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

	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.

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

Mikaela SMIT[1,2,3], Annalisa MARINOSCI[1], Giovanni Jacopo NICOLETTI[4], Thomas PERNEGER[2,5], Silvio RAGOZZINO[6], Diego O ANDREY[1,2,7], Marcel P STOECKLE[6], Frédérique JACQUERIOZ[8], Dan LEBOWITZ[9,10], Thomas AGORITSAS[2,11,12], Benjamin MEYER[13], Hervé SPECHBACH[8], Julien SALAMUN[8], Moritz BACK[14], Carla SCHAUBHUT[14], Simon FUCHS[14], Laurent DECOSTERD[15], Manuel BATTEGAY[6], Idris GUESSOUS[8], Francois CHAPPUIS[8], Laurent KAISER[16,17], Niklaus D LABHARDT[4,6,], Alexandra CALMY[1,2]

From: [1]HIV Unit, Geneva University Hospitals, Switzerland; [2]Faculty of Medicine, University of Geneva, Switzerland; [3]Department of Infectious Disease Epidemiology, Imperial College, Faculty of Medicine, London, UK; [4]Department of Medicine, Swiss Tropical and Public Health Institute, Switzerland; [5]Division of Clinical Epidemiology, Geneva University Hospitals, Switzerland; [6]Department of Infectious Diseases and Hospital Epidemiology, University Hospital of Basel, Switzerland; [7]Division of Laboratory Medicine, Diagnostic Department, Geneva University Hospitals, Switzerland; [8]Department of Primary Care, Geneva University Hospitals, Switzerland; [9]Infection Control Programme, Geneva University Hospitals, Switzerland; [10]Direction Générale de la Santé, Canton de Genève, Switzerland; [11]Departement of Medicine, Geneva University Hospitals, Switzerland; [12]Departement of Health Research Methods, Evidence, and Impact, Hamilton, Ontario, Canada; [13]Centre for Vaccinology, Department of Pathology and Immunology, University of Geneva, Switzerland, [14]Gesundheitsdepartement des Kantons Basel-Stadt; [15]Laboratory of Clinical Pharmacology, Lausanne University Hospital, Switzerland; [16]Division of Infectious Diseases, Geneva University Hospitals, Switzerland; [17]Geneva Centre for Emerging Viral Diseases Geneva University Hospitals, Switzerland.

Keywords: COVID-19; SARS-CoV-2, prophylaxis; cluster randomized trial; hydroxychloroquine; lopinavir

Running title: COPEP trial

Word count: 2,621

Corresponding author:

Dr Mikaela Smit, [1]HIV Unit, Geneva University Hospitals, Switzerland.

Email: Mikaela.smit@hcuge.ch

40 Word Summary:

COPEP is a three-arm cluster randomized open-label clinical trial to test the efficacy of hydroxychloroquine and of lopinavir/ritonavir versus the standard of care as post-exposure ring prophylaxis for adults exposed to SARS-CoV-2.

Abstract

Introduction

Hydroxychloroquine (HCQ) and lopinavir/ritonavir (LPV/r) have both been proposed as repurposed for pre- and post-exposure prophylaxis as well as therapy of Coronavirus Disease (COVID-19). COPEP 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 three-arm open-label cluster-randomized trial conducted in two cantons of Switzerland. Asymptomatic adult (≥18 years) contacts of individuals diagnosed with COVID-19 will be randomized (1:1:1) to: a single-dose hydroxychloroquine (HCQ) 800mg, lopinavir/ritonavir (LPV/r) (400mg/100mg twice daily) for 5 days, or a standard of care arm (no treatment). 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 COVID-19, 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 140 participants per arm, 420 participants in total.

Ethics and Dissemination Ethics approval has been granted by the Commission cantonale d'ethique de la recherche and Ethikkommission Nordwest- und Zentralschweiz (ref 2020-00864) and Swissmedic (2020DR3056). Results from this trial will be disseminated via journal articles and presentations at national and international conferences.

Trial registration: Clinicaltrials.gov (NCT04364022); Swiss National Clinical Trial Portal (SNCTP 000003732)

Registered Report Identifier: CCER 2020-0864

Strengths and Limitations:

- Amongst the first clinical trials to study two prophylaxtic candidates for COVID-19 in the general population as well as health care workers.
- The trial will test pragmatic ring prophylactic strategies that can be prescribed the same day with minimal clinical and laboratory assessment
- Recruitment may be slowed down by the evolution of the epidemic.

Introduction

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

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

Two drugs have been identified as possible prophylactic candidates; hydroxychloroquine (HCQ), an anti-malarial drug[1] and the protease inhibitors lopinavir/ritonavir (LPV/r) used for the treatment of HIV.[2,3] HCQ acts as an endosomal acidification fusion inhibitor and thus may blocks, at least *in vitro,* viral entry into the host cell.[4] Protease inhibitors work by preventing viral replication and LPV/r has been shown to bind to active site of the SARS-CoV protease *in vitro*, with studies confirming that the spatial structure of the binding site was conserved between SARS-CoV and SARS-CoV-2.[5–7] Both drugs are licensed in most countries, are part of the World Health Organization essential list, and are available globally and at low cost.[8]

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

Methods

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

Participants

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

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

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion 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;	1. Fever (temperature >38.0°) 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 <30mL/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*

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

Intervention

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.

Outcomes

Primary Endpoint

The primary endpoint is the 21-day incidence of COVID-19 in individuals exposed to SARS-CoV-2 who are asymptomatic at baseline. The primary analysis includes all individuals enrolled, irrespective of their baseline oropharyngeal swab results or the baseline SARS-CoV-2 serology (intent-to-treat (ITT) analysis).

Secondary endpoints

- 21-day incidence of COVID-19 in individuals exposed to SARS-CoV-2 who are asymptomatic, and have negative SARS-CoV-2 PCR and serology at baseline (modified ITT),
- 21-day incidence of SARS-CoV-2 infection in individuals exposed to SARS-CoV-2 who are asymptomatic, and have negative SARS-CoV-2 PCR and serology at baseline (modified ITT)
- Severity of clinical COVID-19 on a 7-point ordinal scale
- Incidence of serious adverse events.

Explorative endpoints include;

i) acceptability of a prophylaxis for COVID-19,

ii) reported adherence to LPV/r for participants on the LPV/r arm and HCQ and LPV/r drug levels on day 5 amongst all individuals.

Measurements

The following clinical definitions will be used. COVID-19 is defined as ≥ 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.

New SARS-CoV-2 infection is defined as

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.

Seroconversion for SARS-CoV-2 is defined as negative results for IgG in ELISA at baseline and either

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

ii) doubtful result for IgG in ELISA at day 21 and confirmation by S-rIFA. In case of negative result for IgG in ELISA at day 21 seroconversion can alternatively be defined as follows: Negative result of IgA in ELISA at baseline and i) positive or doubtful result for IgA in ELISA at day 21 and ii) positive result for IgG in S-rIFA at day 21.

Procedures

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

During follow-up, individuals will be asked to complete a daily online COVID-19 symptoms questionnaire. The online questionnaire generates alerts when individuals report a symptom associated with COVID-19 and if participants do not complete the questionnaire for 2 consecutive days. The online questionnaire also serves as a reminder for those on the LPV/r arm, to take their daily medication up to Day 5. Paper questionnaires will be made available for those without access to internet. All questionnaires are available in several languages.

The team will contact the participant in case an alert is triggered and do a first clinical assessment by phone. Participants who report COVID-related symptoms (e.g. dyspnoea, cough, fever (>38.0C), anosmia) will be asked to come on site for an extra visit and undergo clinical assessment and an oropharyngeal swab to confirm/exclude SARS-CoV-2 infection. If found positive, participants will be provided with appropriate care, as per local protocol. A follow-up visit 14 days after a positive diagnosis will be conducted, in order to establish the worst clinical manifestation of disease.

On Day 21, participants will further complete a questionnaire on adverse events and acceptability of the treatment.

Sample size

The sample size for the primary endpoint assumes that without treatment 20% of close contacts will develop COVID-19, based on the clinical observations made by the team. 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% and accounting for design effect of cluster design of circa 1.1 (based on $=(n-1)\rho+1$, where n=3 denotes the average cluster size, and ρ=0.05 is the assumed intraclass correlation coefficient). A sample size of 140 participants in each per arm, 420 in total will thus be needed.

For the first of the secondary endpoint (occurrence of new SARS-CoV-2 infection) we assume 40% of close contact without prophylaxis will become infected and 16% with prophylaxis; but we also expect a baseline prevalence of positive PCR of 30% (these participants will be excluded from this analysis in a modified ITT). With an effective sample size of 98 individuals per arm (140*0.7) the power will be 95% for this endpoint.

Randomization and blinding

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

Statistical analysis

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

Both intervention arms, HCQ and LPV/r, will be compared to the surveillance arm, using separate indicator variables for the active treatment arms. Because the hypotheses about treatment efficacy are unrelated and independent, and because we will focus on estimation and confidence intervals rather than on statistical tests, no adjustment will be done for multiplicity. Since individual observations will be clustered within households (randomization units), themselves nested within index cases, we will use mixed complementary log-log

regression models for the main analysis (complementary log-log regression is similar to logistic regression, but yields relative hazards, rather than odds ratios; relative hazards are more readily interpretable in the context of disease incidence). The outcome variable will be the occurrence of COVID-19 by day 21. A random intercept will be defined by each household, nested within the index case. The main fixed effect will be treatment (separate indicators for HCQ versus surveillance, and LPV/r versus surveillance). The main statistical model will be adjusted for potential confounding variables, guided by the most up to date evidence. We foresee that for the incidence of COVID-19, adjustment variables are: age, presence of comorbidities (specifically cardiac, liver or pulmonary disease), treatment of the index case, occupational versus non-occupational exposure, and/or positive serology.

In a modified intent to treat analysis we will evaluate the secondary endpoints; i) 21-day incidence of COVID-19 in individuals exposed to SARS-CoV-2 who are asymptomatic, PCR-confirmed SARS-CoV-2 negative and have negative SARS-CoV-2 serology at baseline (modified ITT), ii) 21-day incidence of SARS-CoV-2 infection in individuals exposed to SARS-CoV-2 who are asymptomatic, PCR-confirmed SARS-CoV-2 negative and have negative SARS-CoV-2 serology at baseline (modified ITT)

To ensure that the adjustment model is identical for the two treatment effects, we will run a single model including all participants, with separate indicators for treatments. The output will be an adjusted relative hazard of each treatment effect versus surveillance, with a 95% confidence interval.

For the secondary outcome “severity of disease”, rated on a 7-point scale, we will use a Mann-Whitney test to compare this ordinal outcome variable between intervention arms and surveillance. For the analysis of individual-reported adverse events, the population will include all randomized participants, and the comparisons will be by cross-tabulations and chi-square tests, since the probability of experiencing adverse events will likely not be affected by

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

Data collection and management

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

Patient and public involvement

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

Table 2. SPIRIT table.

	Screening Phone	**Baseline: Day 0** On-site	**Day 1-21 (Daily self-assessment)** Participant's home	**Day 5[9]**	**Day 21** 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 prophylaxis[6]		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]					

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

Ethics and Dissemination

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 with a dedicated member of the research team. This trial will be conducted in accordance to Good Clinical Practice and the Helsinki Declaration. The WHO Trial Registration Data Set is in online supplementary appendix 2.

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

or LPV/r reduces the severity of clinical COVID-19 over surveillance alone, and whether these prophylaxes are safe and acceptable for post-exposure prophylaxis of SARS-CoV-2 and COVID-19.

If effective, such a pragmatic approach with prescription the same day and without waiting for laboratory results, will provide a feasible and relatively low-cost strategy to contain local COVID-19 outbreaks in future. All results will be dessimanted in peer-reviewed journals and national and international conferences.

Fig 1. CONSORT Flow Diagram.

Funding: Fondation privée des HUG, SNF grant submitted

Role of funding source: The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Author Contributions:

AC and NL conceived the overall trial, including the overall design and therapeutic candidates and are the PI and Co-PI. AC, NL, MS, TP, MPS, and AM designed the trial, including decision on intervention dosage and administration, study endpoints and procedures. MS and TP developed all statistical aspects of the trial design. DL and SF contributed to the formulation of recruitment via the cantonal health authorities. AM and DA developed the patient and laboratory pathways. BM, LK, and LD helped with all laboratory aspects of the trial design. MS wrote the first draft of this manuscript. All authors contributed to the re-drafting of the manuscript and in the process of approving the final draft.

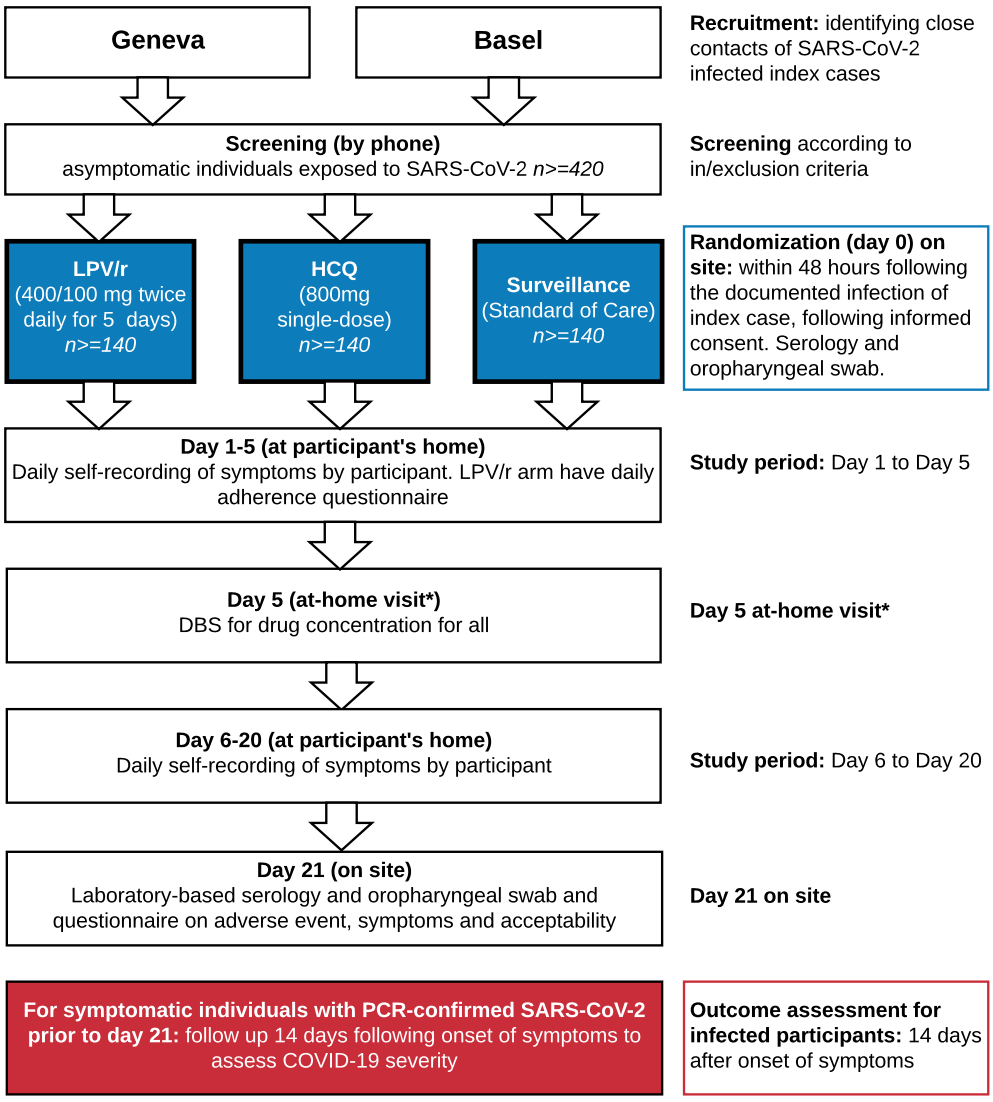
Conflicts of interest: We declare that we have no conflicts of interests.

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

References

1. Organización Mundial de la Salud. *Guidelines for the treatment of malaria.* (World Health Organization, 2015).
2. European AIDS Clinical Society. *Guidelines*. http://www.europeanaidsclinicalsociety.org/index.php?option=com_content&view=article&id=59&Itemid=41 (2019).
3. World Health Organization. WHO | Antiretroviral therapy for HIV infection in adults and adolescents. http://www.who.int/hiv/pub/arv/adult/en/index.html.
4. Cortegiani, A., Ingoglia, G., Ippolito, M., Giarratano, A. & Einav, S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *J Crit Care* (2020) doi:10.1016/j.jcrc.2020.03.005.
5. Anand, K. *et al.* Structure of coronavirus main proteinase reveals combination of a chymotrypsin fold with an extra α-helical domain. *The EMBO Journal* **21**, 3213–3224 (2002).
6. Lin, C.-W. *et al.* Characterization of trans- and cis-cleavage activity of the SARS coronavirus 3CLpro protease: basis for the in vitro screening of anti-SARS drugs. *FEBS Letters* **574**, 131–137 (2004).
7. Harrison, C. Coronavirus puts drug repurposing on the fast track. *Nature Biotechnology* (2020) doi:10.1038/d41587-020-00003-1.
8. World Health Organization. WHO | WHO Model Lists of Essential Medicines. *WHO* http://www.who.int/medicines/publications/essentialmedicines/en/.

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 -coronaviraus 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 SPIRITreporting 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

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	16
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7

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
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
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
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10-11
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
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
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
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
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10-11
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	12

		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13-14
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13-14
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
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	14
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	NA
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

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 agregée
Director of the HIV Unite

10. Scientific Title
Chef de Clinique Scientifique
Epidemiologist

11. Countries of Recruitement
Switzerland

12. Health Conditions(s) or Problem(s) Studied
COVID-19

13. Intervention(s)

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 Citeria

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°) 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 <30mL/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. Recuitement 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

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

	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

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.

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

Mikaela SMIT[1,2,3], Annalisa MARINOSCI[1], Giovanni Jacopo NICOLETTI[4], Thomas PERNEGER[2,5], Silvio RAGOZZINO[6], Diego O ANDREY[1,2,7], Marcel P STOECKLE[6], Frédérique JACQUERIOZ[8], Dan LEBOWITZ[9,10], Thomas AGORITSAS[2,11,12], Benjamin MEYER[13], Hervé SPECHBACH[8], Julien SALAMUN[8], Moritz BACK[14], Carla SCHAUBHUT[14], Simon FUCHS[14], Laurent DECOSTERD[15], Manuel BATTEGAY[6], Idris GUESSOUS[8], Francois CHAPPUIS[8], Laurent KAISER[16,17], Niklaus D LABHARDT[3,6,], Alexandra CALMY[1,2]

From: [1]HIV Unit, Geneva University Hospitals, Switzerland; [2]Faculty of Medicine, University of Geneva, Switzerland; [3]Department of Infectious Disease Epidemiology, Imperial College, Faculty of Medicine, London, UK; [4]Department of Medicine, Swiss Tropical and Public Health Institute, Switzerland; [5]Division of Clinical Epidemiology, Geneva University Hospitals, Switzerland; [6]Department of Infectious Diseases and Hospital Epidemiology, University Hospital of Basel, Switzerland; [7]Division of Laboratory Medicine, Diagnostic Department, Geneva University Hospitals, Switzerland; [8]Department of Primary Care, Geneva University Hospitals, Switzerland; [9]Infection Control Programme, Geneva University Hospitals, Switzerland; [10]Direction Générale de la Santé, Canton de Genève, Switzerland; [11]Departement of Medicine, Geneva University Hospitals, Switzerland; [12]Departement of Health Research Methods, Evidence, and Impact, Hamilton, Ontario, Canada; [13]Centre for Vaccinology, Department of Pathology and Immunology, University of Geneva, Switzerland, [14]Gesundheitsdepartement des Kantons Basel-Stadt; [15]Laboratory of Clinical Pharmacology, Lausanne University Hospital, Switzerland; [16]Division of Infectious Diseases, Geneva University Hospitals, Switzerland; [17]Geneva Centre for Emerging Viral Diseases Geneva University Hospitals, Switzerland.

Keywords: COVID-19; SARS-CoV-2, prophylaxis; cluster randomized trial; lopinavir

Running title: COPEP (Coronavirus post-exposure prophylaxis) trial

Word count: 2,621

Corresponding author:

Dr Mikaela Smit, [1]HIV Unit, Geneva University Hospitals, Switzerland.

Email: Mikaela.smit@hcuge.ch

40 Word Summary:

COPEP is a two-arm cluster randomized open-label clinical trial to test the efficacy of lopinavir/ritonavir versus the standard of care as post-exposure ring prophylaxis for adults exposed to SARS-CoV-2.

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 of 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

be disseminated via journal articles and presentations at national and international conferences.

Trial registration: Clinicaltrials.gov (NCT04364022); Swiss National Clinical Trial Portal (SNCTP 000003732)

Registered Report Identifier: CCER 2020-0864

Strengths and Limitations:

- Amongst the first clinical trials to study two prophylactic candidates for COVID-19 in the general population as well as health care workers.
- The trial will test pragmatic ring prophylactic strategies that can be prescribed the same day with minimal clinical and laboratory assessment
- Recruitment may be slowed down by the evolution of the epidemic.
- This is an unblinded trial

Introduction

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

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

Several drugs have been identified as possible prophylactic candidates. These include the protease inhibitors lopinavir/ritonavir (LPV/r) used for the treatment of HIV.[1,2] Protease inhibitors work by preventing viral replication and LPV/r has been shown to bind to active site of the SARS-CoV protease *in vitro*, with studies confirming that the spatial structure of the binding site was conserved between SARS-CoV and SARS-CoV-2.[3–5] LPV/r is licensed in most countries, are part of the World Health Organization essential list, and are available globally and at low cost.[6]

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

Methods

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

Participants

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

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

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°) 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

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

Intervention

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 standard of care (no treatment). The first dose of LPV/r will be taken during the baseline visit, as directly observed therapy.

Outcomes

Primary Endpoint

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

Secondary endpoints

- 21-day incidence of COVID-19 in individuals exposed to SARS-CoV-2 who are asymptomatic, and have negative SARS-CoV-2 PCR and serology at baseline (modified ITT),
- 21-day incidence of SARS-CoV-2 infection in individuals exposed to SARS-CoV-2 who are asymptomatic, and have negative SARS-CoV-2 PCR and serology at baseline (modified ITT)
- Severity of clinical COVID-19 on a 7-point ordinal scale
- Incidence of serious adverse events.

Explorative endpoints include;

i) acceptability of a prophylaxis for COVID-19,

ii) reported adherence to LPV/r for participants on the LPV/r arm and HCQ and LPV/r drug levels on day 5 amongst all individuals.

Measurements

The following clinical definitions will be used. COVID-19 is defined as ≥ 1 symptom compatible with COVID-19 (cough, dyspnea, anosmia, ageusia, elevated temperature (>38°)) 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.

New SARS-CoV-2 infection is defined as

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.

Seroconversion for SARS-CoV-2 is defined as negative results for IgG in ELISA at baseline and either

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

ii) doubtful result for IgG in ELISA at day 21 and confirmation by S-rIFA. In case of negative result for IgG in ELISA at day 21 seroconversion can alternatively be defined as follows: Negative result of IgA in ELISA at baseline and i) positive or doubtful result for IgA in ELISA at day 21 and ii) positive result for IgG in S-rIFA at day 21.

Procedures

All participants will be followed-up for 21 days (Fig 1 and Table 2). Participants will undergo an oropharyngeal swab for SARS-CoV-2 PCR and a SARS-CoV-2 serology at baseline and on Day 21. In addition, participants will be asked to provide on day 5 a capillary puncture on dried blood spot (DBS) to assess blood levels of LPV/r. Participants will be given the option of "self-test", or of a home-visit for this DBS procedure.

During follow-up, individuals will be asked to complete a daily online COVID-19 symptoms questionnaire. The online questionnaire generates alerts when individuals report a symptom associated with COVID-19 and if participants do not complete the questionnaire for 2 consecutive days. The online questionnaire also serves as a reminder for those on the LPV/r arm, to take their daily medication up to Day 5. Paper questionnaires will be made available for those without access to internet. All questionnaires are available in several languages.

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

On Day 21, participants will further complete a questionnaire on adverse events and acceptability of the treatment. Participants on the LPV/r arm are asked to bring the vials which contained the medication to the Day 21 visit, so that the study team can record the number of returned pills, as per Good Clinical Practice standard.

Sample size

The sample size for the primary endpoint assumes that without treatment 20% of close contacts will develop COVID-19, based on the clinical observations made by the team. 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% and accounting for design effect of cluster design of circa 1.1 (based on $=(n-1)\rho+1$, where n=3 denotes the average cluster size, and ρ=0.05 is the assumed intraclass correlation coefficient). A sample size of 200 participants on LPV/r and 100 on standard of care arm, or 300 in total will thus be needed.

For the first of the secondary endpoint (occurrence of new SARS-CoV-2 infection) we assume 40% of close contact without prophylaxis will become infected and 16% with prophylaxis; but we also expect a baseline prevalence of positive PCR of 30% (these participants will be excluded from this analysis in a modified ITT). With an effective sample size of 140 individuals on the LPV/r arm (200*0.7) and 70 on the standard of care arm (100*0.7) the power will be 95% for this endpoint.

Randomization and blinding

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

Statistical analysis

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

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

incidence of COVID-19, adjustment variables are: age, presence of comorbidities (specifically cardiac, liver or pulmonary disease), treatment of the index case, occupational versus non-occupational exposure, and/or positive serology.

In a modified intent to treat analysis we will evaluate the secondary endpoints; i) 21-day incidence of COVID-19 in individuals exposed to SARS-CoV-2 who are asymptomatic, PCR-confirmed SARS-CoV-2 negative and have negative SARS-CoV-2 serology at baseline (modified ITT), ii) 21-day incidence of SARS-CoV-2 infection in individuals exposed to SARS-CoV-2 who are asymptomatic, PCR-confirmed SARS-CoV-2 negative and have negative SARS-CoV-2 serology at baseline (modified ITT). The output will be an adjusted relative hazard of the treatment effect versus surveillance, with a 95% confidence interval.

For the secondary outcome “severity of disease”, rated on a 7-point scale, we will use a Mann-Whitney test to compare this ordinal outcome variable between intervention arm and surveillance. For the analysis of individual-reported adverse events, the population will include all randomized participants, and the comparisons will be by cross-tabulations and chi-square tests, since the probability of experiencing adverse events will likely not be affected by clustering. For the analysis of acceptability/compliance, only the intervention arm will be evaluated. We will use R software version 1.2.5019 and Stata software version 16 for the analysis.

Data collection and management

Any data collected during the course of this study will be protected under secure password, or kept under lock and key in the research office. No records bearing patient identification will be provided to anyone outside of the institution except regulatory agencies. Patients will not be identifiable as individuals in any publication or presentation of this study. Data will be recorded in RedCap and analysed as described above. The trial will follow all standard

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

Patient and public involvement

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

Table 2. SPIRIT table.

	Screening Phone	**Baseline: Day 0** On-site	**Day 1-21 (Daily self-assessment)** Participant's home	**Day 5[9]**	**Day 21** 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 prophylaxis[6]		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]					

[1] Study information will be provided to participants by phone
[2] Eligibility criteria will be checked with participant by phone

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

Ethics and Dissemination

The study (protocol v3 09.06.2020) 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 and Swissmedic (Swiss Agency for Therapeutic Products).

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

The COPEP-trial will establish whether LPV/r is effective as post-exposure chemoprophylaxis against clinical COVID-19 and / or SARS-CoV-2 infection compared to surveillance amongst asymptomatic individuals with recent contact to a person infected with SARS-CoV-2. Furthermore, this trial will aim to investigate whether LPV/r reduces the severity of clinical COVID-19 over surveillance alone, and whether these prophylaxes are safe and acceptable for post-exposure prophylaxis of SARS-CoV-2 and COVID-19.

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

Fig 1. CONSORT Flow Diagram.

Funding: Fondation privée des HUG (no grant number), Swiss National Fund (project number: 33IC30_166819)

Role of funding source: The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Author Contributions:

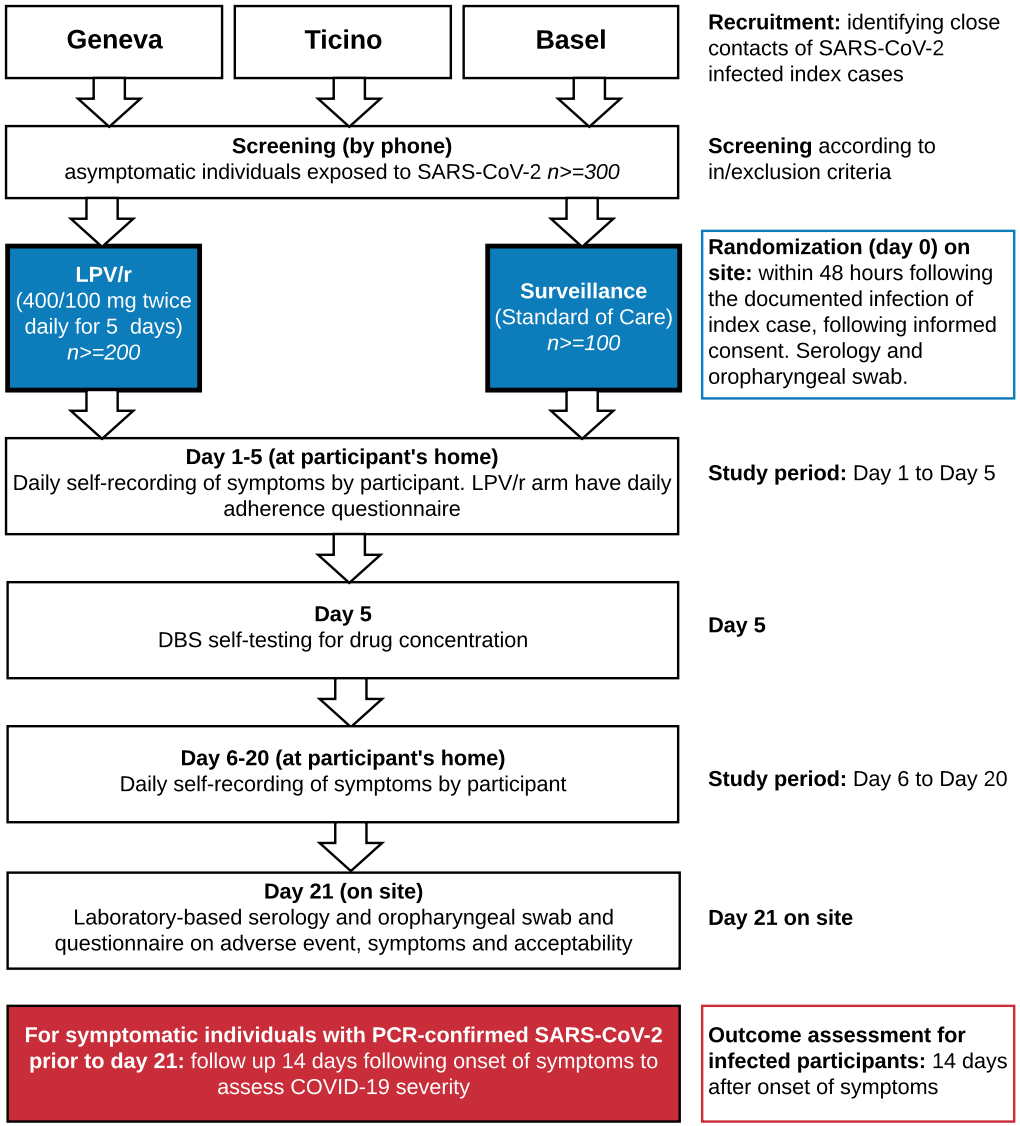
AC and NL conceived the overall trial, including the overall design and therapeutic candidates and are the PI and Co-PI. AC, NL, MS, TP, MPS, and AM designed the trial, including decision on intervention dosage and administration, study endpoints and procedures. MS and TP developed all statistical aspects of the trial design. MS will perform the analysing the trial data, with the support of TP. DL and SF contributed to the formulation of recruitment via the cantonal health authorities, together with MB and CS. AM and DA developed the patient and laboratory pathways. BM, LK, and LD helped with all laboratory aspects of the trial design. MS wrote the first draft of this manuscript. GJN, SR, AM, MPS, NL and AC are the study physicians and together with FJ, TA, HS, JS, MB, IG, FC who manage the respective COVID-19 patients or infectious diseases unit contributed to the patient pathway. All authors contributed to the re-drafting of the manuscript and in the process of approving the final draft.

Conflicts of interest: We declare that we have no conflicts of interests.

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

References

1. European AIDS Clinical Society. *Guidelines*. http://www.europeanaidsclinicalsociety.org/index.php?option=com_content&view=article&id=59&Itemid=41 (2019).
2. World Health Organization. WHO | Antiretroviral therapy for HIV infection in adults and adolescents. http://www.who.int/hiv/pub/arv/adult/en/index.html.
3. Anand, K. *et al.* Structure of coronavirus main proteinase reveals combination of a chymotrypsin fold with an extra α-helical domain. *The EMBO Journal* **21**, 3213–3224 (2002).
4. Lin, C.-W. *et al.* Characterization of trans- and cis-cleavage activity of the SARS coronavirus 3CLpro protease: basis for the in vitro screening of anti-SARS drugs. *FEBS Letters* **574**, 131–137 (2004).
5. Harrison, C. Coronavirus puts drug repurposing on the fast track. *Nature Biotechnology* (2020) doi:10.1038/d41587-020-00003-1.
6. World Health Organization. WHO | WHO Model Lists of Essential Medicines. *WHO* http://www.who.int/medicines/publications/essentialmedicines/en/.


Geneva
Ticino
Basel
Recruitment: identifying close contacts of SARS-CoV-2 infected index cases
Screening (by phone)
asymptomatic individuals exposed to SARS-CoV-2 n>=300
Screening according to in/exclusion criteria
LPV/r
(400/100 mg twice daily for 5 days)
n>=200
Surveillance
(Standard of Care)
n>=100
Randomization (day 0) on site: within 48 hours following the documented infection of index case, following informed consent. Serology and oropharyngeal swab.
Day 1-5 (at participant's home)
Daily self-recording of symptoms by participant. LPV/r arm have daily adherence questionnaire
Study period: Day 1 to Day 5
Day 5
DBS self-testing for drug concentration
Day 5
Day 6-20 (at participant's home)
Daily self-recording of symptoms by participant
Study period: Day 6 to Day 20
Day 21 (on site)
Laboratory-based serology and oropharyngeal swab and questionnaire on adverse event, symptoms and acceptability
Day 21 on site
For symptomatic individuals with PCR-confirmed SARS-CoV-2 prior to day 21: follow up 14 days following onset of symptoms to assess COVID-19 severity
Outcome assessment for infected participants: 14 days after onset of symptoms

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 SPIRITreporting 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

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,16
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	ICF
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants,			

interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
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
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
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
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10-11
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
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
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
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including	11

		clinical and statistical assumptions supporting any sample size calculations	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10-11
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate	13-14

		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	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13-14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13-14
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12-13
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12-13
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13-z14
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13-14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16

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
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#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
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplement
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

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 agregée
Director of the HIV Unite

10. Scientific Title
Chef de Clinique Scientifique
Epidemiologist

11. Countries of Recruitement
Switzerland

12. Health Conditions(s) or Problem(s) Studied
COVID-19

13. Intervention(s)

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 Citeria

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°) 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. Recuitement 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

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