**Supplement 1: Initial COPEP protocol (version 1.0, 10.04.2020)**

Clinical Study Protocol

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

**COPEP-trial**

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| Study Type: | Clinical trial with Investigational Medicinal Product (IMP) |
| Study Categorisation: | HRA category B |
| Study Registration: | Anticipated study registration  Clinicaltrials.gov  EU Clinical Trials Registery (EU-CTR)  Swiss National Clinical trial Portal (SNCTP via BASEC) |
| Study Identifier: | COPEP Trial |
| Sponsor, Principal- Investigator:  Co- Principal Investigator: | Prof. Alexandra Calmy  Prof. Niklaus Labhardt |
| Investigational Product: | LPV/r 400/100mg twice a day for 5 days  Hydroxychloroquine single dose of 800mg |
| Protocol Version and Date: | Version 1.0, 10.04.2020 |

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Signature Page(s)

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| Study number | Study registry and registration number; pending |
| Study Title | Efficacy of pragmatic same-day ring prophylaxis for individuals exposed to SARS-CoV-2 in Switzerland: an open-label cluster randomized trial (COPEP-trial) |

The Sponsor-Investigator and trial statistician have approved the protocol version 1.0 of 10.04.2020 and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

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I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

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**Site: Basel**

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I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

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**Study synopsis**

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| **Sponsor / Sponsor-Investigator** | Prof. Alexandra Calmy |
| **Study Title:** | Efficacy of pragmatic same-day ring prophylaxis for individuals exposed to SARS-CoV-2 in Switzerland: an open-label cluster randomized trial (COPEP-trial) |
| **Short Title / Study ID:** | COPEP Trial |
| **Protocol Version and Date:** | Version 1.0, 10.04.2020 |
| **Trial registration:** | Anticipated:  Clinicaltrials.gov  EU Clinical Trials Registery (EU-CTR)  Swiss National Clinical trial Portal (SNCTP via BASEC) |
| **Study category and Rationale** | Category B according to article 19 of Clinical Trials Classification:   * Both hydroxychloroquine (HCQ) and lopinavir/ritonavir (LPV/r) are authorised in Switzerland * This trial is proposing an indication different from that specified in the prescribing information. |
| **Clinical Phase:** | Phase 3 |
| **Background and Rationale:** | Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2) is a novel coronavirus strain that was declared a pandemic by the WHO on 11th March 2020.  The availability of simple and effective prophylaxis to prevent either SARS-CoV-2 infection and/or Coronavirus Disease (COVID-19) will play a crucial role in protecting at risk individuals including front-line workers. Furthermore, effective prophylaxis will provide an important tool both in order to reopen countries from confinement measures and as a rapid containment tool to protect non-immune individuals during subsequent outbreaks.  Here we propose to investigate prophylactic strategies that can be prescribed the same day with limited laboratory exams. Two drugs were identified as strong candidates for prophylaxis; HCQ, an anti-malarial and arthritis drug,1 and LPV/r, a boosted protease inhibitor used for the treatment of HIV.2,3 Their efficacy will be evaluated in an open-label, cluster randomized control trial against surveillance. All three arms will include active surveillance with daily questionnaires and a prompt oro-pharyngeal swab upon the occurrence of COVID-19 associated symptoms.  This trial will provide fundamental evidence on both the efficacy and feasibility of a prophylaxis for asymptomatic individuals following a documented exposure to SARS-CoV-2. |
| **Objective(s):** | **Main:**   * To assess, in a three-arm open-label cluster randomized clinical trial, the efficacy of a single-dose of HCQ treatment and of a 5-day course of LPV/r treatment in preventing COVID-19 in asymptomatic individuals exposed to a SARS-CoV-2 documented index patient, compared to surveillance alone.   **Secondary:**   * To assess the efficacy of single-dose of HCQ treatment and a 5-days course of LPV/r in preventing SARS-CoV-2 infection (assessed by SARS-CoV-2-specific PCR or spike protein-based serological assays detecting IgG and IgA isotypes) in asymptomatic individuals exposed to a SARS-CoV-2 documented index patient, compared to surveillance alone; * To assess the ability of primary or secondary prophylaxis with a single-dose HCQ treatment or a 5-days course of LPV/r to reduce the clinical severity of COVID-19, compared to surveillance alone; * To evaluate the safety, adherence and acceptability of a single-dose HCQ and LPV/r-based prophylaxis in the context of the COVID-19 pandemic. |
| **Outcome(s):** | **Primary endpoint:**   * 21-day incidence of COVID-19 in individuals exposed to SARS-CoV-2 who are asymptomatic at baseline (intent-to-treat (ITT) analysis).   **Secondary endpoints:**   * 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) * 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 * Severity of clinical COVID-19 on a 7-point ordinal scale (1: not hospitalized, no limitations on activities, 2: not hospitalized, limitation on activities, 3: hospitalized, not requiring supplemental oxygen, 4: hospitalized, requiring supplemental oxygen, 5: hospitalized, on non-invasive mechanical ventilation 6: hospitalized, on invasive mechanical ventilation or ECMO and 7: death) * Serious adverse events   **Explorative endpoints**   * Acceptability of a prophylaxis for COVID-19 * 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. |
|  | **We use the following definitions:**  **SARS-CoV-2 infection:**   * a positive PCR for SARS-CoV-2 (oro-pharyngeal swab) amongst those with a negative PCR at baseline   AND/OR   * 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 immunofluoresence assay (S-rIFA)   **COVID-19:** ≥ 1 symptom compatible with COVID-19 (cough, odynodysphagia, dyspnea, anosmia, headache, myalgia, asthenia, nausea, diarrhea, elevated temperature (>38°) and:   * a positive PCR for SARS-CoV-2 in oro-paryngeal swab   AND/OR   * 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 immunofluoresence assay (S-rIFA)   **Seroconversion for SARS-CoV-2**:  Negative results for IgG in ELISA at baseline and:   * positive result for IgG in ELISA at day 21   OR   * 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:   * positive or doubtful result for IgA in ELISA at day 21   AND   * Positive result for IgG in S-rIFA at day 21 |
| **Study design:** | 1:1:1 cluster randomized, open-label trial |
| **Inclusion / Exclusion criteria:** | **Inclusion criteria:**   1. Documented close contact with a PCR-confirmed SARS-CoV-2 positive individual within the last 48 hours; 2. ≥ 18 years of age; 3. Informed consent as 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 lopinavir/ritonavir and hydroxychloroquine using the website [www.covid19-druginteractions.org](http://www.covid19-druginteractions.org) 9. Inability to be followed-up for the trial period   \*Where necessary, additional biological and clinical assessment will be performed, based on clinical judgement.  **We use the following definition:**  A close contact is defined as a person who spent >15 minutes in < 2 meter distance, who 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 PCR-confirmed SARS-CoV-2 diagnosis of index case or 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. |
| **Measurements and procedures:** | **Screening:** Asymptomatic individuals will be screened on the phone if they had a close contact with newly diagnosed SARS-CoV-2 index cases, as early as possible, and invited to a baseline visit on the same day and not later than 48 hours after the documented diagnosis of the index case.  **Randomisation/baseline:** Individuals will undergo the baseline visit on site. Oro-pharyngeal swab and SARS-CoV-2 serology will be performed, and participants will be randomised 1:1:1 to either a single dose of 800 mg HCQ (4 tablets of 200 mg), LPV/r 400/100 mg twice daily for 5 days versus surveillance. The single-dose of HCQ and the first dose of LPVr will be taken during the baseline visit, as directly observed therapy. All swabs and serologies will be batch analysed at the end of the study, as per the current gold standard in a central accredited laboratory.  **Day 1-21:** 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; red alert for severe symptoms (dyspnea, fever) and amber for non severe symptom (all other symptoms). The online questionnaire also send reminders at the end of the day in case of non-completion and triggers an alerts if particpants do not complete the questionnaire for 2 consecutive days. The team will contact the participant as soon as possible and no later than the 24 hours after a red alert was triggered. For all other alerts (amber alert and non-completion) the team will contact the participant as soon as possible and no later than the next working day. Paper questionnaires will be made available for those without internet infastructure, with the option of daily phone or self-reported outcomes.  Participant who report COVID-related symptoms (dyspnea, cough, fever (>38.0C), anosmia), will be asked to come on site for an extra visit and undergo clinical assessment and an oro-pharyngeal swab to confirm/exclude SARS-CoV-2 infection. If found positive, participant will be provided with appropriate care, as per local protocol.  Particpants on the LPV/r arms will take their medication as instructed for 5 days. The daily online questionnaire for particpants on LPV/r will consist of additional daily questions about their adherence to LPV/r between baseline and Day 5.  **Day 5:** This will consist of a home-visit for a capillary puncture on dry blood spot (DBS) to assess levels of HCQ and LPV/r in all participants. In addition, on Day 5 all participants will receive additional questions in their daily online questionnaire, enquiring about adverse events.  **Day 21:** Participants will undergo a follow-up visit on site. This will include a final questionnaire on symptoms, a second round of questions on adverse events and a questionnaire on acceptability of a prophyalxis. This visit will also include an oro-pharyngeal swab and a serology. These will be batch analysed at the end of the study, as per the current gold standard in a central accredited laboratory.  **Follow-up for COVID-19 participants:** all participants who develop COVID-19 during the study will be followed as per the standard of care. A follow-up visit at Day 14 after onset onset of symptoms will be conducted, in order to establish severity of disease. |
| **Study Product / Intervention:** | Hydroxychloroquine sulfate, 800 mg (4 x 200mg) single dose (PO)  LPV/r, 400mg/100mg (2x 100mg/50mg) twice daily for 5 days (bid, PO) |
| **Control Intervention (if applicable):** | Surveillance |
| **Number of Participants with Rationale:** | Total number of participants: 420  Number in each arm: 140  The sample size assumes that without treatment 20% of close contacts will develop COVID-19. To detect a relative risk reduction of 60% (from 20% to 8%), with a power of 80%, an alpha of 5% and accounting for design effect (DE) of cluster design of circa 1.1, calculated sample size is n=140 close contacts per arm, 420 participants in total. |
| **Study Duration:** | 4.5 months |
| **Study Schedule:** | First-Participant-In (planned): Mid-April 2020  Last-Participant-Out (planned): August 2020 |
| **Investigator(s):** | Sponsor, Principal-Investigator:   * Prof Alexandra Calmy, University Hospital of Geneva, Department of Infectious Diseases   Principal-Investigator:   * Prof Niklaus Labhardt, University Hospital of Basel, Department of Infectious Diseases and Hospital Epidemiology and Swiss Tropical and Public Health Institute (Swiss TPH)   Co-Investigators:   * Prof. Laurent Kaiser, Head of the Virology Laboratory, Division of Infectious Diseases, HUG * Prof. Dr. Francois Chappuis, Department of Primary Care, Infection Control Programme, HUG * Prof. Dr. Idris Guessous, Departement de médecine de premier recours, HUG * Dre. Frédérique Jacquerioz, Service de médecine de premier recours, HUG * Dr. Dan Lebowitz, Infection Control Programme, HUG and Direction Générale de la Santé, Genève * Prof. Thomas Agoritsas, Service of Internal Medicine, HUG * Dre. Annalisa Marinosci, HIV Unit, Division of Infectious Diseases, HUG * Dr. Diego Andrey, HIV Unit, Division of Infectious Diseases, HUG * Dre. Mikaela Smit, HIV Unit, Division of Infectious Diseases, HUG * Dr. Benjamin Meyer, Center for Vaccinology, University of Geneva * Dr. Hervé Spechbach, Service de médecine de premier recours, HUG * Dr. Julien Salamun, Division de médecine de premier recours, HUG * Prof. Dr Manuel Battegay, University Hospital Basel, Department of Infectious Diseases and Hospital Epidemiology * Dr. Marcel Stoeckle, University Hospital of Basel, Department of Infectious Diseases and Hospital Epidemiology * Dr. Simon Fuchs, Gesundheitsdepartement des Kantons Basel Stadt * Dr. Giovanni Jacopo Nicoletti, Swiss Tropical and Public Health Institute * Moritz Back, Gesundheitsdepartement des Kantons Basel-Stadt * Carla Schaubhut, dipl. Ärztin, Gesundheitsdepartement des Kantons Basel-Stadt * Dr. Silvio Ragozzino, University Hospital Basel, Department of Infectious Diseases and Hospital Epidemiology * Dr. Laurent Decosterd, Laboratory of Clinical Pharmacology, Lausanne University Hospital and University of Lausanne |
| **Study Centre(s):** | Multicentric:   * **Geneva:** University Hospital of Geneva, Division of Infectious Diseases * **Basel:** University Hospital of Basel, Department of Infectious Diseases and Hospital Epidemiology in collaboration with Swiss Tropical and Public Health Institute |
| **Statistical Considerations:** | Sample size  The sample size is calculated to power the primary endpoint of COVID-19, as it requires the larger sample size. The sample size 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% (from 20% to 8%), with a power of 80%, an alpha of 5% and accounting for design effect (DE) of cluster design of circa 1.1 (based on , where DE stands for design effect, n=3 denotes the average cluster size, and ρ=0.05 is the intraclass correlation coefficient).  This results in a sample size n=140 close contacts per arm, 420 participants in total.  Basic description of statistical analysis  We will perform an intention to treat analysis (ITT), including all individuals who were randomized. Both intervention arms, LPV/r and HCQ, will be compared to the surveillance arm, using separate indicator variables for the active treatment arms, no adjustement for multiplicity will be performed. We will use mixed complementary log-log regression models for the main analysis. The outcome variable will be the occurrence of COVID-19 by day 21.  We will perform a modified ITT for the first of the secondary endpoints, a Manne-Whitney test for severity of disease and Chi-Square tests for adverse events. |
| **GCP Statement:** | This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements. |

**Abbreviations**

|  |  |
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| AE | Adverse Event |
| BASEC | Business Administration System for Ethical Committees, (<https://submissions.swissethics.ch/en/>) |
| CA | Competent Authority (e.g. Swissmedic) |
| CEC | Competent Ethics Committee |
| CRF | Case Report Form |
| ClinO | Ordinance on Clinical Trials in Human Research *(in German: KlinV, in French: Oclin, in Italian: OSRUm)* |
| COVID-19 | Coronavirus Disease 19 |
| eCRF | Electronic Case Report Form |
| CTCAE | Common terminology criteria for adverse events |
| DBS | Dried blood spots |
| DSUR | Development safety update report |
| GCP | Good Clinical Practice |
| IB | Investigator’s Brochure |
| Ho | Null hypothesis |
| H1 | Alternative hypothesis |
| HCQ | Hydroxychloroquine |
| HIV | Human Immunodeficiency virus |
| HRA | Federal Act on Research involving Human Beings *(in German: HFG, in French: LRH, in Italian: LRUm)* |
| IMP | Investigational Medicinal Product |
| IIT | Investigator-initiated Trial |
| ISO | International Organisation for Standardisation |
| ITT | Intention to treat |
| LPV/r | Lopinavir/ritonavir |
| PI | Principal Investigator |
| SARS-CoV-2 | Severe Acute Respiratory Coronavirus 2 |
| SDV | Source Data Verification |
| SOP | Standard Operating Procedure |
| SmPC | Summary of product characteristics |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TMF | Trial Master File |

**Study schedule**

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|  | **Screening** | **Baseline: Day 0** | **Day 1-21**  **(Daily self-assessment)** | **Day 5** | **Day 21** |
|  | Phone | On-site | Participant’s home | Participant’s home | On-site |
| **Informed consent procedure** | X1 | X3 |  |  |  |
| **Eligibility check; inclusion and exclusion criteria** | X2 | X4 |  |  |  |
| **Oro-pharyngeal swab** |  | X | Prompted by COVID-19 compatible symptoms5 |  | X |
| **Laboratory-based serology** |  | X |  |  | X |
| **Randomization** |  | X |  |  |  |
| **Administration of prophylaxis6** |  | X | X7 |  |  |
| **Daily Self-assessment** |  |  | X |  |  |
| **Questionnaire on adherence of intervention78** |  |  | X78 |  |  |
| **Questionnaire on adverse events** |  |  |  | X | X |
| **Dried blood spot collection for plasma 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 oro-pharyngeal 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 particpants randomized to HCQ or LPV/r, as directly observed therapy

7 Only for particpants randomized to LPV/r

8 Only between baseline and Day 5

# STUDY ADMINISTRATIVE STRUCTURE

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## 1.4 Statistician ("Biostatistician")

**Dre. Mikaela Smit (Epidemiologist),** Division of Infectious Diseases, Hôpitaux Universitaires de Genève (HUG), Rue Gabrielle Perret-Gentil 4, 1211 Genève, +41 22 372 9809, Mikaela.Smit@hcuge.ch

* **Dr. Thomas Perneger (Methodologist),** Centre de Recherche Clinique (CRC), Hôpitaux Universitaires de Genève (HUG), Rue Gabrielle Perret-Gentil 4, +41 22 372 90371211 Genève, [Thomas.Perneger@hcuge.ch](mailto:Thomas.Perneger@hcuge.ch)

## 1.5 Laboratories

* Geneva Virology Laboratory, HUG (head: Laurent Kaiser)
* Laboratory of clinical Pharmacology CHUV (head: Laurent Decosterd): drugs levels in DBS by mass spectrometry.

## 1.6 Monitoring institution

Clinical Trial Unit (CTU) of Geneva University Hospital will be responsible for developing a central monitoring plan. The Geneva CTU will also be responsible for the monitoring activities in Geneva Site. The Clinical Operations Unit of the Swiss Tropical and Public Health Institute will be responsible for the monitoring activities in Basel Site.

## Data Safety Monitoring Committee

* **Dr. Daniel R. Kuritzkes,**Chief Division of Infectious Diseases, Brigham and Women’s Hospital, Boston, MA Harriet Ryan Albee Professor of Medicine, Harvard Medical School, Boston, MA
* **Dr. Jennifer Cohn,** MD, MPH, Assistant Professor, Division of Infectious Diseases, Perelman School of Medicine, University of Pennsylvania
* **Dr. Bernard Cerutti,** PhD, MPH, University of Geneva, Faculty of Medicine, Geneva
* **Dr. Nathan Ford,** PhD Departement of HIV, Hepatitis, and Sexually Transmitted Infections, World Health Organization, Geneva

## 1.8 Any other relevant Committee, Person, Organisation, Institution

- **Tamara Da Silva**, Clinical Research Consultant at GALSER SA, chemin Jean-Baptiste Vandelle 3A, 1290 Versoix, [td@galser.ch](mailto:td@galser.ch), 079 955 8252; Study protocol writing, Study set-up and Study coordination

- **Charlotte Barbieux,** Clinical Research Associate at HIV Unit, Division of Infectious diseases, HUG, Rue Gabrielle-Perret-Gentil 4, 1211 Genève, [charlotte.barbieux@hcuge.ch](mailto:charlotte.barbieux@hcuge.ch), 078 951 9826; Study set up and Study coordination

# ETHICAL AND REGULATORY ASPECTS

## 2.1 Study registration

The study will be registered in clinicaltrials.gov registry, EU Clinical Trials Registry (EU-CTR) and in the Swiss National Clinical trial Portal (SNCTP via BASEC) in French and in German.

## 2.2 Categorisation of study

This study is Category B according to Article 19 of Clinical Trials Classification:

* Both **HCQ** and **LPV/r are authorised in Switzerland**
* This trial is proposing an **indication different from that specified in the prescribing information**.

## 2.3 Competent Ethics Committee (CEC)

The Sponsor- Principal Investigator ensures that approval from CEC is sought for the clinical study. It is the Investigators duty to report all changes in the research activity and all unanticipated problems involving risks to humans.

No changes are made to the protocol without prior Sponsor and CEC approval, except where necessary to eliminate apparent immediate hazards to study participants. Such urgent changes to the protocol due to immediate hazards must be reported to the Sponsor within 72h.

Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.10.

## 2.4 Competent Authorities (CA)

This study is a Category B study, according to article 19 of Clinical Trials Classification.

The trial is submitted for Swissmedic approval.

## 2.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, the Swiss Law and Swiss regulatory authority’s requirements. The CEC will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

## 2.6 Declaration of interest

The Sponsor- Principal Investigator and all Investigators have no conflict of interest to declare. They have no financial relationships with any organisations that might have an interest in the present study, neither other relationships (or activities) that could appear to influence the results of the study.

## 2.7 Patient Information and Informed Consent

**2.7.1 Study information provided by phone**

- The nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail will be clearly explained to each participant. The informed consent will be shared preferably by e-mail, if necessary read-out-loud over the phone.

- Participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.

- Participants will be informed that there is no trial participation renumeration.

**2.7.2 Study information on study site**

- Participants will be provided with the Participant Infromation Sheet and the Informed Consent Form, describing the study and providing all necessary information.

- Both participant and medical investigator will sign and date the Informed Consent Form. A copy of the signed document will be given to the participant and the original will be retained as part of the study records.

- The formal consent of a participant, using the approved consent form, will be obtained before the participant is randomized.

## 2.8 Participant privacy and confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers.

For data verification purposes, authorised representatives of the Sponsor (e.g. auditors, monitors), a competent authority, or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants’ medical history.

## 2.9 Early termination of the study

The Sponsor-Investigator, or the Competent Authority, may terminate the study prematurely according to certain circumstances, for example:

* ethical concerns,
* insufficient participant recruitment,
* when the safety of the participants is doubtful or at risk
* alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
* early evidence of benefit or harm of the experimental intervention

## 2.10 Protocol amendments

Substantial amendments are only implemented after CEC approval.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC. Such deviations shall be documented and reported to the sponsor and the CEC as soon as possible. All Non-substantial amendments are communicated to the CEC within the Annual Safety Report (ASR).

# 3. Background and Rationale

## 3.1 Background and Rationale

Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2) is a novel coronavirus strain that was declared a pandemic by the World Health Organization on 11th March 2020. The novel coronavirus generates intense pressure on health systems across the world, with the sudden and uncontrolled influx of severe cases causing depletion of all hospital-based resources.

Containing the pandemic will necessitate a multi-pronged strategy, including immunization, treatment, and (primary and secondary) prophylaxis. The latter is required for the containment of future outbreaks of the disease in non-immunized populations, but also as a key preventive measure for vulnerable populations in absence of safe and effective treatments. Prophylaxis will also be facilitate the reopening of countries, while protecting its population and health care infastructure. Finally, this first pandemic wave will undoubtedly be followed by subsequent outbreaks and it seems inconceivable that subsequent outbreaks will be accompanied by the same strict isolation measures seen during this current pandemic outbreak.

A simple and effective prophylactic strategy, that can be prescribed the same day with limited laboratory exams, will provide a crucial preventative strategy for both the current pandemic and future outbreaks. Even if effective vaccination and treatment become available, prophylaxis will play an important role in safeguarding individuals at highest risk, which include front-line health care workers, and will be crucial for rapid containment of future epidemics.

We identify two strong candidates for prophylaxis, HCQ and LPV/r. 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 (Appendix 4).4–6 HCQ acts as anendosomal acidification fusion inhibitor and thus blocks viral entry into the host cell (Appendix 3).7

This trial will provide fundamental evidence on both the efficacy and feasibility of same-day prophylaxis in preventing infections and disease. The strategy evaluated in this protocol is of a rapid, simple prophylaxis for asymptomatic individuals with a documented exposure to SARS-CoV-2.

## 3.2 Investigational Product and Indication

Two drugs were identified as strong candidates for prophylaxis ;

1. **Lopinavir/ritonavir (LPV/r): protease inhibitors indicated for the treatment of HIV**2,3

In this trial we will use LPV/r, 400mg/100mg twice daily for 5 days (bid, PO)

The high genetic-barrier of LPV/r means that it can be prescribed the same-day without risk of developing HIV-related resistance even in HIV-undiagnosed patients.

1. **Hydroxychloroquine (HCQ): indicated to treat malarial, lupus and rheumatoid arthritis.**1

In this trial we will use Hydroxychloroquine sulfate, 800 mg (4 x 200mg) single dose (PO)

HCQ, is a chloroquine derivative, which has lower toxicity and equivalent efficacy profile compared to chloroquine.8,9

Both LPV/r and HCQ are licensed in Switzerland and are available globally and at low cost, including in low-and-middle income countries (LMICs), due to their on-label use for HIV and malaria/lupus/rheumatologic diseases.

Demonstrating their efficacy as prophylaxis would thus not only be useful in high-income countries but certainly assist counties in LMICs in safeguarding their fragile health systems.

## 3.3 Preclinical Evidence

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 (Appendix 4).4–6

Several authors report high in-vitro activity of chloroquine against SARS-CoV-2 and the derivate HCQ shows even higher activity at less toxicity10,11. Several studies have demonstrated that chloroquine is effective in limiting SARS-CoV-2 replication *in vitro* and that it may be a suitable drug for chemoprophylaxis against SARS-CoV-2 (Appendix 3). 12,13 HCQ acts as anendosomal acidification fusion inhibitor and thus blocks viral entry into the host cell.7 Compared to LPV/r, HCQ has the potential advantage of single-dose prophylaxis due to its long half-life and a lower potential of drug interactions in individuals on chronic medication.8

Both drugs are licensed in Switzerland, and are available globally and at low cost.

## 3.4 Clinical Evidence to Date

**Evidence for HCQ:**

Early clinical trial data from China and France have shown that treated patients had significant reduction in viral load carriage, fewer exacerbations, improved lung imaging, promoted virus-negative conversion and shortening disease course (Appendix 3).14,15

A small open-label randomized trial conducted in China showed a faster improvement of pneumonia and less progress to severe illness as compared to the control group16. This trial has, however, been criticized for substantial methodological flaws17. A very controversial observational study from research group of Didier Raoult reports that HCQ in combination with arithromycin was associated to faster decline in viral shedding18. A second study from another group in France found, however, no effect of HCQ on rapid viral clearence19. On March 29, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization to allow HCQ in the treatment of COVID-1920. However, as of writing of this proposal, there is no real evidence for or against the use of HCQ in COVID-19.

**Evidence for LPV/r:**

LPV/r has been proposed as both therapeutic and prophylactic candidate for SARS-CoV-2 and is included in both Chinese guidelines 21,22 and in protocols used in Italian hospitals for patients with mild disease. Although darunavir/ritonavir, another group of protease inhibitors, has also been put forward as a hypothetical candidate, current evidence does not support its use in SARS-CoV-2 infection.23 Two studies reported a possible protective effect of LPV/r as post-exposure prophylaxis.24 One study specifically tested the chemoprophylactic effect of LPV/r. The study, from South Korea, retrospectively enrolled health care workers considered at high risk of MERS-CoV infection.25 Of 22 health care workers given post-exposure prophylaxis (PEP) comprising ribavirin and LPV/r, none were infected; this compared to 9 of 21 health care workers not given PEP who became infected (0% vs. 28.6%; Odds ratio = 0.405, 95% confidence interval = 0.274–0.599; *P* = 0.009).25 The second study, a retrospective observational study from China, reported that none of 19 HIV-positive patients hospitalized on the same floor as SARS patients contracted the disease, whereas six of 28 medical workers contracted SARS while caring for these patients.26Of the 19 patients, 11 were on differing regimens of antiretroviral therapy; two received regimens containing boosted PIs.26

The absence of solid evidence on the efficacy of LPV/r against SARS-CoV-2 acquisition and Covid-19 justifies formal investigation of these as PEP candidates.

## 3.5 Dose Rationale

**Lopinavir/ritonavir (LPV/r):**

Study dose and intake duration: 400/100 mg (2 tablets of 200/50mg) twice daily for 5 days.

Based on currently available evidence, and in accordance with current use of LPV/r in COVID-19 treatment at the Geneva University Hospitals, we propose a similar duration of 5 days LPV/r for prophylaxis .

**Hydroxychloroquine sulfate (HCQ):**

Study dose and intake duration: 800 mg (4 tablets of 200 mg), single-dose.

A single dose is considered to be a very practical option in real-life and believed to be effective based on its long half-life (30 days). Pharmacokinetic studies, including a simulation by Prof Youssef Daali (HUG) demonstrated that pulmonary tissue concentration is extremely high following a single dose of 800 mg of HCQ sulfate (ref. Caroline Samer, personal communication), and that the half life in the lung tissue is as long as in the blood. HCQ is currently used in several settings, including the University Hospitals in Switzerland (including HUG) to treat COVID-19.

## 3.6 Explanation for choice of comparator

In this study, the comparator arm is the surveillance arm without use of an investigational drug, which is the current standard of care.

## 3.7 Risks / Benefits

**Risks:**

No major risks are to declare;

* Both active substances are approved in Switzerland and globally, and have been used in clinical care for many years;
* The HCQ dose we are using is below the dose normally used to treat acute malaria;
* The daily LPV/r dose we are using corresponds to the routine dose given for HIV, but is limited to 5 days as opposed to lifelong treatment in HIV patients;
* The safety profile both drugs is well described and regularly prescribed doses will not be exceeded in this protocol;
* The contraindications of both drugs are well known and will be respected (Appendix 1 and 2)

**Minor risks:**

* Contacts of index cases are advised to remain at home for 10 days. The baseline visit is an on-site visit in the hospital and may be counter this current recommendation regarding self-isolation upon a documented contact. We have considered another alternative which would be to have a dedicated member of the study team travel to participant's home; but in this case we would expose the study member to SARS-CoV-2 in an environment that is *certain* to have one (the index case). Whereas if the participant comes to the hospital, there is only a *possible* exposure. Moreover, individuals will be asked to respect all current recommendations when they travel to site: they will have to wear a mask, avoid public transport, and respect social distancing. Finally, participants will be seen in a dedicated space, and will not be in contact with COVID-19 patients.

**Benefits:**

* Currently, as part of the routine, contacts of SARS-CoV-2 index cases are usually not closely monitored, do not get tested for SARS-CoV-2. All participants will benefit from active surveillance beyond the current standard of care in healthcare settings in Switzerland and may provide the benefit or early identification and treatment of cases. Beyond the benefits to the individual, early detection and treatement has proven to be efficacious in other settings.
* In addition, the study has a potential public health benefit, by contributing to containement of SARS-CoV-2 through tracing and testing of contacts, which is not done in Switzerland.
* For the individual, the benefit is that they will have a oro-phyrangeal swab and serology, to know their status. This is not routine currently.

## 3.8 Justification of choice of study population

The population to be studied comprises asymptomatic individuals exposed to individuals diagnosed with SARS-CoV-2, including healthcare workers and other individuals who are at high risk of getting infected. These would be the target population of prophylaxis both during the current epidemic and subsequent epidemics. Besides, the contribution of asymptomatic (or pauci-symptomatic) individuals to the transmission events is yet not clarified and rarely addressed in the current clinical trials.

# 4. STUDY OBJECTIVES

## 4.1 Overall Objective

The overall purpose of the study is to assess the efficacy, safety and acceptability of same-day HCQ and LPV/r-based prophylaxis compared to surveillance alone in asymptomatic individuals exposed to individuals diagnosed with SARS-CoV-2.

## 4.2 Primary Objective

To assess, in a three-arm open-label cluster randomized clinical trial, the efficacy of a single-dose of HCQ treatment and of a 5-day course of LPV/r treatment in preventing COVID-19 in asymptomatic individuals exposed to a SARS-CoV-2 documented index patient, compared to surveillance alone.

## 4.3 Secondary Objectives

* To assess the efficacy of single-dose of HCQ treatment and a 5-days course of LPV/r in preventing SARS-CoV-2 infection (assessed by SARS-CoV-2 PCR or IgG/IgA-based serologies) in asymptomatic individuals exposed to a SARS-CoV-2 documented index patient, compared to surveillance alone;
* To assess the ability of primary or secondary prophylaxis with a single-dose HCQ treatment or a 5-days course of LPV/r to reduce the clinical severity of COVID-19, compared to surveillance alone;
* To evaluate the safety, adherence and acceptability of a single-dose HCQ and LPV/r-based prophylaxis in the context of the COVID-19 pandemic.

## 4.4 Safety Objectives

We will collect information on adverse events for each participant on Day 5 (following the end of the study intervention) as well as Day 21. In addition, participants can report adverse events to the team, via the dedicated study line. We will compare the ocurrence of adverse events between the three arms.

# 5. STUDY OUTCOMES

**Definitions:**

**SARS-CoV-2 infection:**

* a positive PCR for SARS-CoV-2 (oro-pharyngeal swab) amongst those with a negative PCR at baseline

AND/OR

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

**COVID-19:** ≥ 1 symptom compatible with COVID-19 (cough, odynodysphagia, dyspnea, anosmia, headache, myalgia, asthenia, nausea, diarrhea, elevated temperature (>38°)) and:

* a positive PCR for SARS-CoV-2 in oro-pharyngeal swab

AND/OR

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

**Seroconversion for SARS-CoV-2**

Negative results for IgG in ELISA at baseline and:

* positive result for IgG in ELISA at day 21

OR

* 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:

* positive or doubtful result for IgA in ELISA at day 21

AND

* Positive result for IgG in S-rIFA at day 21

## 5.1 Primary Outcome

This trial has one primary endpoint:

* 21-day incidence of COVID-19 in individuals exposed to SARS-CoV-2 who are asymptomatic at baseline (intent-to-treat (ITT) analysis).

## 5.2 Secondary Outcomes

* 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)
* 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)
* Severity of clinical COVID-19 on a 7-point ordinal scale (1: not hospitalized, no limitations on activities, 2: not hospitalized, limitation on activities, 3: hospitalized, not requiring supplemental oxygen, 4: hospitalized, requiring supplemental oxygen, 5: hospitalized, on non-invasive mechanical ventilation 6: hospitalized, on invasive mechanical ventilation or ECMO and 7: death)
* Serious adverse events

## 5.3 Explorative endpoints

* Acceptability of a prophylaxis for COVID-19
* 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.

## 5.4 Other Outcomes of Interest

Not applicable.

## 5.5 Safety Outcomes

We will collect information on adverse events for each participant on Day 5 (following the end of the study intervention) as well as Day 21. In addition, participants can report adverse events to the team, via the dedicated study line. We will compare the ocurrance of adverse events between the three arms.

# 6. STUDY DESIGN

## 6.1 General study design and justification of design

This is an open-label, category B, cluster randomised controlled trial, establishing the efficacy of either a single dose of 800 mg HCQ (4 tablets of 200 mg) versus LPV/r 400/100 mg twice daily for 5 days versus surveillance for the prevention of COVID-19.

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) these will be cluster randomized by household. Randomization will be stratified by site (Geneva and Basel). Treatment will be identical within households because of the risk of cross-contamination and problems in implementation of individuals in the same household being allocated to different treatment arms.

We anticipate that an oro-pharyngeal swab between baseline and Day 21 prompted by COVID-19 compatible symptoms will detect the majority of symptomatic infections given the time since contact with a confirmed index case. For serology, we anticipate that by Day 21 after exposure to index-patient the majority with infection will develop IgA and a considerable share IgA and IgG antibodies. Serologies for SARS-CoV-2 are relatively new and it remains unclear if all individuals mount an antibody response and the sensitivity and specificity of these tests. A SARS-CoV-2 serology validation study is currently conducted at the Virology Laboratory at the HUG to define assay cut-offs for the Euroimmun SARS-CoV-2 IgG and IgA ELISA to maximize positive and negative predictive value, define assay cut-offs between which samples are considered doubtful and need further confirmatory assays, i.e. S-rIFA (3) define a serological testing algorithm to confirm SARS-CoV-2 infection in the absence of a positive PCR result. Unpublished results showed the following:

* For ELISA, IgG is more specific than IgA. IgA has a specificity of only around 90%, as determined through negative sera collected in 2013/14 and 2018
* For ELISA, IgG is less sensitive in COVID-19 patients below 3 weeks post onset of symptoms compared to IgA.
* For ELISA, high sensitivity of IgG in COVID-19 patients after 3 weeks post onset of symptoms
* For S-rIFA, IgG has a comparable sensitivity to IgA in COVID-19 patients below 3 weeks post onset of symptoms

(Benjamin Meyer; personal communication)

Interpretation and cut-off of serologies will be adapted following the final results of the serology validation study; all serologies will be performed by batch at this end of the study period and analyzed by the same laboratory at the HUG.

## 6.2 Methods of minimising bias

### 6.2.1 Randomisation

Randomisation will be done in variable-sized blocks (sizes 6 or 9) in random sequence. Randomisation will be stratified by study site. Participants will be assigned to either LPV/r, HCQ or surveillance at randomiaation prior to receiving the PCR-confirmed SARS-CoV-2 results, and will be dispensed the full treatment regimen on-site, including instructions on intake and explanations of side-effects.

We will ensure concealed allocation, the randomisation list will be unknown to recruiters.

### 6.2.2 Blinding procedures

This is an unblinded study but outcome assessment will be done using standardized definitions.

### 6.2.3 Other methods of minimising bias

All laboratory tests will be performed in the same laboratory.

## 6.3 Unblinding Procedures (Code break)

Not applicable.

# 7. STUDY POPULATION

## 7.1 Eligibility criteria

**Inclusion criteria:**

Participants fulfilling all of the following inclusion criteria are eligible for the study:

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 as documented by signature;

**Exclusion criteria\*:**

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

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 (Appendix 3);
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 lopinavir/ritonavir and hydroxychloroquine using established reference material (Appendix 1 and 2) and the website [www.covid19-druginteractions.org](http://www.covid19-druginteractions.org)
9. Inability to be followed-up for the trial period

\*Where necessary, additional biological and clinical assessment will be performed, based on clinical judgement.

## 7.2 Recruitment and screening

**7.2.1 Recruitment:**

Recruitment of participants to this study will be performed through several routes, all operating simultaneously. These planned recruitment ways are described below:

For Geneva Site:

1. The Primary Care Division of the University Hospital of Geneva (“Service de Médecine de Premier Recours” aux HUG) are responsible for testing about 30% of individuals for SARS-CoV-2 in Geneva. As part of this trial, and in addition to the aforementioned procedure, an individual coming in for testing will be informed about the COPEP-trial and asked to provide contact details of their close contacts\* should they be found posititive. The index case will be given the choice to provide these contact informations or alternatively, given the option to tell their contacts about the study and ask them to call research team. Where details are provided, these will be forwarded to the study team upon confirmed diagnosis. We will contact the close contacts and screened for enrolment to the study.
2. As standard of care, the Direction Général de la Santé (DGS) in the Canton of Geneva contacts all individuals tested positive for SARS-CoV-2 by PCR the same-day. During the phone call the following is done as part of routine procedure:
   * Instructions to index-cases on isolation procedures
   * clinical assessment, assessment of risk-factors for severe COVID-19
     + If index-cases at risk or lives alone: daily follow-up by phone or via designated app
     + If index-cases not at risk: call or contact via app on day 5 of isolation and on the day before end of isolation
   * With regard to contacts: same-household individuals receive a letter on quarantaine procedures. No personal contact

As part of this trial and in addition to the ususal procedure of the DGS will mention the COPEP study to the index case and ask if their contact details can be forwarded to our team. The index case will be given the choice to provide their contact informations or alternatively, given the option to tell their contacts about the study and ask them to call research team.

1. Geneva health-care workers will be informed and recruited via social platforms (twitter and facebook) and announcements on the intranet of the Geneva University Hospital.
2. Index-patients who are hospitalized are approached directly by the COPEP-trial team (study-nurses or investigators). In case index patients report contacts and agrees the team to contact them, contacts will be called by the study-nurse or an investigator and assessed for eligibility.

For Basel Site\*\*:

1. Ambulant setting

* As standard of care, the Department of Health of the Canton of Basel-Stadt contacts all individuals tested positive for SARS-CoV-2 by PCR the same-day. During the phone call the following is done as part of routine procedure:
  + Instructions to index-cases on isolation procedures
  + clinical assessment, assessment of risk-factors for severe COVID-19
    - If index-cases at risk or lives alone: daily follow-up by phone or via designated app
    - If index-cases not at risk: call or contact via app on day 5 of isolation and on the day before end of isolation
  + With regard to contacts: same-household individuals receive a letter on quarantaine procedures. No personal contact
* As part of this trial, and in addition to the above described routine procedure, index-patients with contacts will be informed about the COPEP-trial and asked if their contact details can be handed to the COPEP-trial team so that the investigators can call them to assess if they qualify for the trial. The index case will be given the choice to provide their contact informations or alternatively, given the option to tell their contacts about the study and ask them to call research team.
* Depending on the number of new cases per day, the Department of Health will sends by email the contact-details of index-cases who agreed for their contact details being communicated to the COPEP-trial team.
* The study-nurse or investigators will then call the contacts by phone to assess their eligibility for COPEP.

1. Hospital setting

Index-patients who are hospitalized are approached directly by the COPEP-trial team (study-nurses or investigators). In case index patients report contacts and agrees the team to contact them, contacts will be called by the study-nurse or an investigator and assessed for eligibility.

*\*A close contact is defined as a person who spent >15 minutes in < 2 meter distance, who 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 diagnosis of the index case or 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.*

*\*\*In order to assure appropriate care for individuals who develop COVID-19 during follow-up, recruitement in Basel will be limited to Basel-Stadt.*

**For both sites:** we will also ask index cases for an informed consent in order to obtain information on their treatment throughout their COVID-19 infection. This information will be used for statistical analysis (see Section 11).

**7.2.2 Screening:**

Close contacts of confirmed SARS-CoV-2 index case will be contacted by the study team by phone. They will be informed of the study and asked if they are willing to participate. If they are happy to participate, they will be screened for eligibility based on a standard eligibility questionnaire. If eligible, the baseline visit will be scheduled with the participant for the same day or the next day, and participants will be sent the Participant Information Sheet and the informed consent form by e-mail. Where participants do not have an e-mail address, Participant Information Sheet will be read out over the phone. The baseline will be performed the same day, or the next day, but either way within 48 hours following the documented confirmed positive SARS-CoV-2 test of the index case.

## 7.3 Assignment to study groups

Every close contact will be randomized to one of the three arms; HCQ versus LPV/r versus surveillance. Where close contacts reside in the same household (for example the family of the index case or a group of friends that live together) these will be cluster randomized by household. Treatment will be identical within households because secondary transmission within households can occur during follow-up, and this may influence trial outcomes.

## 7.4 Criteria for withdrawal / discontinuation of participants

Participants will be withdrawn from the trial if:

1. the subject withdraws consent;
2. Clinical reasons believed to be life-threatening by the physician;
3. Subject is judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol (i.e not adhering to study treatment or study procedures) and/or to cause harm to self or seriously interfere with the validity of the study result.
4. Study routine procedure must be stopped due to safety concerns.

Withdrawn participants will be replaced.

# 8. STUDY INTERVENTION

## 8.1 Identity of Investigational Products

### 8.1.1 Experimental Intervention

1. **Lopinavir/ritonavir** is an HIV boosted protease inhibitor (PI) currently indicated, in combination with other ARV, for the treatment of HIV-1 infected adults, adolescents and children ≥2 years old.2,3 Lopinavir/ritonavir is licensed in Switzerland and commercialized by AbbVie under the trade name of Kaletra®. Due to the current epidemic, the originators licenses have been dropped and the generic version of Kaletra is now available in Switzerland (Mylan) under the trade name of Alltera®.

Participants randomised in the LPV/r arm will receive a dose of 400 mg /100 mg film-coated tablets twice daily for 5 days.

1. **Hydroxychloroquine sulphate**, is licensed in Switzerland under the brand name Plaquenil® and is indicated for the treatment of uncomplicated malaria, and for the treatment of acute and chronic rheumatoid arthritis in adults.1

Participants randomised in the HCQ arm will receive a single dose of 800 mg at baseline.

### 8.1.2 Control Intervention

The control intervention is the current Standard of Care, which is no drug intervention.

### 8.1.3 Packaging, Labelling and Supply (re-supply)

Labeling: The study drugs will be labeled with the following information in the local language: IMP name with tablet dosage, name and number of the clinical trial, batch number, expiry date, patient/randomisation number, name of Sponsor/Principal Investigator, storage requirements and « for clinical trial only ». Labels are prepared and bottles will be labeled by the HUG central pharmacy.

Packaging: The HUG central pharmacy will re-package HCQ in 150 bottles with 4 tables each, and LPV/r will be re-packed in 150 bottles with 20 tablets of in each.

Labeling and packaging are performed in line with internal HUG validated procedures. IMP intended for use in Basel site will be sent to site by the HUG pharmacy.

Distribution of IMP to participants: Participants randomised in the HCQ arm will receive a single dose on site, as directly observed therapy. Participants randomised in the LPV/r arm will be given at baseline the exact dose needed for the entire period of IMP intake (i.e daily dose of 400mg/ 100 mg twice daily for 5 days). The first dose will be taken on site, as a directly observed therapy.

### 8.1.4 Storage Conditions

All IMP (LPV/r and HCQ) supplies at study site will be kept in a secure, limited access storage area under the recommended storage conditions. All drugs will be stored in the corresponding site’s hospital pharmacy, who will monitor the temperature and manage temperature excursion.

## 8.2 Administration of experimental and control intervention

### 8.2.1 Experimental Intervention

**Hydroxychloroquine:** HCQ will be administrated orally, in a **single dose** of 800 mg, corresponding to 4 tablets of 200 mg, which will be taken with the study physician at the baseline visit.

**LPV/r:** will be administrated orally, twice a day. Each dose will be of 400 mg /100 mg, which corresponds to 800 mg/ 200mg per day. The first dose (first dose of the first day), will be taken at the baseline visit with the study physician and the other doses will be self administrated by the patient.

### 8.2.2 Control Intervention

The control intervention is the current Standard of Care, which is no drug intervention.

## 8.3 Dose modifications

Doses will not be modified.

## 8.4 Compliance with study intervention

The single dose of HCQ and the first dose of LPV/r will be taken during baseline visit, as directly observed therapy. Individuals on LPV/r, will receive daily adherence questionnaire between baseline and Day 5, to check that they are taking their drug as prescribed, which will also serve as reminders. Furthermore, we will perform DBS on Day 5 to evaluate drug concentration of HCQ and LPV/r in each study arm. This will not only serve as a second marker of compliance (in addition to the daily questionnaire) for the LPV/r arm but also ensure that individuals did not percure and take a study drug outside the scope of the study and in contradiction to their allocated arm.

## 8.5 Data Collection and Follow-up for withdrawn participants

All relevant data collection and follow-up will be stopped upon participant withdrawal.

## 8.6 Trial specific preventive measures

All particpants area asymptomatic for COVID-19 and will benefit from active daily surveillance. Any individual who develops symptoms for COVID-19 will undergo an oro-pharyngeal swab and if found positive will be followed by the standard of care.

Both drugs can be used during pregnancy and breastfeeding (Appendix 3 and 4). For this reason we will include women of childbearing age, pregnant women and women who breastfeed and will not ask about effective contraception (Annexe). The gynaecologist of women who fall pregnant during the study will be contacted to inform them about any treatment given and these women will be followed-up until resolution of the pregnancy.

## 8.7 Concomitant Interventions (treatments)

Routine medications of each participant are allowed as long as there is not contra-indication with the intervention treatments (Appendix 1 and 2) or prolong the QT interval (as per <https://crediblemeds.org>). If the participant’s healthcare professional starts a treatment which is known to prolong the QT interval, while the patient is enrolled in the study, then an ECG should be performed by this professional and checked for QT prolongation.

## 8.8 Study Drug Accountability

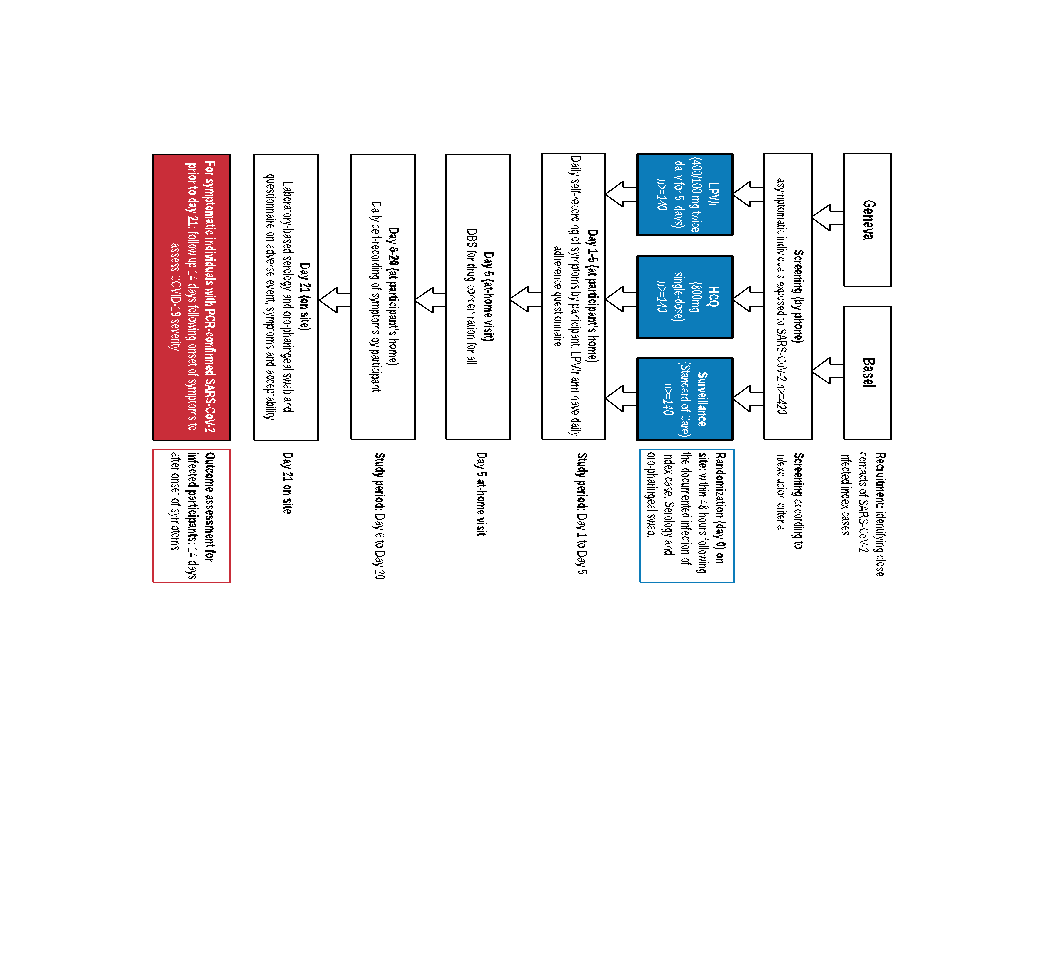
The IMP drug bottles will be labelled with study specific labels. Participants will be asked to return IMP bottles (full, partially empty and completely empty) to the study nurse at the end of the study. The study sites will maintain adequate documentation of the IMP distribution and collection. Sample documentation will be prepared and provided to all participating study sites by the Sponsor-Investigator.

## 8.9 Return or Destruction of Study Drug

Returned IMP bottles (full, partially empty and completely empty) will be registered in the study drug accountability log for each participant at each study site. Empty bottles will be thrown away, and remaining IMP will be destroyed according to local/site guidelines on destruction of IMP. Destruction of IMP and empty bottles should be done only once drug accountability logs were reviewed and validated by the study monitor. Return and destruction should be clearly documented.

# 9. STUDY ASSESSMENTS

## 9.1 Study flow chart(s)



## 9.2 Procedures at each visit

### 9.2.1. Screening and recruitment

Procedure as specified in 7.2 above.

### 9.2.2 Baseline (Day 0)

**An in-person visit on site§ including:**

* Check of informed consent clarity and confirmation by participant and medical investigator signatures
* Confirmation of eligibility criteria
* Fill-in baseline CRF
* Where necessary, additional biological and clinical assessment will be performed, based on clinical judgement.

SARS-CoV-2 tests:

* Oro-pharyngeal swab
* Serology

These will be batch analysed at the end of the study, as per the current gold standard in a central accredited laboratory in Geneva.

Randomisation and start of intervention:

* Randomization\* 1:1:1 to either a single dose of 800 mg HCQ (4 tablets of 200mg) versus LPV/r 400/100 mg twice daily for 5 days versus surveillance
* Directly observed therapy administration of the single dose of HCQ, or first dose of LPV/r

Further study organisation:

* Provide link and login for online questionnaire to be completed by participant from day 1 to day 21 and explain the active surveillance system.
* Provide with thermometer for daily axillary temperature record
* For participants on LPV/r or HCQ: label and distribute IMP, record distribution in drug accountability log
* Schedule a home visit at day 5 and on site day 21 visit

*§* Contacts of index cases are advised to remain at home for 10 days. The baseline visit is an on-site visit in the hospital and may be counter this current recommendation regarding self-isolation upon a documented contact. We have considered another alternative which would be to have a dedicated member of the study team travel to participant's home; but in this case we would expose the study member to SARS-CoV-2 in an environment that is *certain* to have one (the index case). Whereas if the participant comes to the hospital, there is only a *possible* exposure. Moreover, individuals will be asked to respect all current recommendations when they travel to site: they will have to wear a mask, avoid public transport, and respect social distancing. Finally, participants will be seen in a dedicated space, and will not be in contact with COVID-19 patients.

*\*Every close contact will be randomized to one of the three arms; HCQ versus LPV/r versus surveillance. Where close contacts reside in the same household (for example the family of the index case or a group of friends that live together) these will be cluster randomized by household. Treatment will be identical within households because secondary transmission within households can occur during follow-up, and this may influence trial outcomes.*

### 9.2.3 Day 1 to 21

Participants will be asked to complete a daily online self-assessment questionnaire including:

* Assessment of clinical symptoms associated with COVID-19
* Record of daily axillary temperature

The online questionnaire generates alerts when individuals report a symptom associated with COVID-19; red alert for severe symptoms (dyspnea, fever) and amber for non severe symptom (all other symptoms). The online questionnaire also send reminders at the end of the day in case of non-completion and triggers an alerts if particpants do not complete the questionnaire for 2 consecutive days. The team will contact the participant as soon as possible and no later than the 24 hours after a red alert was triggered. For all other alerts (amber alert and non-completion) the team will contact the participant as soon as possible and no later than the next working day. Paper questionnaires will be made available for those without internet infrastructure, with the option of daily phone or self-reporting outcomes. All alerts will trigger a phone evaluation with participants, and all infromation will be transcribed directly into the CRF.

Participant who report COVID-19 related symptoms (dyspnea, cough, fever (>38.0C), anosmia) will be asked to come on site for an extra visit and undergo clinical assessment and an oro-pharyngeal swab to confirm/exclude infection. If diagnoses positive, participant will be provided with appropriate care, as per local protocol. See chapter 9.2.6 for details for follow-up of participants who are symptomatic or infected prior to day 21.

Participants on the LPV/r arms will take their medication as instructed for 5 days. The daily online questionnaire for particpants on LPV/r will consist of additional daily questions about their adherence to LPV/r between baseline and Day 5.

### 9.2.4 Day 5

**A visit at participant’s home by a delegated member of the study team:**

* Dry capillary blood spot for plasma concentration.
* Collect any IMP from participants and record in drug accountability log
* Transcribe above information into CRF

In addition, on Day 5 all participants will receive additional questions in their daily online questionnaire, enquiring about adverse events. Serious adverse events will trigger a phone consultation and appropriate care. All other adverse events will transcribed into CRF at completions of the study.

### 9.2.5 Day 21

**An in-person visit on site***§* **including:**

* COVID-19 associated symptoms adverse events and acceptability questionnaire
* Oro-pharyngeal swab
* Phlebotomy for laboratory-based serology
* Fill-in day 21 CRF

An extra visit will be scheduled for individuals presenting with severe COVID-19 related symptoms or those reporting severe adverse events.

*§Participants will be seen in a dedicated space, and will not have contact with COVID-19 patients.*

### 9.2.6 Follow-up of COVID-19 participants (symptomatic and PCR-confirmed SARS-CoV-2 positive prior to or on Day 21)

All participants who develop COVID-19 prior to or on Day 21 will be followed as per the standard of care. A follow-up will be conducted 14 days after onset of symptoms, in order to establish severity of disease. The severity of disease will be graded on a 7-point ordinal scale (1: not hospitalized, no limitations on activities, 2: not hospitalized, limitation on activities, 3: hospitalized, not requiring supplemental oxygen, 4: hospitalized, requiring supplemental oxygen, 5: hospitalized, on non-invasive mechanical ventilation 6: hospitalized, on invasive mechanical ventilation or ECMO and 7: death).

## 9.3 Laboratory procedures

### 9.3.1 Oro-pharyngeal Swab collected at baseline analysed at HUG

Baseline oro-pharyngeal swabs collected in accordance with standard operating procedures and frozen to -80 degrees within 24 hours in their collection tubes. At time of study-completion all samples will be transported from Basel to Geneva, maintaining the cold chain at all times. All samples from both sites will be batch analysed in the reference laboratory at the HUG in Geneva. The study team will adhere to the safety protocol for the collection of sample, including recommendations on personal protective equipment.

### 9.3.2 Laboratory based serology analysed in batch in HUG

At baseline and on Day 21, 10mls of venous blood will be taken [EDTA (4mL) and clotted bottle (6mL)]. Both samples will be centrifuged at 1500g for 10 minutes. Three aliquots of serum from the clotted bottle and three aliquots of plasma from the EDTA tube will then be frozen at -80°C and stored until further notice. Additionally, a single aliquot of the cell fraction from the EDTA tube will also be aliquoted and frozen immediately at minus 80°C. At time of study-completion all samples will be transported from Basel to Geneva, maintaining the cold chain at all times. All samples from both sites will be batch ananlysed in the reference laboratory at the HUG in Geneva.

### 9.3.3 Dried Blood Samples

On Day 5, participants will undergo DBS testing. This will be done as a second check of drug adherence for the LPV/r arm, to check that individual did not percure and take LPV/r or HCQ from elsewhere when they were not randomized to that arm and to check drug level for toxicity.

This involves a finger prick. 200μl of blood will be spotted onto filter paper and allowed to dry. These samples will then be packed and placed with an absorbent packet, stored securely on site and sent to the central laboratory in Geneva at the end of the study for ananlysis.

The determination of hydroxychloroquine and LPV/r in dried blood samples (Dried Blood Spots, DBS) is carried out by liquid chromatography coupled with tandem mass spectrometry, using an adaptation of the method developed for antimalarials (including chloroquine).27 This methodology was applied for the analysis of 6500 DBS samples within the framework of a clinical field study in Africa.28 The methodology has been expanded more recently for the determination of the 15 most used antibiotics in Africa (ongoing SNF project, Prof Blaise Genton P.I., Unisanté Lausanne).

The capillary blood sample is taken by skin puncture at a fingertip with a lancet, and and collected in a graduated heparin-coated capillary tube (heparinised Haematokrit-Kapillaren HIRSCHMANN , 75mm/60microl). Two separate 10-µl drops of capillary blood are deposited next to each other with the capillary tube onto DBS cards (FTA DMPK-B cards, Whatman®, Maidstone, UK). These cards are impregnated with a component so that the blood is immediately hemolyzed when the drop of blood is applied. The cards are allowed to dry for 30 min at room temperature in a dedicated quiet place, before being sealed in a zip-lock bag. The card is then placed in a transparent plastic bag with zip closure.

The exact **date and time of the last drug intake**, **and skin puncture** must be recorded on the CRF.

These cards in the plastic bags are stored at 4C or -20C, conditions in which the samples have been shown to be stable for at least 72 h.

# 10. SAFETY

## 10.1 Drug studies

During the entire duration of the study, all adverse events (AEs) and all serious adverse events (SAEs) will be collected, investigated and documented in source documents and case report forms (CRF).

Study duration encompassed the time from when the participant has been randomized, in one of the three study arms, i.e. starting from the baseline visit (day 0) until the last protocol-specific procedure has been completed, including a follow-up period.

### 10.1.1 Definition and assessment of (serious) adverse events and other safety related events

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

A **Serious Adverse Event (SAE)** is classified as any untoward medical occurrence that:

* results in death,
* is life-threatening,
* requires in-patient hospitalization or prolongation of existing hospitalisation,
* results in persistent or significant disability/incapacity, or
* is a congenital anomaly/birth defect.

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious.

SAEs should be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination (including follow-up visit) will be further followed up until recovery or until stabilisation of the disease after termination. See details in section 10.1.3.

**Unexpected Adverse Drug Reaction**

An “unexpected” adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Product Information for approved drugs).

**Suspected Unexpected Serious Adverse Reactions (SUSARs)**

The Sponsor-Investigator evaluates any SAE that has been reported regarding seriousness, causality and expectedness. If the event is related to the investigational product and is both serious and unexpected, it is classified as a SUSAR.

**Assessment of Causality of (Serious) Adverse Events and other safety related events**

Both Investigator and Sponsor-investigator make a causality assessment of the event to the study drug, based on the criteria listed in the ICH E2A guidelines:

|  |  |
| --- | --- |
| Relationship | Description |
| Certain | Temporal relationship +  Improvement after dechallenge +  Recurrence after rechallenge  (or other proof of drug cause) |
| Probable | Temporal relationship + Improvement after dechallenge  No other cause evident |
| Possible | Temporal relationship  Other cause possible |
| Unlikely | Any assessable reaction that does not fulfil the above conditions |
| Excluded | Causal relationship can be ruled out |
| Not assessable | Not assessable |

**Assessment of Severity**

Grading of AEs will be done according CTCAE v5.0.

### 10.1.2 Reporting of serious adverse events (SAE) and other safety related events

**Reporting of SAEs**

All SAEs must be reported immediately and within a maximum of 24 hours to the Sponsor-Investigator of the study. The Sponsor-Investigator will re-evaluate the SAE and return the form to the site.

SAEs resulting in death are reported to the Ethics Committee via BASEC within 7 days.

The other in the trial involved Ethics Committees receive SAEs resulting in death in Switzerland via Sponsor-Investigator via BASEC within 7 days.

**Reporting of SUSARs**

A SUSAR needs to be reported to the Ethics Committee (local event via local Investigator) via BASEC and to Swissmedic via Sponsor-Investigator within 7 days, if the event is fatal, or within 15 days (all other events).

The Sponsor-Investigator must inform all Investigators participating in the clinical study of the occurrence of a SUSAR. All in the trial involved Ethics Committees will be informed about SUSARs in Switzerland via Sponsor-Investigator via BASEC according to the same timelines.

**Reporting of Safety Signals**

All suspected new risks and relevant new aspects of known adverse reactions that require safety-related measures, i.e. so called safety signals, must be reported to the Sponsor-Investigator within 24 hours. The Sponsor-Investigator must report the safety signals within 7 days to the Ethics Committee (local event via local Investigator) via BASEC and to Swissmedic.

The Sponsor-Investigator must immediately inform all participating Investigators about all safety signals. The other in the trial involved Ethics Committees will be informed about safety signals via the Sponsor-Investigator.

**Periodic reporting of safety**

An annual safety report is submitted once a year to the local Ethics Committee via local Investigator and to Swissmedic via Sponsor-Investigator.

The annual safety report contains information from all sites. The Sponsor-Investigator prepares it, and then submits it to the participating Investigators. The participating Investigators submit it to the local committees.

### 10.1.3 Follow up of (Serious) Adverse Events

Participants with ongoing SAEs, SUSARs at the last study visit will be further followed will be further followed up until recovery or until stabilisation of the disease after termination. Ongoing pregnancies at the last study visit will be further followed-up until pregnancy resolution. Extension of this duration can be proposed for event of particular interest for the study. Follow up may include but is not limited to physical examination, laboratory tests, vital signs, telephone calls. Outcomes and resolution of events will be recorded in the Case Report Forms. In case of lost to follow up, efforts will be made to contact the patient or to ascertain the vital status of the participant.

# 11. STATISTICAL METHODS

## 11.1 Hypothesis

H0: There is no true difference between either LPV/r or HCQ compared to surveillance in preventing COVID-19.

## 11.2 Determination of Sample Size

The sample size is calculated to power the primary endpoint of COVID-19, as it requires the larger sample size. The sample size 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% (from 20% to 8%), with a power of 80%, an alpha of 5% and accounting for design effect (DE) of cluster design of circa 1.1 (based on , where DE stands for design effect, n=3 denotes the average cluster size, and ρ=0.05 is the intraclass correlation coefficient).

This results in a sample size n=140 close contacts per arm, 420 participants in total.

For the first of the secondary endpoint (occurrence of new SARS-CoV-2 infection) we assume 40% of close contact without PEP will become infected and a 16% with PEP; 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.

## 11.3 Statistical criteria of termination of trial

No interim analysis will be perfomed.

## 11.4 Planned Analyses

### 11.4.1 Datasets to be analysed, analysis populations

All databases and participants will be analysed, unless specified in section 11.4 for modified ITT.

### 11.4.2 Primary Analysis

For the analysis of the first co-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 immune by serology).

Both intervention arms, LPV/r and HCQ, will be compared to the surveillance arm, using separate indicator variables for the active treatment arms. Because the hypothesis 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 LPV/r versus surveillance, and for HCQ 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 co-morbidities (specifically cardiac, liver or pulmonary), treatment of the index case, and occupational versus non-occupational exposure, and / or positive serology.

### 11.4.3 Secondary Analyses

In a modified intent to treat analysis we will evaluate three of the secondary endpoints:

* 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)
* 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, “severe disease”, we will use a Manne-Whitney test, to perform a gradual scale ananlysis to compre ourtcome between interventions arms and surveillance. For the analysis of individual-reported adverse events, the population will include all randomized participants, and the comparisons will be simple 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.

### 11.4.4 Interim analyses

Not applicable.

### 11.4.5 Safety analysis

For the analysis of individual-reported adverse events, the population will include all randomized participants, and the comparisons will be simple cross-tabulations and chi-square tests, since the probability of experiencing adverse events will likely not be affected by clustering.

### 11.4.6 Deviation(s) from the original statistical plan

Describe how any deviation(s) from the planned analyses will be justified and reported.

## 11.5 Handling of missing data and drop-outs

We will anlyse available data, no imputation will be performed.

# 12. QUALITY ASSURANCE AND CONTROL

## 12.1 Data handling and record keeping / archiving

### 12.1.1 Case Report Forms

All study data will be entered in an Electronic Data Capture (EDC) system, RedCap, by the site study team. CRFs will be kept current to reflect subject status at each phase during the course of the study. Study-related data of the participant will be collected in a coded manner. The names of the participant will not be disclosed. A code (unique) will be attributed to each enrolled participant.

Persons authorized by the sponsor-investigator to perform data entry or data review will be communicated to the data manager who will provide individual access codes according to the function assigned. CRF data entry authorization will be documented on each delegation log and a list of all authorized persons and their function stored with the data manager.

### 12.1.2 Source data

Source data must be available at each study site to document the existence of the study participants.

Source data will include the original documents relating to the study, such as:

* Eligibility criteria questionnaire
* Original signed informed consent form
* Print out from CRF for allocation of randomization
* Laboratory reports for oro-pharingeal swabs, serologies, plasma concentration (result and date)
* All questionnaires (symptoms based questionnaire, adherence questionnaire, adverse event questionnaire, and study intervention acceptability)

### 12.1.3 Analysis and Record keeping / archiving

All study data will be archived for a minimum of 10 years after study termination or premature termination of the clinical trial.

## 12.2 Data management

### 12.2.1 Data Management System

The data management will be performed by the UIC (Unité d‘Investigation Clinique), which is part of the Clinical Research Center (CRC; Centre de Recherche Clinique) at the Geneva University Hospitals (Hôpitaux Universitaires de Genève, HUG) and the Faculty of Medicine of the University of Geneva.

REDCapTM, a certified GCP-compliant electronic clinical data management system, will be used to develop the CRF electronically (eCRF). Data are physically stored in a mySQL ver.14, a relational database management system (RDBMS) using a dedicated Clinical Database Management System (CDMS) software (REDCapTM).

This eCRF will reflect the study plan and all subject-related data to be collected, as described by the study protocol, and which cover the following areas/topics:

* Inclusion criteria and consent
* Demographics
* Symptom questionnaire
* Adherence questionnaire
* Acceptability of PEP questionnaire
* Comorbidities
* AE/SAE
* Concomitant medication
* End of study

### 12.2.2 Data security, access and back-up

Electronic data protection, backup and archiving will be under the responsibility of the CRC, with the collaboration of the HUG Department of Information System (DSI):

* Physical access to the data centers is logged and limited to authorized personnel using badge authentication. On a regular basis, vulnerability testing is performed to reduce potential exposure.
* Remote access to servers is limited only to authorized personnel. Connections to servers are encrypted using SSH. System logs are stored in a dedicated centralized system for audit purposes. The internal HUG network is protected by multiple firewalls, proxy, reverse-proxy, and anti-virus solutions.
* Web servers operate under SSL (HTTPS) certifications, ensuring Web connections are encrypted and secure.
* At the CDMS level, only people part of the investigation team, the sponsor team, the affiliated reviewers or auditors, as well as inspection authorities (Swissmedic) are given access to data. Personal accounts are granted individually for each person. Identification is made by a personnel ID and a password. Failure to provide the correct password after a limited number of attempts automatically deactivates the faulty account (protection against non-authorized attacks).
* Only institutional e-mail addresses will be accepted for any communication of sensitive data regarding account creation and management.
* Pen-Tests (simulation of malware attacks) are regularly performed, and measures taken whenever necessary.
* Data transfer: Exports of all or any kind of partial data will be systematically password encrypted before being transferred. Use of hashing encoding will ensure that no data alteration may have occurred during the transfer.
* Backups operations are frequently performed by the DSI service at HUG, in accordance with UIC policies. Using the best enterprise backup solutions at HUG, the backups are physically stored in a fire-proof safe. Backup strategy compromises an optimized hourly, daily, monthly and yearly retention plan.

The COPEP platform facilitates data collection from study participants. After enrollment, participants receive a daily SMS or Email with a personal link to upload data. Access to submitted data is restricted to study personnel and regulated through personal user profiles (username and password). The platform and data are stored in an ISO-27001 and FINMA certified data center in Switzerland (Interxion, managed by Hostpoint AG). Data in-transit is encrypted with Secure Sockets Layer (SSL) encryption.

### 12.2.3 Analysis and archiving

Data and metadata will be exported from REDCapTM in plain text (CSV, SPSS) for analysis. These exports might be post-processed programmatically by UIC to facilitate data analysis and data visualisation.

At the end of the project, the entire database will be archived in a reusable format. Redeployment of the entire database is therefore possible whenever needed. The comprehensive archive will remain propriety of the sponsor and will be preserved during a minimum period of 10 years.

### 12.2.4 Electronic and central data validation

Prior to analysis, the data captured in the eCRF will be checked and validated (review) by an investigator, study nurse or dedicated collaborator.

## 12.3 Monitoring

For quality control of the study conduct and data retrieval, all study sites will have regular monitoring activities performed by appropriately trained and qualified monitors. Monitoring activities consist of on-site monitoring as well as remote and centralized monitoring.

Prior to study start (first participant enrolled), a central monitoring plan will be developed detailing all monitoring-related procedures and activities planned during the study.

Investigators at the participating study sites will support the monitor in his/her activities. All source data and relevant documents will be accessible to monitors and questions of monitors will be answered during site visits.

Any findings and comments will be documented in monitoring visit reports and communicated to the local Investigator and to the Sponsor as applicable.

## 12.4 Audits and Inspections

The study documentation, the source data/documents and study related reports will be accessible to auditors/inspectors (also CEC and CA) and questions will be answered during inspections. All involved parties must keep the participant data strictly confidential.

## 12.5 Confidentiality, Data Protection

The obtained data will be handled strictly confidentially. For each participant, original medical data will be accessible for the purposes of source data verification by the Monitor, audits and regulatory inspections, but participant confidentiality will be strictly maintained. Personal data will be anonymized for data analysis. No names will be published at any time and published reports will not allow for identification of single participants.

The Investigator will assign a unique identifier to participants after obtaining their informed consent. This number will serve as the participant’s identifier in the study database. All participant records or datasets transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred. Only the Investigator or designee will be able to link study data to an individual participant via an identification list kept at the site.

## 12.6 Storage of biological material and related health data

As part of the trial we will store oro-pharyngeal swabs and serology from each participant from baseline. We will also store DBS and oro-haryngeal swabs and serology from each participant from Day 5 and Day 21, respectively. Samples will be stored in the site specific hospital laboratory. Samples from Basel will be transported to Geneva for analysis upon study completion and ananlysed in batches at earliest convenience. All samples will be stored, transported, analysed and labelled in accordance with standard operating procedure. Once all analyses are performed, all biological material will be destroyed.

# 13. PUBLICATION AND DISSEMINATION POLICY

The final data will be presented at one or more scientific meetings and published in scientific journal(s). No patient data will be presented that could permit identification of any individual study participant. Publication of data derived from this protocol will be supervised by the Sponsor, Principal-Investigator and by the Co-Principal Investigator in conjunction with all study investigators. No publication will be made without prior approval of the Sponsor, Principal-Investigator and Co-Principal Investigator.

# 14. FUNDING AND SUPPORT

The study is funded and supported by the Geneva University Hospital (Fondation privée des HUG).

University Hospital of Basel will also support the study by providing HCQ for the purpose of this study.

Any additional funding or support will be notified to the leading Ethics Committee.

# 15. INSURANCE

Study Insurance will be provided by the Geneva University Hospital.

A copy of the insurance policy will be filed in each Investigator Site File and in the Trial Master File.

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