscript. GJN, SR, AM, MPS,
39
40 357 NL and AC are the study physicians and together with FJ, TA, HS, JS, MB, IG, FC who
41
42 358 manage the respective COVID-19 patients or infectious diseases unit contributed to the
43
44 359 patient pathway. All authors contributed to the re-drafting of the manuscript and in the
45
46 360 process of approving the final draft.

47
48
49 361

50
51 362 **Conflicts of interest:** We declare that we have no conflicts of interests.

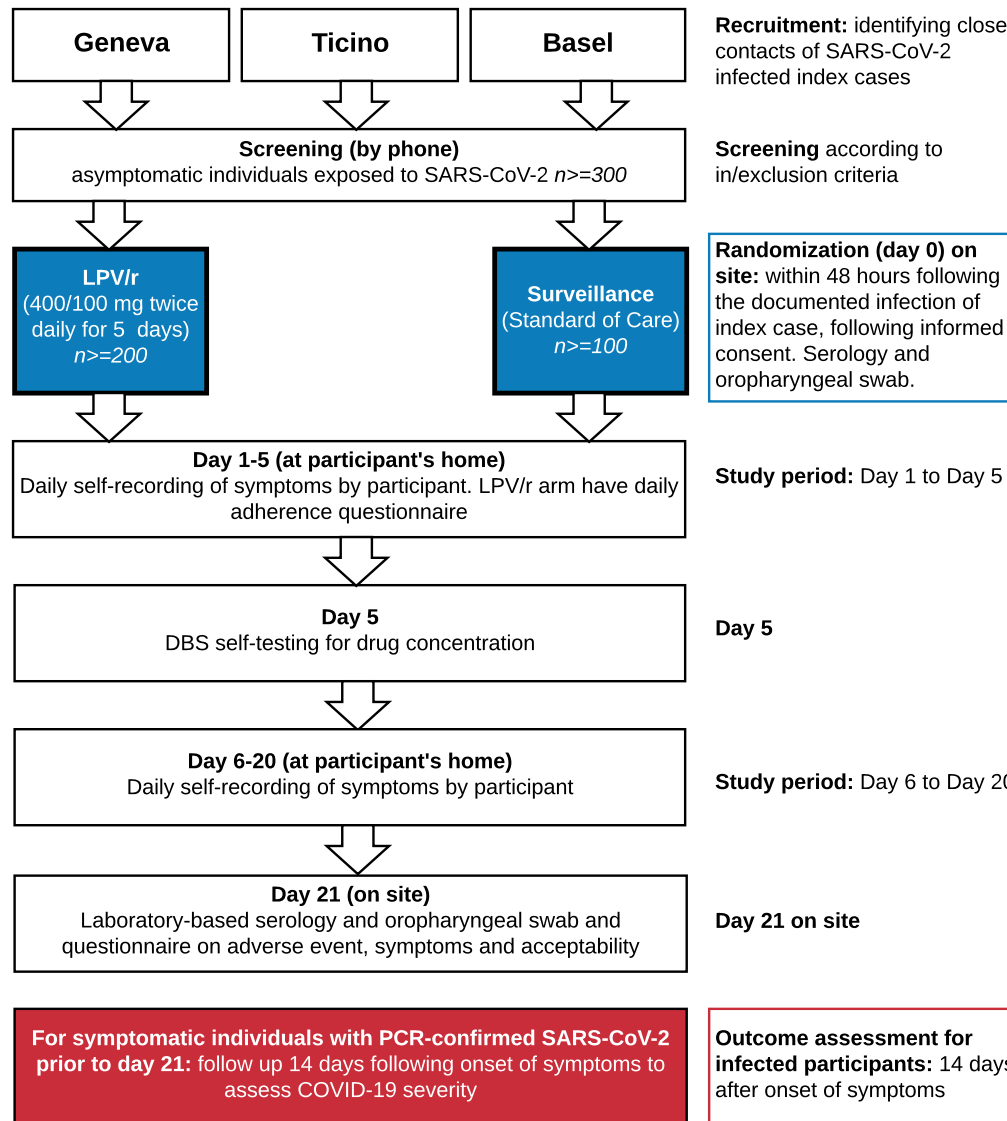
52
53 363

54
55 364 **Acknowledgements:** The authors thank the funders for supporting this work.

56
57 365

58
59 366 **References**

- 1
2
3 367 1. European AIDS Clinical Society. *Guidelines*.
4
5 368 http://www.europeanaidsclicalsociety.org/index.php?option=com_content&view=article
6
7 369 [&id=59&Itemid=41](http://www.europeanaidsclicalsociety.org/index.php?option=com_content&view=article&id=59&Itemid=41) (2019).
8
9 370 2. World Health Organization. WHO | Antiretroviral therapy for HIV infection in adults and
10
11 371 adolescents. <http://www.who.int/hiv/pub/arv/adult/en/index.html>.
12
13 372 3. Anand, K. *et al*. Structure of coronavirus main proteinase reveals combination of a
14
15 373 chymotrypsin fold with an extra α -helical domain. *The EMBO Journal* **21**, 3213–3224
16
17 374 (2002).
18
19 375 4. Lin, C.-W. *et al*. Characterization of trans- and cis-cleavage activity of the SARS
20
21 376 coronavirus 3CLpro protease: basis for the in vitro screening of anti-SARS drugs. *FEBS*
22
23 377 *Letters* **574**, 131–137 (2004).
24
25 378 5. Harrison, C. Coronavirus puts drug repurposing on the fast track. *Nature Biotechnology*
26
27 379 (2020) doi:10.1038/d41587-020-00003-1.
28
29 380 6. World Health Organization. WHO | WHO Model Lists of Essential Medicines. *WHO*
30
31 381 <http://www.who.int/medicines/publications/essentialmedicines/en/>.
32
33 382



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,2
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	15
Protocol version	#3	Date and version identifier	15
Funding	#4	Sources and types of financial, material, and other support	16

1	Roles and	#5a	Names, affiliations, and roles of protocol contributors	1,16
2	responsibilities:			
3	contributorship			
4				
5				
6	Roles and	#5b	Name and contact information for the trial sponsor	ICF
7	responsibilities:			
8	sponsor contact			
9	information			
10				
11				
12				
13	Roles and	#5c	Role of study sponsor and funders, if any, in study	16
14	responsibilities:		design; collection, management, analysis, and	
15	sponsor and funder		interpretation of data; writing of the report; and the	
16			decision to submit the report for publication, including	
17			whether they will have ultimate authority over any of	
18			these activities	
19				
20				
21				
22				
23	Roles and	#5d	Composition, roles, and responsibilities of the	NA
24	responsibilities:		coordinating centre, steering committee, endpoint	
25	committees		adjudication committee, data management team, and	
26			other individuals or groups overseeing the trial, if	
27			applicable (see Item 21a for data monitoring	
28			committee)	
29				
30				
31				
32				
33	Introduction			
34				
35	Background and	#6a	Description of research question and justification for	6
36	rationale		undertaking the trial, including summary of relevant	
37			studies (published and unpublished) examining	
38			benefits and harms for each intervention	
39				
40				
41				
42	Background and	#6b	Explanation for choice of comparators	6
43	rationale: choice of			
44	comparators			
45				
46				
47	Objectives	#7	Specific objectives or hypotheses	6
48				
49	Trial design	#8	Description of trial design including type of trial (eg,	6
50			parallel group, crossover, factorial, single group),	
51			allocation ratio, and framework (eg, superiority,	
52			equivalence, non-inferiority, exploratory)	
53				
54				
55				

Methods:
Participants,

interventions, and outcomes

1				
2				
3				
4	Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
5				
6				
7				
8				
9				
10				
11	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
12				
13				
14				
15				
16				
17	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
18				
19				
20				
21				
22				
23	Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	NA
24				
25				
26				
27				
28				
29				
30	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10-11
31				
32				
33				
34				
35	Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
36				
37				
38				
39	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-9
40				
41				
42				
43				
44				
45				
46				
47				
48				
49				
50	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10-11
51				
52				
53				
54				
55				
56				
57	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including	11
58				
59				
60				

clinical and statistical assumptions supporting any sample size calculations

1
2
3
4 Recruitment [#15](#) Strategies for achieving adequate participant enrolment to reach target sample size 10-11
5
6

7
8 **Methods:**
9 **Assignment of**
10 **interventions (for**
11 **controlled trials)**
12
13

14 Allocation: sequence [#16a](#) Method of generating the allocation sequence (eg, 12
15 generation computer-generated random numbers), and list of any
16 factors for stratification. To reduce predictability of a
17 random sequence, details of any planned restriction
18 (eg, blocking) should be provided in a separate
19 document that is unavailable to those who enrol
20 participants or assign interventions
21
22
23
24

25 Allocation [#16b](#) Mechanism of implementing the allocation sequence 12
26 concealment (eg, central telephone; sequentially numbered,
27 opaque, sealed envelopes), describing any steps to
28 conceal the sequence until interventions are assigned
29 mechanism
30
31

32 Allocation: [#16c](#) Who will generate the allocation sequence, who will 12
33 implementation enrol participants, and who will assign participants to
34 interventions
35
36
37

38 Blinding (masking) [#17a](#) Who will be blinded after assignment to interventions NA
39 (eg, trial participants, care providers, outcome
40 assessors, data analysts), and how
41
42

43 Blinding (masking): [#17b](#) If blinded, circumstances under which unblinding is NA
44 emergency permissible, and procedure for revealing a
45 unblinding participant's allocated intervention during the trial
46
47

48 **Methods: Data**
49 **collection,**
50 **management, and**
51 **analysis**
52
53
54

55 Data collection plan [#18a](#) Plans for assessment and collection of outcome, 13-14
56 baseline, and other trial data, including any related
57 processes to promote data quality (eg, duplicate
58
59
60

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

1
2
3
4
5
6
7
8
9 Data collection plan: [#18b](#) Plans to promote participant retention and complete 13-14
10 retention
11 follow-up, including list of any outcome data to be
12 collected for participants who discontinue or deviate
13 from intervention protocols

14
15 Data management [#19](#) Plans for data entry, coding, security, and storage, 13-14
16 including any related processes to promote data
17 quality (eg, double data entry; range checks for data
18 values). Reference to where details of data
19 management procedures can be found, if not in the
20 protocol
21
22
23
24

25 Statistics: outcomes [#20a](#) Statistical methods for analysing primary and 12-13
26 secondary outcomes. Reference to where other
27 details of the statistical analysis plan can be found, if
28 not in the protocol
29
30

31
32 Statistics: additional [#20b](#) Methods for any additional analyses (eg, subgroup 12-13
33 analyses and adjusted analyses)
34

35
36 Statistics: analysis [#20c](#) Definition of analysis population relating to protocol 12-13
37 population and
38 missing data non-adherence (eg, as randomised analysis), and any
39 statistical methods to handle missing data (eg,
40 multiple imputation)
41

42 **Methods:**

43 **Monitoring**

44
45
46 Data monitoring: [#21a](#) Composition of data monitoring committee (DMC); NA
47 formal committee summary of its role and reporting structure; statement
48 of whether it is independent from the sponsor and
49 competing interests; and reference to where further
50 details about its charter can be found, if not in the
51 protocol. Alternatively, an explanation of why a DMC
52 is not needed
53
54
55
56
57
58
59
60

1	Data monitoring:	#21b	Description of any interim analyses and stopping	NA
2	interim analysis		guidelines, including who will have access to these	
3			interim results and make the final decision to	
4			terminate the trial	
5				
6				
7				
8	Harms	#22	Plans for collecting, assessing, reporting, and	13-z14
9			managing solicited and spontaneously reported	
10			adverse events and other unintended effects of trial	
11			interventions or trial conduct	
12				
13				
14	Auditing	#23	Frequency and procedures for auditing trial conduct, if	NA
15			any, and whether the process will be independent	
16			from investigators and the sponsor	
17				
18				
19				
20	Ethics and			
21	dissemination			
22				
23				
24	Research ethics	#24	Plans for seeking research ethics committee /	15
25	approval		institutional review board (REC / IRB) approval	
26				
27	Protocol amendments	#25	Plans for communicating important protocol	NA
28			modifications (eg, changes to eligibility criteria,	
29			outcomes, analyses) to relevant parties (eg,	
30			investigators, REC / IRBs, trial participants, trial	
31			registries, journals, regulators)	
32				
33				
34				
35				
36	Consent or assent	#26a	Who will obtain informed consent or assent from	15
37			potential trial participants or authorised surrogates,	
38			and how (see Item 32)	
39				
40				
41	Consent or assent:	#26b	Additional consent provisions for collection and use of	NA
42	ancillary studies		participant data and biological specimens in ancillary	
43			studies, if applicable	
44				
45				
46	Confidentiality	#27	How personal information about potential and enrolled	13-14
47			participants will be collected, shared, and maintained	
48			in order to protect confidentiality before, during, and	
49			after the trial	
50				
51				
52				
53	Declaration of	#28	Financial and other competing interests for principal	16
54	interests		investigators for the overall trial and each study site	
55				
56				
57				
58				
59				
60				

1	Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13-14
2				
3				
4				
5				
6	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
7	trial care			
8				
9				
10				
11	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	15
12	trial results			
13				
14				
15				
16				
17				
18				
19				
20				
21	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
22	authorship			
23				
24				
25	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
26	reproducible research			
27				
28				
29	Appendices			
30				
31	Informed consent	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplement
32	materials			
33				
34				
35	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	NA
36				
37				
38				
39				
40				
41				

The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist was completed on 05. May 2020 using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)

Supplementary material

BMJ Open

Supplement 2. The World Health Organization Trial Registration Data Set for the COPEP trial

1. Primary Registry and Trial Identifying Number

Swiss National Clinical Trial Portal (SNCTP 000003732)

2. Date of Registration in Primary Registry

17.04.2020

3. Secondary Identifying Numbers

Clinicaltrials.gov (NCT04364022);

4. Source of Monetary or Material Support

Fondation privée des HUG

5. Primary Sponsor

Fondation privée des HUG

6. Secondary Sponsor(s)

SNF grant submitted

7. Contact for Public Queries

Professeur Alexandra Calmy

Hôpitaux Universitaires de Genève (HUG)

Rue Gabrielle-Perret-Gentil 4, 1205 Genève, Switzerland

Email : alexandra.calmy@hcuge.ch

8. Contact for Scientific Queries

Dr Mikaela Smit

Hôpitaux Universitaires de Genève (HUG)

Rue Gabrielle-Perret-Gentil 4, 1205 Genève, Switzerland

Email : mikaela.smit@hcuge.ch

9. Public Title

Médecin adjointe agréée

Director of the HIV Unite

10. Scientific Title

Chef de Clinique Scientifique

Epidemiologist

11. Countries of Recruitment

Switzerland

12. Health Conditions(s) or Problem(s) Studied

COVID-19

13. Intervention(s)

Supplementary material

BMJ Open

Participants will be randomized in household clusters, 2:1 to receive either LPV/r, 400mg/100mg (2x 200mg/50mg pills) twice daily for 5 days; or surveillance. The first dose of LPV/r will be taken during the baseline visit, as directly observed therapy.

14. Key Inclusion and Exclusion Criteria

Inclusion Criteria

1. Documented close contact with a PCR-confirmed SARS-CoV-2 positive individual;
2. ≥ 16 years of age;
3. Informed consent documented by signature (including parent's or legal guardian's signature if the participant is 16 and 18 y.o.);

Exclusion Criteria

1. Fever (temperature $>38.0^\circ$) and/or respiratory symptoms (cough, dyspnoea) and/or new anosmia/ageusia;
2. Individuals with previous confirmed SARS-CoV-2 infection within the last six months;
3. Known impairment of liver function;
4. Known hypersensitivity to any of the study medications;
5. Use of any medications that are contraindicated with LPV/r using the website www.hiv-druginteractions.org/checker
6. Individuals on boosted protease inhibitor as part of an antiretroviral therapy
7. Inability to be followed-up for the trial period

15. Study type:

Study type: interventional

Method of allocation: randomized

Masking: open

16. Date of First Enrollment

23/04/20

17. Sample Size

300

18. Recruitment Status

Recruiting

19. Primary outcomes:

Outcome: incidence of COVID-19

Measurement: ≥ 1 symptom compatible with COVID-19 and either

i) a positive PCR for SARS-CoV-2 in oropharyngeal swab and/or

ii) a seroconversion of IgG only or IgG and IgA for SARS-CoV-2 at day 21 in individuals with negative serology at baseline. In case of seroconversion of IgA only, seroconversion of IgG using more sensitive spike-based recombination immunofluorescence assay (S-rIFA) will be assessed.

Timepoint: 21 days

Supplementary material

*BMJ Open***20. Key Secondary Outcomes**

Outcome: incidence of COVID-19

Measurement: modified ITT (negative SARS-CoV-2 PCR and serology at baseline)

Timepoint: 21 days

Outcome: incidence of SARS-CoV-2

Measurement: i) a positive PCR for SARS-CoV-2 (oropharyngeal swab) amongst those with a negative PCR at baseline and/or

ii) a seroconversion of IgG only or IgG and IgA for SARS-CoV-2 at day 21 in individuals with negative serology at baseline. In case of seroconversion of IgA only, seroconversion of IgG using more sensitive S-rIFA will be used.

Timepoint: 21 days

Outcome: severity of COVID-19

Measurement: 7-point ordinal scale

Timepoint: 14 days post onset of disease, end of hospitalization where applicable

21. Ethics review

The study has been approved by the following boards: Commission cantonale d'éthique de la recherche, Geneva, Switzerland (2020-00864), Ethikkommission Nordwest- und Zentralschweiz, Comitato Etico Cantonale Swissmedic (Swiss Agency for Therapeutic Products).

All participants will be asked for written informed consent. This trial will be conducted in accordance to Good Clinical Practice and the Helsinki Declaration.

22. Completion data

N/A

23. Summary Results:

N/A

24. IPD sharing statement:

Plan to share IPD: the IPD for this trial will not be made available

Plan description: study protocol