Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Mitjà O, Corbacho-Monné M, Ubals M, et al. A cluster-randomized trial of hydroxychloroquine for prevention of Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2021801

This supplement contains the following items:

Study protocol

- Original protocol (v11 of March 13, 2020)
- Final protocol (v15 of May 12, 2020)
- Summary of changes

Statistical analysis plan (SAP)

- Original plan (March 17, 2020)
- Changes to the SAP (October 8, 2020)

Treatment of non-severe confirmed cases of COVID-19 and chemoprophylaxis of their contacts as prevention strategy: the BCN PEP CoV-2 Study

Short name: CQ4COV19

EudraCT: 2020-001031-27

ClinicalTrials.gov Identifier: NCT04304053

Principal Investigator Name: Oriol Mitja

Protocol: v11.0, 13/03/2020

Sponsor Name:

1. Fundación FLS de Lucha contra el Sida, las enfermedades infecciosas y la promoción de la salud y la ciencia

Funding partners:

2. Institut Català de la Salut, Generalitat de Catalunya
3. Departament de Salut, Generalitat de Catalunya
4. Laboratorios Rubió SA
5. Laboratorios Gebro pharma SA

Principal investigator signature

Title: Treatment of non-severe confirmed cases of COVID-19 and chemoprophylaxis of their contacts as prevention strategy: the BCN PEP CoV-2 Study

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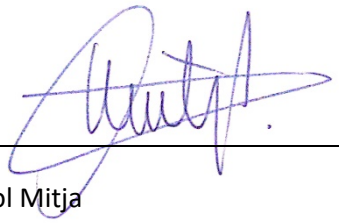
I, the undersigned, have read and understood the protocol specified above and agree on its content. I agree to perform and conduct the study as described in the protocol and in accordance with the relevant laws/regulations and standards outlined in the Clinical Trial Agreement.

Study investigator:

Signed: Date: 13/03/2020



Name Oriol Mitja

Title Associate Professor, Infectious Diseases and Global Health
Hospital Universitari Germans Trias I Pujol, Badalona
omitja@flsida.org

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1 BRIEF SUMMARY

This study is a research project to evaluate the efficacy of hydroxychloroquine for post-exposure prophylaxis and early treatment of Covid-19. The intervention entails administering prophylactic hydroxychloroquine to all contacts **(Substudy 1, contacts)** and treating non severe confirmed cases with hydroxychloroquine **(Substudy 2, cases).** Therefore, the present document must be read as a master protocol including the two evaluations.

Substudy contacts Prophylactic hydroxychloroquine treatment administered to all contacts of confirmed index cases aims to protect all potential individuals that could become infected and develop the disease.

Substudy cases Treatment of patients can reduce viral shedding in respiratory secretions to undetectable levels resulting in a reduction on the probability of onward transmission of SARS-CoV-2.

Substudy	Condition or disease	Intervention/treatment	Phase
1 - Contacts	**Contact of COVID-19 case (index case confirmed with PCR)**	Pharmacological intervention: treat with hydroxychloroquine	Proof of concept (Phase III)
2 - Cases	**Confirmed non severe case of COVID-19: SARS-CoV-2 positive by PCR plus mild respiratory symptoms**	Pharmacological intervention: treat with hydroxychloroquine	Proof of concept (Phase III)

2 BACKGROUND

2.1 THE USE OF CHEMOPROPHYLAXIS AS PREVENTION IN INFECTIOUS DISEASES

The current COVID-19 emergency warrants the urgent development of potential strategies to protect high risk subjects (close contacts, health care workers, and others). The reason is that secondary attack rate of households (SARh) is ~15%, and that of close contacts (SARc)~ 10%. (1,2) This means that the risk of becoming infected after contact with a COVID-19 case is very high. The SARc is like influenza (10%) and much higher than meningococcal disease (<1%).

Postexposure prophylaxis (PEP) using antimicrobial agents is effective in preventing illness after potential or documented exposure to a variety of microbial pathogens and in reducing the risk of secondary spread of infection. The most similar situation to SARS-CoV-2 infection is influenza infection. High risk people exposed to Influenza (oseltamivir 75mg, twice daily for five days). Previous research on influenza has indicated that antiviral drugs administered before o short after symptom onset can reduce infectiousness to others by reducing viral loads in the respiratory secretions of patients and targeted prophylactic use of contacts reduce the risk of becoming infected (3,4). The measure of providing antiviral treatment to patients and prophylaxis to the close contacts of influenza patients has been recommended by the World Health Organization as a principle of early aggressive measures to prevent pandemic influenza (5) and the strategy was shown highly effective in reducing the incidence of secondary cases. The same principle could be applied to all type of respiratory infections with epidemic potential spread by droplet transmission, including SARS-CoV-2. We consider that this approach might be successful also if performed during the current SARS-CoV-2 epidemic due to the similarities of both infections.

2.2 CURRENT KNOWLEDGE OF THE EFFICACY OF DRUGS TO TREAT COVID-19

2.2.1 HYDROXYCHLOROQUINE

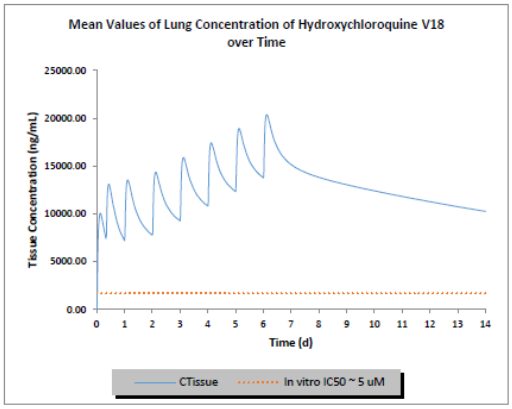
There are some reports and clinical trials that describe and investigate the efficacy of different drugs, among which the aminoquinolines.

In vitro studies: Hydroxychloroquine (HCQ) is a drug that has been extensively used for the prevention of malaria. HCQ showed excellent in vitro results and strong antiviral effects on SARS-CoV-2 infection of primate cells at low concentration. The EC50's were 0.72uM and 6.1 at 48 and 24 hrs incubation, respectively.(6,7) In SARS-CoV and MERS infections, an IC50 of approximately 5uM provides a reasonable and achievable target concentration to reach in plasma and lung (7). HQQ was found to be more potent than chloroquine (EC50 5.47uM, and 1.1uM in a previous study [6]) to inhibit SARS-CoV-2 in vitro. This family of drugs appears to interfere with terminal glycosylation of the cellular receptor, angiotensin-converting enzyme 2 which is the main host cell receptor of SARS-CoV-2.(8) This may negatively influence the virus-receptor binding and abrogate the infection, with further ramifications by the elevation of vesicular pH, resulting in the inhibition of infection and spread of SARS-CoV at clinically admissible concentrations.

In vivo studies: An open-label non-randomized controlled trial in 36 patients diagnosed of SARS-CoV-2 reported that hydroxychloroquine alone or in combination with azithromycin reduced detection of SARS-CoV-2 RNA in upper respiratory tract specimens compared with a non-randomized control group but did not assess clinical benefit (9). The results showed that patients in the treatment group were

significantly more likely to test negative for the virus on Day 6 than patients in the control group (70% vs 12.5% virologically cured, p<0.001). Moreover, all the six patients who were treated with a combination of HCQ and azithromycin tested negative on Day 6. The authors argue that this finding speaks to the effectiveness of HCQ and a potential synergistic effect of its combined treatment with azithromycin. A study in China reported that chloroquine treatment of COVID-19 patients had clinical and virologic benefit versus a comparison group and chloroquine was added as a recommended antiviral for treatment of COVID-19 in China(10).

Pharmacological aspects: According to pharmacological modelling conducted (*Figure* - Scott Miller, 16/03/2020) higher dose regimen (OHCQ 800mg d1, 400mg d2-7 (total dose 3,2g) will give good plasma levels and corresponding lung levels. Plasma troughs will be nearer to 100ng/ml, compared to 70ng/ml for a lower dose regimen OHCQ 800mg d1, 400mg d2-4 (total dose 2,0g). Lung concentrations will be much higher (2-2.5 log higher), but the free log concentration in lung epithelial cells are what will matter (which is not known).



Side Effects: Hydroxychloroquine has a good safety profile (60% reduction of AEs compared to chloroquine) with a 3-day treatment course (Total dose (adults): 2.0 hydroxychloroquine sulfate in 3 days (drug datasheet). Gastrointestinal upset has been reported with HCQ intake. Retinal toxicity has been described with long-term use of CQ and HCQ, and may also be related to over-dosage of these medications (daily doses of hydroxychloroquine sulfate greater than 6.5 mg/kg (5 mg/kg base) of actual body weight, durations of use greater than five years). Isolated reports of cardiomyopathy and heart rhythm disturbances caused by treatment with CQ have been reported. Chloroquine should be avoided in patients with psoriasis and porphyria. Both CQ and HCQ are metabolized in the liver with renal excretion of some metabolites, hence they should be prescribed with care in people with liver or renal failure.

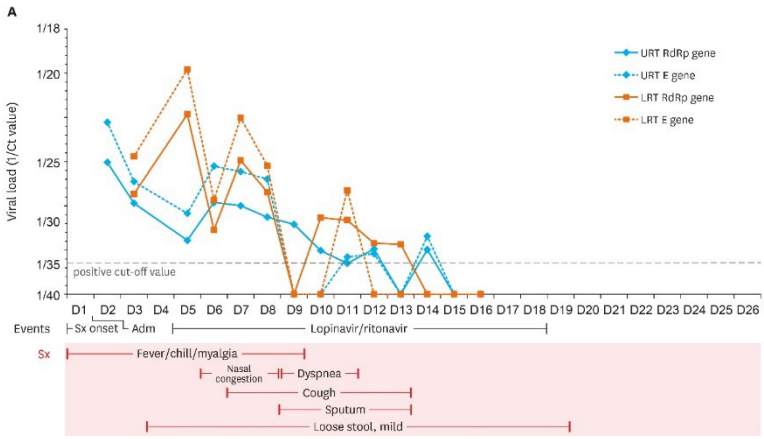
2.2.2 PROTEASE INHIBITORS

Lopinavir/ritonavir, a protease inhibitor used to treat HIV/AIDS, was found to inhibit the *in vitro* cytopathic effect of SARS-CoV and MERS-CoV at concentrations (Half maximal effective concentration EC50 ~4.0µg/ml) achievable in humans.(7) Lopinavir/ritonavir 400/100, pharmacokinetic parameters for lopinavir are as follows: Cmax 9.6µg/ml, T1/2 5h, AUC24 186 µg*h/ml. In addition, preliminary results show that this drug, either alone or with various combinations could provide some clinical benefit to the treatment of hospitalized patients with SARS-CoV-2 infection. However, the drug is so far offered to sick patients only and we believe that it should also be evaluated in mild cases in which it could contribute to halt transmission. Common side effects include diarrhea, nausea, abdominal pain in about 27% of patients treated.

Darunavir (DRV)/Cobicistat, is also a protease inhibitor used to treat and prevent HIV/AIDS. Its mechanism of action is very similar to Lopinavir/ritonavir. This drug combination was shown to be as effective as lopinavir/ritonavir for the treatment of HIV/AIDS. However, this combination is better tolerated tan lopinavir/ritonavir because the adverse effects rate is lower (diarrhea 2% vs 27%). Besides, the drug is being trialed currently for COVID-19 and preliminary seem promising (clinicaltrials.gov/ct2/show/NCT04252274).

2.3 MONITORING EFFICACY OF TREATMENT, CLINICAL AND VIROLOGICAL OUTCOMES

The virus is detected from URT specimens on day 2 (10*7 copies/ml) of symptom onset, increasing levels on day 5-7 (10*8 copies/ml) and then peak become spontaneously negative by day 14. In serum, plasma, urine, and stool samples, the virus is detected at very low levels. In a study including the 66 confirmed cases, (13) the median time from the onset of symptoms to first negative RT-PCR results for oropharyngeal swabs in convalescent patients was 9.5 (6.0-11.0) days, for stool samples was 11 (9-16) days. The Figure shows the Viral load kinetics of respiratory specimen presented by reverse Ct value. Positivity of urine samples was low (7%) and all blood specimens were negative. Exceptionally, 4 cases have been found to have positive rt-PCR after clinical and molecular cure (2 consecutive negative tests) (14).



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3 STUDY SITES

The study will be conducted over the course of a COVID-19 outbreak in Catalonia and for the selection and case definitions of the participants we will follow the current Catalan/Spanish protocols in line with WHO. The detection and notification of confirmed cases and contacts is centralized by the Catalan epidemiological surveillance system (SUVEC). Thus, for the purpose of this study randomization will be performed by a member of this team.

The study outbreak team, consisting of 120 health care workers, will visit all eligible cases and contacts at home for baseline assessment, administration of intervention drugs (in the experimental arm) and follow-up assessments to explore the effect of the intervention.

Individuals who choose not to participate in the study will be managed following the current protocols.

4 SUBSTUDY 1 – CHEMOPROPHYLAXYS OF CONTACTS

4.1 STUDY DESIGN

Study Type:	Interventional (ring treatment trial)
Estimated Enrolment:	2850 contacts (average 15 contacts in each cluster)
Allocation:	Cluster-randomized
Masking:	Open-label
Contacts:	As defined by the current protocol of the Catalan epidemiological surveillance system
Intervention:	Pharmacological (Hydroxychloroquine in index cases and in contacts)
Primary Purpose:	Prevention at population level
Actual Study Start Date:	March 16, 2020
Estimated Primary Completion Date:	Apr 30, 2020
Estimated Study Completion Date:	Apr 30, 2020
Site:	Catalonia

Design considerations

The design intervention is based on the design used during the vaccination trial developed for Ebola in 2015 (ref1). This was a cluster randomized controlled trial with the aim of evaluating vaccines against the disease in Guinea, West Africa. In the ring vaccination trial, a person newly diagnosed with the disease becomes the index case around whom an epidemiologically defined ring is formed. This ring is then randomized to either immediate vaccination (intervention) or delayed vaccination (control) in a 1:1 ratio on an open label basis. The incidence of disease is compared between the two arms over equivalent time periods measured from the time of randomization of each ring. Comparing the hazard ratio in those enrolled in the study allows estimation of vaccine efficacy, while overall vaccine effectiveness can be estimated by comparing incidence across all members of the rings, including those not eligible for vaccination in the study. This design permits to track the epidemic, recruiting individuals at increased risk of infection due to their connection to a case and thus, may both contribute to transmission interruption and have a higher power to detect vaccine efficacy than other study designs.

In our scenario, after the Catalan epidemiological surveillance system detects a person newly diagnosed with the COVID-19, this individual will be considered the index case and an epidemiological ring of contacts will be formed. These rings of contacts will include all the index case contacts on day 1, as are defined in the Catalan/Spanish protocol and eventually new cases that could be also linked with the index case a posteriori taking into account the incubation period. In our intervention, the index case will be randomized (experimental arm vs control arm). The ring assigned to the index case receiving experimental intervention will be treated too.

*[Ref1]: Ebola ça Suffit Ring Vaccination Trial Consortium. The ring vaccination trial: a novel cluster randomized controlled trial design to evaluate vaccine efficacy and effectiveness during outbreaks, with special reference to Ebola. BMJ. 2015 Jul 27;351:h3740. doi: 10.1136/bmj.h3740.

4.2 INTERVENTIONS

Arm	Intervention/treatment
CONTROL ARM	**No treatment. Standard surveillance** Contacts will complete a survey collecting demographic, epidemiological and clinical data and provides a swab for RT-PCR testing at baseline and day 14. Isolation of patient and contact tracing as per national guidelines.
EXPERIMENTAL ARM	**Prophylaxis of contacts** Contacts receive Hydroxychloroquine prophylaxis. Contacts will complete a survey collecting demographic, epidemiological and clinical and provides a swab for RT-PCR testing at baseline and day 14. Follow-up symptom diaries will be collected for 14 days. Prophylactic regimen: Hydroxychloroquine 800 mg (620 mg base) followed by 400 mg daily for 3 days [OHCQ 800mg d1, 400mg d2-4]

Supply, packaging, and storage

All treatments will be stored at and administered by the Pharmacy Department of Hospital Universitari Germans Trias i Pujol (HUGTIP). Hydroxychloroquine and will be stored in a safe place during the study, in accordance with conditions defined in its Summary of Products Characteristics (SmPC). Being marketed medication, specific temperature control for the study will not be performed. The medication will be supplied in blister packs and the primary packaging will not be altered by the Pharmacy office. An information sheet with the relevant information on instructions for use, pharmaceutical form, dosage and safety aspects will be attached. The distribution of the treatments will be performed through field teams consisting of health care workers. The treatments will be prepared for each participant. To check compliance with study treatment, the investigators will ask the subject about treatment adherence and this data is to be written in the database. Pills will not be counted to assess compliance.

4.3 AIM AND OUTCOME MEASURES

Hypothesis: Our primary hypothesis is that implementation of an antiviral prophylaxis among contacts of confirmed Covid-19 cases, detected by the Catalan epidemiological surveillance system will reduce the transmissibility of SARS-CoV-2 within the study population over the course of the outbreak.

4.3.1 Objectives and Endpoints

Objectives:

- Evaluate the transmissibility of SARS-CoV-2 and reduction of disease progression within the study population over the course of the outbreak.

Outcome Measures

1. Incidence of secondary Covid-19 cases among contacts of a case [Time Frame: Up to 14 days after start of treatment]
2. Incidence of new infections measured by PCR conversion to positive of contacts that are negative at baseline [Time Frame: Up to 14 days after start of treatment]

4.4 ELIGIBILITY CRITERIA

4.4.1 Inclusion Criteria:

1. Asymptomatic individuals exposed to a PCR confirmed COVID19 case within 5 days as either a healthcare worker or household contact
2. Aged ≥18 years male or female;
3. In women of childbearing potential, negative pregnancy test and commitment to use contraceptive method throughout the study.
4. Willing to take study medication;
5. Willing to comply with all study procedures;
6. Able to provide oral, informed consent and/or assent.

4.4.2 Exclusion Criteria:

1. With known history of cardiac arrhythmia (or QT prolongation syndrome);
2. Unable to take drugs by mouth;
3. With significantly abnormal liver function (Child Pugh C)
4. Need of dialysis treatment, or GFR≤30 mL/min/1.73 m^2;
5. Participants with psoriasis, myasthenia, hematopoietic and retinal diseases, CNS-related hearing loss or glucose-6-phosphate dehydrogenase deficit; 6. Persons already treated with any of the study drugs during the last 30 days;
7. Pregnant or lactating women;
8. Any contraindications as per the Data Sheet of Hydroxychloroquine.

If a contact is symptomatic at the time of the baseline visit, he/she will be classified as a co-primary case, and we will collect epidemiological information but will not be enrolled in the study as a contact participant.

4.5 RANDOMIZATION AND STATISTICAL ANALYSIS

Sample size calculation: Approximately 190 rings of size 15 contacts per ring (total 2850 contacts) are required to have 90% power to reject the null hypothesis (10% difference in incidence of secondary cases among contacts, expected 15% in control arm, and 5% in intervention arm). The final sample size achieved will depend on the number of new index cases accumulating during the study period.

Stratified randomization: Random allocation of intervention (the ring includes the index case plus its contacts) is done remotely, by a member of the study team not involved in the definition of rings. We will use block randomization to achieve balanced sample size in each group.

Allocation: The study is open label. Oral pre-informed consent is obtained before randomization in order to ask willingness to participate in the trial. With a positive answer to participate, informed consent and eligibility are done after randomization. Communicable disease control measures other than ring treatment are identical in the two groups.

Population: The primary analysis will be per protocol including all randomized individuals who completed the study procedures to day 14 with no major protocol deviations. Safety was assessed in the safety population, which included all participants who received any therapy, including usual care.

Analyses: We will analyze outcomes at the cluster level using the cumulative incidence for each cluster. If no cases of SARS-CoV-2 virus disease occurs in one group, we will derive a 95% CI for the intervention effect by fitting a β-binomial distribution to the cluster-level numerators and denominators. For comparisons in which cases of SARS-CoV-2 virus disease occurred in both groups, we will fit a Cox proportional hazards model using a cluster-level frailty term to adjust for clustering within rings. The primary analysis will be per protocol. We will conduct secondary analysis adjusted for baseline values of delay between symptom onset and isolation/treatment.

Planned interim analysis: We plan an interim analysis for sample size re-estimation and possible early trial termination for superiority or futility of the experimental therapy. The trial is open-label and does not need unblinding. The interim analysis will be performed by an independent statistician. The analysis will be performed on the primary endpoint when 25% (n=48) of patients have been randomized and have completed 14 days follow-up. Randomization will be done by blocks, so we expect similar numbers in each group at interim analysis. We will look at the 95% CI for the difference between groups. The Peto approach will be used: the trial will be ended using symmetric stopping boundaries at P<0.01, both in case of superiority or futility.

Interruption criteria: Incidence of secondary cases among contacts of a case is < 2% (stop for futility) or >8% (stop for superiority).

4.6 PROCEDURES AND STUDY VISITS

- Active surveillance, laboratory confirmation of cases of COVID-19, and the list of contacts is independently undertaken by Catalan epidemiological surveillance system (SUVEC).
- After notification of the disease the SUVEC will process the data and notify the researchers team.
- The researcher's team will call the positive cases to offer people diagnosed with coronavirus to participate in a clinical trial.
- An oral inform consent will be obtained by phone. The researcher will inform about the trial to individuals that fulfil inclusion criteria (based on online medical records and clinical history taken by phone) and the randomization process will start (for index cases and their contacts).
- Dedicated outbreak field-teams will visit candidates and verify the inclusion criteria eligibility on day 1.
-The SUVEC or researcher's team will provide the list of contacts. Oral inform consent and inclusion criteria verification) will be done for each contact.
-Kits will be numbered to ease traceability

1. Baseline visit

- Nasopharyngeal swab (or sputum if possible) will be collected and sent to the microbiology department for testing.
- Everyone will be asked and examined when needed for signs of COVID-19 infection:
    - Symptoms of acute respiratory infections (cough, odynophagia, rhinorrhea, myalgia, headache). Severe (any duration) or mild (lasting at least 48h - two nights)
    - Dyspnea of any duration
    - Fever (> 37.5) of any duration
    - Diarrhea accompanied by 1, 2, or 3

- Epidemiological investigation will include questions about:
    - number of days that has been in contact with the index case,

- place of contact (home, work, nursing care facility, hospital),
- use of mask (both case and contact)

- Contacts on the experimental arm will be offered prophylactic treatment as per regimen in Fig 1.

Fig 1. Treatment schedule for contacts of a COVID-19 case

Days	1	2	3	4	5	6	7	14
AM	♣♣♣♣ †	♣♣	♣♣*	♣♣			*	†

♣ Hydroxychloroquine 200 mg ; *Telephone check; † Home visit

2. Follow up day-3 (by telephone call)
- Everyone will be examined for signs of COVID-19 infection and will be asked about Adverse Events and Compliance to treatment.

3. Follow up day-7 (by telephone call)
- Evaluation of health status, adverse events, and compliance to treatment

4. Follow up day-14 (home visit)
- Evaluation of health status, adverse events, and compliance to treatment
- A nasopharyngeal swab will be collected from the contact.

5. Unscheduled follow up due to symptom presentation (home visit)
At any follow visit, if a participant presents with a clinical condition that might need a detailed medical evaluation (including, but not only respiratory distress with respiratory rate >=30 breaths/min; Temperature >38ºC, Blood pressure <90/60mmHg) will be referred to the reference hospital for further management. In a less severe symptomatic situation not requiring hospitalization we will take a nasopharyngeal swab at this time from contacts at home.

6. Evaluation of primary outcome - health status of contacts for 14 days follow-up-
- The Catalan epidemiological surveillance system (SUVEC) will initiate active surveillance of any asymptomatic person who meets the definition of contact, following the protocols.
- If during the 14 days after the exposure the contact develop symptoms, he/she is asked to immediately contact the SUVEC
- The SUVEC will investigate that contact to rule out infection by SARS-CoV-2
- The SUVEC will inform the outbreak team of the occurrence of any positive event (contact with symptoms and positive PCR)

7. Evaluation of Adverse Events
Safety outcomes will include the frequency and severity of adverse events (AE), serious AE (SAE), and AE of special interest (e.g., cardiac) up to 28 days from treatment start
See definitions and procedures below.

8. Evaluation of Compliance to treatment
We will use a self-reported questionnaire for assessment of adherence to treatment (Brief Medication Questionnaire – BMQ).
The tool includes a 5-item Regimen Screen that asks patients how they took each medication in the past week, a 2-item Belief Screen that asks about drug effects and bothersome features,

Fig 2. Workplan timeline for a contact

	Baseline	**Day 3**	**Day 7**	**Day 14**
Written Informed Consent	X			
Pregnancy test	X			
Clinical examination	X			
Inclusion criteria checks	X			
Nasopharyngeal Swab	X			X
Blood sample (Rapid Test)				
Adverse events assessment		X	X	X
Compliance assessment		X	X	
Follow up assessment			X	X

5 SUBSTUDY 2- EARLY TREATMENT OF OUTPATIENT CASES WITH COVID-19

5.1 STUDY DESIGN

Study Type:	Interventional
Estimated Enrolment:	190 COVID-19 cases
Allocation:	Randomized
Masking:	Open-label
Index Cases	Those individuals diagnosed of mild COVID-19 (SARS-CoV-2 PCR positive plus symptoms)
Intervention:	Pharmacological (Hydroxychloroquine in index cases)
Primary Purpose:	Prevention of disease progression
Actual Study Start Date:	March 16, 2020
Estimated Primary Completion Date:	May 13, 2020
Estimated Study Completion Date:	May 13, 2020
Site:	Catalonia

5.2 INTERVENTIONS

Arm	Intervention/treatment
CONTROL ARM	**No treatment. Standard surveillance.** Index case completes a survey collecting demographic, epidemiological and clinical data and provides a swab for RT-PCR testing at baseline and on day 3. Isolation of patient and contact tracing as per national guidelines.
EXPERIMENTAL ARM	**Treatment of COVID-19 (index case).** Index case receives Hydroxychloroquine*. Index case completes a survey collecting demographic, epidemiological and clinical data and provides a swab for RT-PCR testing at baseline and on day 3. Eligible individuals will be offered with hydroxychloroquine 800 mg (620 mg base) followed by 400 mg daily for 3 days] and darunavir 800 mg / cobicistat 150 mg tablets (oral, 1 tablet q24h, taking for 7 days). Isolation of patient and contact tracing as per national guidelines

5.2.1 Supply, packaging, and storage

All treatments will be stored at and administered by the Pharmacy Department of Hospital Universitari Germans Trias i Pujol (HUGTIP). Hydroxychloroquine and darunavir/cobicistat will be stored in a safe place during the study, in accordance with conditions defined in its Summary of Products Characteristics (SmPC). Being marketed medication, specific temperature control for the study will not be performed. The medication will be supplied in blister packs and the primary packaging will not be altered by the Pharmacy office. An information sheet with the relevant information on instructions for use, pharmaceutical form, dosage and safety aspects will be attached. The distribution of the treatments will be performed through field teams consisting of health care workers. The treatments will be prepared for each participant. To check compliance with study treatment, the investigators will

ask the subject about treatment adherence and this data is to be written in the database. Pills will not be counted to assess compliance.

5.3 AIM AND OUTCOME MEASURES

Hypothesis: Our primary hypothesis is that implementation of an early antiviral treatment intervention among confirmed cases with COVID-19 presenting mild symptoms will improve virological and clinical outcomes.

5.3.1 Objectives and endpoints

Objectives:

- Determine the virological and clinical outcome in SARS-CoV-2 positive cases.

Outcome Measures

Ring prophylaxis effectiveness to reduce development of disease assessed by Incidence Endpoints

1. Viral load reduction in nasopharyngeal swabs at day 3 after treatment start [Time Frame: Up to 3 days after start of treatment]
2. Time to complete resolution of symptoms [Time Frame: Up to 14 days after start of treatment]

Other outcomes

3. Hospitalization and death rate at day 14 after treatment start [Time Frame: Up to 14 days after start of treatment]

5.4 ELIGIBILITY CRITERIA

5.4.1 Inclusion Criteria

1. Patients who meet the requirements of the New Coronavirus Infection Diagnosis (Acute respiratory infection symptoms, fever, cough, shortness of breath, acute olfactory loss, and positive PCR)
2. Aged ≥18 years male or female
3. In women of childbearing potential[1], negative pregnancy test and commitment to use contraceptive method[2] throughout the study.
4. Willing to take study medication
5. Willing to comply with all study procedures, including repeat nasal swab at day 3
6. Able to provide oral and written informed consent

[1]A woman will be considered of childbearing potential if not permanently sterilized nor postmenopausal. Permanent sterilization methods include tubal ligation, hysterectomy and bilateral oophorectomy. Postmenopausal is defined as 12 months with no menses without an alternative medical cause.

[2]Contraceptive methods: male or female condom with or without spermicide, cap, diaphragm or sponge with or without spermicide, intrauterine device, bilateral tubal occlusion, vasectomized partner, sexual abstinence during the study.

5.4.2 Exclusion Criteria

1. Hospital admission or Serious condition meeting one of the following: (1) respiratory distress with respiratory rate ≥30 breaths/min; (2) oxygen saturation ≤93% on quiet status; (3) Arterial partial pressure of oxygen (PaO2)/oxygen concentration ≤300mmHg;

2. Critically ill patients meeting one of the following: (1) Experience respiratory failure and need to receive mechanical ventilation; (2) Experience shock; (3) Complicated with other organs failure and need intensive care and therapy in ICU;
3. Participants under treatment with medications likely to interfere with experimental drugs
4. Unable to take drugs by mouth;
5. With significantly abnormal liver function (Child Pugh C)
6. Need of dialysis treatment, or GFR ≤30 mL/min/1.73 m^2;
7. Participants with psoriasis, myasthenia, hematopoietic and retinal diseases, CNS-related hearing loss or glucose-6-phosphate dehydrogenase deficit
8. Participants with severe neurological and mental illness;
9. Pregnant or lactating women;
10. Inability to consent and/or comply with study protocol;
11. Individuals with known hypersensitivity to the study drugs;
12. Persons already treated with any of the study drugs during the last 30 days.
13. Concomitant administration of enzyme inducers (such as carbamazepine) which could lead to ineffectiveness of darunavir; and those who receive CYP3A4 substrates (such as statins) because of the risk of increased toxicity.
14. HIV patients (because these are already on antiretroviral treatment)
15. Any contraindications as per the Data Sheet of Rezolsta or Hydroxychloroquine.

5.5 RANDOMIZATION AND STATISTICAL ANALYSIS

Sample size calculation: We estimated that a sample size of 190 patients would provide the trial with 80% power to detect a difference of 0.5 $\log_{10}$ in the mean reduction of SARS-CoV-2 viral load at a two-sided significance level of $\alpha = 0.05$, assuming an expected standard deviation of 1.5. A 0.5 $\log_{10}$ copies/mL difference in reduction was chosen to represent the minimal threshold for a biologically relevant change for our analyses.

Stratified randomization: Random allocation of intervention is done remotely, by a member of the study team not involved in the definition of rings. For the purpose of Study-2 only cases meeting the eligibility criteria above will be included. We will use block randomization to achieve balanced sample size in each group.

Allocation: The study is open label.

Populations: The primary analyses will be performed with the per-protocol (PP) population. Safety will be assessed in the safety population, which included all participants who received any therapy, including usual care.

Statistical analyses: Efficacy will be determined by comparing the mean reduction of the viral load from baseline to day 3, with the use of a mixed effects regression model taking into account the randomization group and repeated measures within each individual. The viral load will be provided in logarithmic scale; specimens with undetectable viral load at a given follow-up assessment were assigned a value of 3 $\log_{10}$ copies per mL (i.e., lower limit of detection) for the purpose of statistical analysis. The secondary clinical outcome regarding between-group differences in disease progression will be assessed using risk ratio (RR) for the predefined events. The time to clinical improvement will be analyzed using Kaplan-Meier survival functions and hazard ratios (HRs), calculated using a Cox proportional hazards regression model based on the assumptions of proportional risks. Kaplan-Meier estimates will be compared using the log-rank test.

5.6 PROCEDURES AND STUDY VISITS

- Active surveillance, laboratory confirmation of cases of COVID-19.
- After notification of the disease the SUVEC will process the data and notify the researchers team.
- The researcher's team will call the positive cases in order to offer people diagnosed with coronavirus to participate in a clinical trial.
-Test and treatment Kits will be numbered to ease traceability
- Dedicated outbreak field-teams will visit candidates and verify the inclusion criteria eligibility on day 1.

1. Baseline visit

- Nasopharyngeal swab (or sputum for patients with productive cough) will be collected and sent to the microbiology department for testing.
    - Nasopharyngeal: Use only synthetic fiber swabs with plastic shafts. Insert a swab into the nostril parallel to the palate. Leave the swab in place for a few seconds to absorb secretions. Place swabs immediately into sterile tubes containing 2-3 ml of viral transport media.
    - Sputum: Have the patient rinse the mouth with water and then expectorate deep cough sputum directly into a sterile, leak-proof, screw-cap sputum collection cup or sterile dry container.
- Everyone will be asked and examined when needed for signs of COVID-19 infection to identify the severity signs (Temperature, Oxygen saturation, Respiratory rate, Blood Pressure)
- Patients on the experimental arm will be offered treatment according to regimen in Fig 3.

Fig 3. Treatment schedule for a COVID-19 mild case

Days	1	2	3	4	5	6	7	14
AM	●♣♣♣♣ †	●♣♣	●♣♣ †	●♣♣	●	●	● *	*

● DRV/c (Rezolsta) 800/150 mg; ♣ Hydroxychloroquine 200 mg ;
* Telephone check

5.6.1 Study visits

2. Follow up day-3 (home visit)
- A nasopharyngeal swab will be collected at home by the outbreak team
- Everyone will be examined for signs of COVID-19 infection and will be asked about Adverse Events and Compliance to treatment.

3. Follow up day-7 (telephone call)
- Evaluation of health status, adverse events, and compliance to treatment

4. Follow up day-14 (telephone call)
- Evaluation of health status

Fig. 4 Workplan timeline for a case.

	Baseline	**Day 3**	**Day 7**	**Day 14**	**Day 28**
Written Informed Consent	X				
Pregnancy test	X				
Inclusion criteria checks	X				
Clinical examination	X	X			
Nasopharyngeal Swab	X	X			
Adverse events assessment		X	X	X	X

Compliance assessment		X	X		
Follow up assessment			X	X	X

6 ADVERSE EVENTS

6.1 DEFINITIONS:

Adverse event (AE): Medical event presented by a patient or clinical research subject administered a pharmaceutical product, and which does not necessarily have a causal relation to the treatment.

Serious adverse event (SAE): Medical event classified as such and which, regardless of the dose involved:

- Causes patient death.
- Produces a life-threatening situation for the patient.
- Requires or prolongs in hospital admission.
- Produces important or persistent incapacitation/handicap or constitutes a congenital defect or anomaly.
- Needs action to prevent any of above situations.
- Is considered medically significant (examples of such events are intensive care in an Emergency Service or at home in a patient with allergic bronchospasm; blood dyscrasias or seizures not giving rise to hospital admission, or the development of drug dependency or abuse).

Unexpected adverse event (UAE): AE related to the product in investigation the nature or intensity of which does not coincide with the information available on the product administered (IB or SmPC).

Serious Unexpected Adverse Reaction (SUSAR): SAE related to the product in investigation the nature or intensity of which does not coincide with the information available on the product administered (IB or SmPC).

6.2 ADVERSE EVENTS ASSESSMENT

6.2.1 Seriousness

An SAE is any medical event that meets the criteria of SAE
Events not considered to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.

- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency out participant treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

6.2.2 Intensity

The following scale will be used:

- Grade 1 (mild): Symptoms causing no or minimal interference with usual social and functional activities.
- Grade 2 (moderate): Symptoms causing greater than minimal interference with usual social and functional activities.
- Grade 3 (severe): Symptoms causing inability to perform usual social & functional activities.
- Grade 4 (potentially life-threatening): Symptoms causing inability to perform basic self-care functions or medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death.
- Grade 5 (death): Any AE where the outcome is death.

6.2.3 Causality

All AEs must have their relationship to study intervention assessed by the physician who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- Related – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

6.2.4 Expectedness

An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention. Risk information of study interventions may be found in the SmPC of each study drug.

The assessment of the expectedness between an AE and the administration of treatment
is a decision to be made by the principal investigator OM or co-investigator MV, who are qualified physicians.

Expectedness will be assessed in relation to the AE being previously documented as per attached Technical Data Sheet – Ficha técnica point 4.8-). A serious unexpected adverse reaction (SUSAR) is a suspected adverse reaction (AR) whose nature, severity or outcome is not consistent with the Technical Data Sheet.

All unexpected serious ARs will be notified through Eudravigilance. For a suspicion of AR considered to be expected only for one of the two treatments (darunavir-cobicistat or hydroxychloroquine, we will consider question 7.25 (The rules governing medicinal products in the European Union VOLUME 10 - Guidance documents applying to clinical trials) on how should SUSARs of combination IMPs be reported? The question and answer document, section 7 of which includes relevant aspects of AR assessment to be considered.

6.2.5 Duration

For both AEs and SAEs, the Investigator will provide a record of start and stop dates of the event (expressed in the shortest time unit possible). Changes in the severity of an AE or SAE will be documented in the clinical record.

6.2.6 Action taken

The Investigator will report the action taken with study intervention as a result of an AE or SAE, as applicable (e.g., discontinuation or reduction of dose, as appropriate) and report whether concomitant and/or additional treatments were given for the event.

6.2.7 Outcome

Any AE or SAE will be followed preferably until:

- Resolution of the event;
- Stabilization of the event; or
- Resetting the baseline situation of the event, in case baseline situation is available.

Otherwise, they will continue until:

- The event can be attributed to products other than the study medication or factors unrelated to the study; or
- It is unlikely to obtain further information

In the event that the subject dies from a SAE, the rest of AE or SAE that are active will be recorded as "not recovered".

6.3 TIME FRAME FOR ADVERSE EVENTS COLLECTION

The investigator must collect all the AE and SAE that occur from the moment the subject signs the informed consent until the last study visit.

6.4 DOCUMENTATION RELATED TO ADVERSE EVENTS

Each AE and SAE to take place during the study should be documented in the medical records of the participant in accordance with standard clinical practice of the investigator. For each SAE, an independent set of SAE form will be used independently. Only if there are multiple SAE at the time of the initial report and these are temporary and / or clinically interrelated can be registered on the same set of SAE form.

The investigator should try to make a diagnosis of the event based on the signs, symptoms and / or other clinical information. An AE diagnosis must be recorded per line, or a sign/symptom if the diagnosis is not available. If a diagnosis subsequently becomes available, this then should be entered, and the sign/symptom crossed out.

SAE pages found in the investigator's file shall be completed as precisely as possible and shall be signed by the investigator before being sent to the sponsor. In the initial page of the SAE form, the investigator must provide his/her opinion in regard to the relationship of the event to the study intervention.

6.5 PREGNANCY

Cases of pregnancy shall be recorded as AE and should only be considered as SAE only if they meet any seriousness criteria. Pregnancy is also a protocol deviation requiring premature termination of the subject. The investigator will provide medical support to the pregnant subject.

No special measures are required in relation to the pregnancy of a partner of a male participant.

6.6 PROCEDURE FOR ADVERSE EVENT REPORTING

6.6.1 Investigator

All AEs and SAEs will be recorded, regardless of the causality, in the corresponding AE form.
The investigator will immediately notify the study sponsor of any SAE. The notification will be performed within 24 hours of first knowledge by the investigator.

6.6.2 Contact details for Sponsor

safety@fls-rs.com
The recording of AEs and SAEs is the responsibility of the trial investigator team, which should indicate the time of appearance of the event (expressed in the shortest time unit possible), its serious / not serious status, and in case it is considered related to investigational products, whether it was expected or unexpected. The intensity of the event (grade 1 to 5) is to be specified, along with the measures adopted (none, treatment, temporal or permanent discontinuation of investigational product), course (complete remission, partial remission, persistence) and causality based on the criteria indicated in section 6.2.3.

6.6.3 Sponsor

A group of researchers designated by the sponsor, will review the list of AEs, SAEs and SUSARs reported by the investigators in the CRF. The objective of this revision is the proper adjudication and notification, if needed, to the Spanish Agency of Medicines and Medical Devices (AEMPS) through the notification to Eudravigilance database, competent authorities of the autonomous region and the Ethics Committee implicated in the clinical trial.

The sponsor will inform the AEMPS, the competent authorities of the autonomous region and the Ethics Committee implicated in the clinical trial about any important information of security of the investigational medicinal product.

The sponsor will inform the Spanish AEMPS of any SUSAR which may be related to the study treatment.

The sponsor will inform competent authorities of the involved autonomous region of any SUSAR which may be related to the study treatment, and that have been happened in subjects in its autonomous region.

The deadlines to notify a SUSAR is, from the first knowledge by the investigator:

- 15 days
- 7 days if the SUSAR has resolved in death or has been life-threatening. Relevant follow-up information for these cases will be subsequently be submitted within an additional 8 days.

If the notification is sent in electronic form, it will not necessary to notify the competent authorities of the autonomous region.

The sponsor will keep a detailed register of all the AE notified by the investigators.

All AE will be notified in table form in the final report of the clinical trial.

7 DATA COLLECTION

The CRF will be administered to all selected participants. Data will be collected using face-to-face questionnaires (paper CRF) by the field clinical teams and data will be entered in a standardized electronic questionnaire (digital CRF) to be accessed online, and which will be merged in a secured web site that uploads data in real time. The chief investigator will be responsible for keeping a subject identification log of all subjects enrolled into the study, their corresponding study number and sample IDs. This information will be kept on a secure server in a password protected file and will only be available to the chief investigator and the study personnel who are directly obtaining clinical data. Identifying information of a SARS-CoV-2 PCR result of some participants will be extracted from the Epidemiological Repository of Catalonia (REC), which is the data platform that aggregates and manages data of Catalan surveillance systems of notifiable diseases including epidemic outbreaks like SUVEC (all are of mandatory declaration), and which is coordinated by the general sub-directorate for public health emergencies surveillance and response of the Public Health Agency of Catalonia, Health Department, Government of Catalonia. Subjects will be assigned a linked-anonymized study number to ensure subject confidentiality throughout the duration of the study.

8 DATA MANAGEMENT

The clinical trial has created a data management system and procedures to warrant homogenization, traceability, and data quality. Paper CRF will be used to collect the CRF's data during home visits, and electronic CRF for telephone visits. Data will be entered in a digital CRF. Quality control procedures will be put in place for data checking by an external data management group. Rigorous consistency checks will be created in order to reduce errors during data entry. The data management group and statisticians will be responsible for the final analysis of the data. Study data will be sent from paper CRF to a central FLS database. This database will enter and store the final data and will be on a server hosted at a secure Data Center with appropriate series of protocols to test and maintain network security, and to provide access management policies for network drives, databases and remote access.

For data safety purposes each person entering data in the digital CRF will be required to define clear data access. Data management team and researchers will be the only ones to access the database. The backup of the data will be done on a timely basis. The final stored data will be placed on the FLS server and will be anonymous; the tools used to identify individuals may have individual identifiers, but this information will only be associated to a numerical identification number. This information will uniquely identify project participants will be associated with the rest of the captured sensitive information. If information that could enable to identify individuals has to be stored, used or shared, it will be encrypted. Consequently, those receiving the final data for analysis will not have access to any information that might help to physically identify individuals.

9 DATA QUALITY INSPECTION TEAM

People from FLS will be selected to constitute a data quality inspection team in order to undertake periodic quality reviews of the entered data. The Data Quality inspection team will identify potential data entry errors, inconsistencies and missing data.

9.1 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

Data will be stored in accordance with the Data Protection Law (LOPD, the organic Law 3/2018 of 5 December on the Protection of Personal Data and the Guarantee of Digital Rights complementary to the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data). The chief investigator will have overall control of, and act as the custodian for all data for the full duration of the study. The data will be available for internal monitoring (verification of data using paper CRF validate by research team against the information recorded in the CRF).

10 MONITORING AND GOOD CLINICAL PRACTICE

We will carry out risk-adjusted monitoring since the trial is performed in a clinical care practice setting, with follow-up of the subjects treated in the community or primary care setting.

Data will be entered directly into the application, and it will be considered source data, as the contacts do not have a care episode opened.

Data monitoring tasks defined:

- Verification of the study master file (authorizations, protocol, drug information and other essential documents, pursuant to section 8 of ICH Guide E3),
- Verification of signature of informed consent,
- Checking the dates of visit and verification of absent data not entered in the application
- Verification of the values of serological results
- Detection of unreported adverse effects from the review of data from the medical records with open episodes during the course of the study

11 ETHICS

11.1 GENERAL CONSIDERATIONS

The clinical trial will be conducted according to the principles of the Declaration of Helsinki, (amended Fortaleza, Brazil, October 2013).

This study will be conducted according to Spanish regulations regarding clinical trials (Royal Decree 1090/2015) and biomedical investigations (Organic Law 14/2007 of biomedical investigation and the Royal Decree 1716/2011), which develop the European Directive on clinical trials (Regulation EU No 536/2014). The required documentation prior to the start will be:

- Protocol acceptance by the Sponsor and the Coordinating Investigator
- Protocol approval by the Ethics Committee
- Protocol authorization from the Spanish Drug Agency (Ministry of Health)

All subjects will be guaranteed continued medical and nursing supervision throughout the duration of the study.

This study will conform to the standards of GCP published by ICH (E6 R2).

11.2 DATA HANDLING

The processing of the data will be subject to current legislation as regards data protection (LOPD, The Organic Law 3/2018 of 5 December on the Protection of Personal Data and the Guarantee of Digital Rights complementary to the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data).

The participant will be identified in the records by the corresponding unique code number. The participant is to be guaranteed anonymity and is to be informed that all communication will take place between him/her and the investigator and not the sponsor of the study.

The first contact with the patient will be made by the Epidemiological Surveillance Emergency Service of Catalonia (SUVEC). The SUVEC depends on the Public Health Agency of Catalonia (ASPCAT).

The SUVEC aim is to respond quickly to the diseases of urgent declaration and epidemic outbreaks declared by doctors in the healthcare network of Catalonia through research and control of urgent declaration diseases, outbreaks and public health alerts, as well as the application of prevention and control measures (chemoprophylaxis, vaccination, detection of risk contacts, isolation measures).

On the other hand, the ASPCAT is regulated by Law 5/2019, July 31, of the Public Health Agency of Catalonia and modification of the Law 18/2009, October 22, on public health. Its functions are expressly attributed to "Fostering research in public health and promoting the training of professionals engaged in it, in collaboration with other competent bodies, universities and research centers."

According to the data protection regulations, the ASPCAT, and therefore the SUVEC can process the data of patients (and their contacts) diagnosed with SARS-CoV-2 coronavirus to invite them to participate in the clinical trial. In this sense, Organic Law 3/2018, on the Protection of Personal Data, establishes through its Additional Provision seventeenth in section 2. B that "b) the health authorities and public institutions with powers to monitor the public health can carry out scientific studies without the consent of those affected in situations of exceptional relevance and seriousness to public health. "

Therefore, and understanding that given the current situation of coronavirus, and that ASPCAT, and therefore SUVEC, is a public institution with powers in public health surveillance, and that it specifically has the function of promoting health research public, would be enabled to process the data in order to offer people diagnosed with coronavirus to participate in a clinical trial, without prejudice to the need to sign the subsequent informed consent document to participate in the trial.

11.3 ORAL INFORMED CONSENT AND PARTICIPANT INFORMATION SHEET AND WRITTEN INFORMED CONSENT

The investigator will inform the candidates of the nature, duration and purpose of this study and, in addition, of all the inconveniences and obstacles that, if any, can be expected. In addition, information will be provided to the participant. Subjects must have the legal capacity to give their consent and exercise their freedom of decision. If the subject wishes to participate in the study, his/her oral consent will be obtained by phone.

The consent will be given orally during the enrolment telephone call and will be obtained before starting the participation in the study. The investigator will keep a call recording of the informed consent process.

At the Baseline home-visit, a Written Informed Consent will be obtained.

11.4 INSURANCE POLICY

In accordance with the Royal Decree 1090/2015, of 4th December, the trial sponsor has a policy of liability insurance. The sponsor shall extend this policy or another with equivalent coverage until the end of the trial. This policy also covers the responsibilities of the sponsor, the principal and his/her collaborators, as well as the hospital or site where they carry out the clinical trial.

APPENDIX. LIST OF INVESTIGATORS AND KEY ROLES:

PARTNER/PRINCIPAL INVESTIGATOR (PI) /INVESTIGATOR (I)	**KEY ROLE**
Hospital Universitari Germans Trias i Pujol	
Oriol Mitja, (PI) Infectious Diseases Department,	Conceptualizing a research idea Creating a research design Selection of statistical tests/analyses Performing statistical analyses and computations (including computer work) Interpretation of statistical analyses Laboratory analyses
Marti Vall, (I) Infectious Diseases Department,	
Roger Paredes, (I) Infectious Diseases Department,	
Jordi Ara, (I) Nephrology Department,	
Lurdes Matas, (I) Microbiology Department,	
Ventura Clotet, (I) Infectious Diseases Department,	
Maria Ubals, (I) Infectious Diseases Department	
Carles Quiñones (I), Pharmacy Department	
Departament de Salut	
César Velasco, (PI) Agencia de Qualitat i Avaluació Sanitàries de Catalunya (AQuAs), Barcelona.	Patient identification and enrolment Patient examination, randomization, treatment and follow-up Data collection Creating research design
Rosa M Vivanco Hidalgo, (I) Agencia de Qualitat i Avaluació Sanitàries de Catalunya (AQuAs), Barcelona	
Servei d'Urgències de vigilancia epidemiológica de Catalunya (SUVEC),	
Joan Guix, (I) Secretaria de Salut Pública del Departament de Salut, Generalitat de Catalunya	
Robert Fabregat, (I) Director General de Recerca i Innovacio del Departament de Salut, Generalitat de Catalunya	
Josep Ma Argimon, (I) Institut Català de la Salut, Departament de Salut, Generalitat de Catalunya	
Centre for Epidemiological Studies on Sexually Transmitted Diseases and HIV/AIDS of Catalonia (CEEISCAT)	
Jordi Casabona, (PI)	Building an online survey supervision of data entry Data cleaning and coding Participating in the research design
Alexis Sentís, (I)	

Treatment of non-severe confirmed cases of COVID-19 and chemoprophylaxis of their contacts as prevention strategy: the BCN PEP CoV-2 Study

Short name: CQ4COV19

EudraCT: 2020-001031-27

ClinicalTrials.gov Identifier: NCT04304053

Principal Investigator Name: Oriol Mitja

Protocol: v15.0, 12/05/2020

Track record

Version	Date	Description
v11	06.03.2020	First version approved
v12	17.03.2020	Includes substantial amendment No.1 v1 (17.03.2020) **Sub-studies 1 and 2- Treatment schedule with HCQ (cases, contacts):** Increase of HCQ total dose- Hydroxychloroquine 800 mg (620 mg base) followed by 400 mg daily for 6 days (total dose 3.2g).
v13	30.03.2020	Includes substantial amendment No.2 v1 (17.03.2020) **Sub-study1 and 2**: Sample size re-estimation and SAP adjusted **Sub-study -** Addition of serology measurement on day 14 **Sub-study 2-** DRV no longer included because of cumulative evidence on inefficacy for SARS-CoV-2 **Sub-study 2-** Time frame extension for SARS-CoV-2 PCR assessment because of suspicious of delayed viral dynamics
v14	30.03.2020	Includes additional information requested by the AEMPS on amendment No. 2
V15	12.05.2020	Includes substantial amendment No. 3 v1 (13.05.2020) **Sub-study1 and 2:** Data management and cleaning process by consultancy TRF

Sponsor Name:

1. Fundación FLS de Lucha contra el Sida, las enfermedades infecciosas y la promoción de la salud y la ciencia

Funding partners:

2. Institut Català de la Salut, Generalitat de Catalunya
3. Departament de Salut, Generalitat de Catalunya
4. Laboratorios Rubió SA
5. Laboratorios Gebro pharma SA

SIGNATURE PAGE

Principal investigator signature

Title: Treatment of non-severe confirmed cases of COVID-19 and chemoprophylaxis of their contacts as prevention strategy: the BCN PEP CoV-2 Study

ID: CQ4COV19
Protocol: v15.0, 12/05/2020
EudraCT: 2020-001031-27
ClinicalTrials.gov Identifier: NCT04304053

I, the undersigned, have read and understood the protocol specified above and agree on its content. I agree to perform and conduct the study as described in the protocol and in accordance with the relevant laws/regulations and standards outlined in the Clinical Trial Agreement.

Study investigator:

Signed: Date: 12/05/2020

Name Oriol Mitja

Title Associate Professor, Infectious Diseases and Global Health
Hospital Universitari Germans Trias I Pujol, Badalona
omitja@flsida.org

Table of Contents

1. BRIEF SUMMARY

This study is a research project to evaluate the efficacy of hydroxychloroquine for post-exposure prophylaxis and early treatment of Covid-19. The intervention entails administering prophylactic hydroxychloroquine to all contacts **(Substudy 1, contacts)** and treating non severe confirmed cases with hydroxychloroquine **(Substudy 2, cases).** Therefore, the present document must be read as a master protocol including the two evaluations.

Substudy contacts Prophylactic hydroxychloroquine treatment administered to all contacts of confirmed index cases aims to protect all potential individuals that could become infected and develop the disease.

Substudy cases Treatment of patients can reduce viral shedding in respiratory secretions to undetectable levels resulting in a reduction on the probability of onward transmission of SARS-CoV-2.

Substudy	Condition or disease	Intervention/treatment	Phase
1 - Contacts	**Contact of COVID-19 case (index case confirmed with PCR)**	Pharmacological intervention: treat with hydroxychloroquine	Proof of concept (Phase III)
2 - Cases	**Confirmed non severe case of COVID-19: SARS-CoV-2 positive by PCR plus mild respiratory symptoms**	Pharmacological intervention: treat with hydroxychloroquine	Proof of concept (Phase III)

2. BACKGROUND

2.1 THE USE OF CHEMOPROPHYLAXIS AS PREVENTION IN INFECTIOUS DISEASES

The current COVID-19 emergency warrants the urgent development of potential strategies to protect high risk subjects (close contacts, health care workers, and others). The reason is that secondary attack rate of households (SARh) is ~15%, and that of close contacts (SARc)~ 10% (1,2). This means that the risk of becoming infected after contact with a COVID-19 case is very high. The SARc is like influenza (10%) and much higher than meningococcal disease (<1%).

Postexposure prophylaxis (PEP) using antimicrobial agents is effective in preventing illness after potential or documented exposure to a variety of microbial pathogens and in reducing the risk of secondary spread of infection. The most similar situation to SARS-CoV-2 infection is influenza infection. High risk people exposed to Influenza (oseltamivir 75mg, twice daily for five days). Previous research on influenza has indicated that antiviral drugs administered before o short after symptom onset can reduce infectiousness to others by reducing viral loads in the respiratory secretions of patients and targeted prophylactic use of contacts reduce the risk of becoming infected (3,4). The measure of providing antiviral treatment to patients and prophylaxis to the close contacts of influenza patients has been recommended by the World Health Organization as a principle of early aggressive measures to prevent pandemic influenza (5) and the strategy was shown highly effective in reducing the incidence of secondary cases. The same principle could be applied to all type of respiratory infections with epidemic potential spread by droplet transmission, including SARS-CoV-2. We consider that this approach might be successful also if performed during the current SARS-CoV-2 epidemic due to the similarities of both infections.

2.2 CURRENT KNOWLEDGE OF THE EFFICACY OF DRUGS TO TREAT COVID-19

2.2.1 Hydroxychloroquine

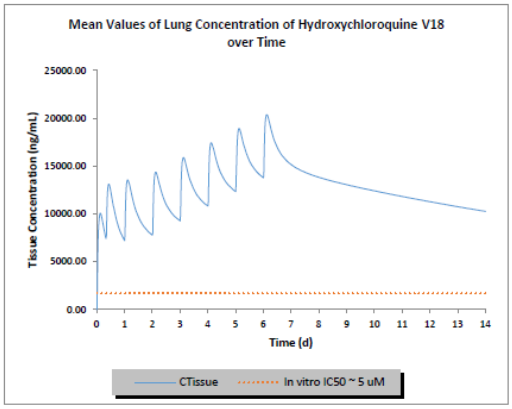
There are some reports and clinical trials that describe and investigate the efficacy of different drugs, among which the aminoquinolines.

In vitro studies: Hydroxychloroquine (HCQ) is a drug that has been extensively used for the prevention of malaria. HCQ showed excellent in vitro results and strong antiviral effects on SARS-CoV-2 infection of primate cells at low concentration. The EC50's were 0.72uM and 6.1 at 48 and 24 hrs incubation, respectively (6,7). In SARS-CoV and MERS infections, an IC50 of approximately 5uM provides a reasonable and achievable target concentration to reach in plasma and lung (7). HCQ was found to be more potent than chloroquine (EC50 5.47uM, and 1.1uM in a previous study [6]) to inhibit SARS-CoV-2 in vitro. This family of drugs appears to interfere with terminal glycosylation of the cellular receptor, angiotensin-converting enzyme 2 which is the main host cell receptor of SARS-CoV-2 (8). This may negatively influence the virus-receptor binding and abrogate the infection, with further ramifications by the elevation of vesicular pH, resulting in the inhibition of infection and spread of SARS-CoV at clinically admissible concentrations.

In vivo studies: An open-label non-randomized controlled trial in 36 patients diagnosed of SARS-CoV-2 reported that hydroxychloroquine alone or in combination with azithromycin reduced detection of SARS-CoV-2 RNA in upper respiratory tract specimens compared with a non-randomized control group but did not assess clinical benefit (9). The results showed that patients in the treatment group were significantly more likely to test negative for the virus on Day 6 than patients in the control group (70% vs 12.5% virologically cured, $p<0.001$). Moreover, all the six patients who were treated with a combination of HCQ and azithromycin tested negative on Day

6. The authors argue that this finding speaks to the effectiveness of HCQ and a potential synergistic effect of its combined treatment with azithromycin. A study in China reported that chloroquine treatment of COVID-19 patients had clinical and virologic benefit versus a comparison group and chloroquine was added as a recommended antiviral for treatment of COVID-19 in China (10).

Pharmacological aspects: According to pharmacological modelling conducted (*Figure* - Scott Miller, 16/03/2020) higher dose regimen (OHCQ 800mg d1, 400mg d2-7 (total dose 3,2g) will give good plasma levels and corresponding lung levels. Plasma troughs will be nearer to 100ng/ml, compared to 70ng/ml for a lower dose regimen OHCQ 800mg d1, 400mg d2-4 (total dose 2,0g). Lung concentrations will be much higher (2-2.5 log higher), but the free log concentration in lung epithelial cells are what will matter (which is not known).



Side Effects: Hydroxychloroquine has a good safety profile (60% reduction of AEs compared to chloroquine) with a 3-day treatment course (Total dose (adults): 2.0 hydroxychloroquine sulphate in 3 days (drug datasheet). Gastrointestinal upset has been reported with HCQ intake. Retinal toxicity has been described with long-term use of CQ and HCQ, and may also be related to over-dosage of these medications (daily doses of hydroxychloroquine sulphate greater than 6.5 mg/kg (5 mg/kg base) of actual body weight, durations of use greater than five years). Isolated reports of cardiomyopathy and heart rhythm disturbances caused by treatment with CQ have been reported. Chloroquine should be avoided in patients with psoriasis and porphyria. Both CQ and HCQ are metabolized in the liver with renal excretion of some metabolites, hence they should be prescribed with care in people with liver or renal failure.

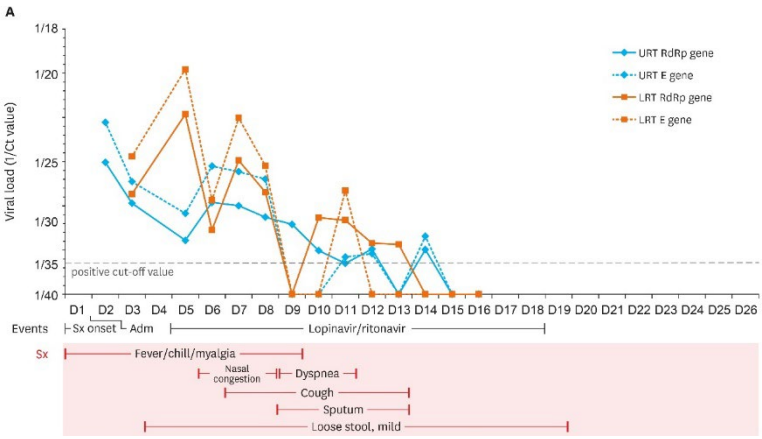
2.2.2 Protease inhibitors

Lopinavir/ritonavir, a protease inhibitor used to treat HIV/AIDS, was found to inhibit the *in vitro* cytopathic effect of SARS-CoV and MERS-CoV at concentrations (Half maximal effective concentration EC50 ~4.0µg/ml) achievable in humans.(7) Lopinavir/ritonavir 400/100, pharmacokinetic parameters for lopinavir are as follows: Cmax 9.6µg/ml, T1/2 5h, AUC24 186 µg*h/ml. In addition, preliminary results show that this drug, either alone or with various combinations could provide some clinical benefit to the treatment of hospitalized patients with SARS-CoV-2 infection. However, the drug is so far offered to sick patients only and we believe that it should also be evaluated in mild cases in which it could contribute to halt transmission. Common side effects include diarrhea, nausea, abdominal pain in about 27% of patients treated.

Darunavir (DRV)/Cobicistat, is also a protease inhibitor used to treat and prevent HIV/AIDS. Its mechanism of action is very similar to Lopinavir/ritonavir. This drug combination was shown to be as effective as lopinavir/ritonavir for the treatment of HIV/AIDS. However, this combination is better tolerated tan lopinavir/ritonavir because the adverse effects rate is lower (diarrhea 2% vs 27%). Besides, the drug is being trialed currently for COVID-19 and preliminary seem promising (clinicaltrials.gov/ct2/show/NCT04252274).

***Amendment:** On 4th April, during the implementation of the trial, Jansen pharmaceuticals released a recommendation to stop the use of DRVc due to lack of in vitro efficacy.(11) In addition human clinical trials demonstrated lack of efficacy of LPVr vs Placebo. It has been considered that the magnitude of the possible clinical benefit of LPVr if it is started in the early stages of the disease is small and does not compensate for the gastrointestinal and renal toxicity of the drug. (12)

2.3 MONITORING EFFICACY OF TREATMENT, CLINICAL AND VIROLOGICAL OUTCOMES



The virus is detected from URT specimens on day 2 (10^7 copies/ml) of symptom onset, increasing levels peak on day 5-7 (10^8 copies/ml) and then become spontaneously negative by day 14. In serum, plasma, urine, and stool samples, the virus is detected at very low levels. In a study including the 66 confirmed cases, (13) the median time from the onset of symptoms to first negative RT-PCR results for oropharyngeal swabs in convalescent patients was 9.5 (6.0-11.0) days, for stool samples was 11 (9-16) days. The Figure shows the Viral load kinetics of respiratory specimen presented by reverse Ct value. Positivity of urine samples was low (7%) and all blood specimens were negative. Exceptionally, 4 cases have been found to have positive rt-PCR after clinical and molecular cure (2 consecutive negative tests) (14).

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3. STUDY SITES

The study will be conducted over the course of a COVID-19 outbreak in Catalonia and for the selection and case definitions of the participants we will follow the current Catalan/Spanish protocols in line with WHO. The detection and notification of confirmed cases and contacts is centralized by the Catalan epidemiological surveillance system (SUVEC). Thus, for the purpose of this study randomization will be performed by a member of this team.

The study outbreak team, consisting of 120 health care workers, will visit all eligible cases and contacts at home for baseline assessment, administration of intervention drugs (in the experimental arm) and follow-up assessments to explore the effect of the intervention.

Individuals who choose not to participate in the study will be managed following the current protocols.

4. SUBSTUDY 1 – CHEMOPROPHYLAXYS OF CONTACTS

4.1 STUDY DESIGN

Study Type:	Interventional (ring treatment trial)
Estimated Enrolment:	2250 contacts (average 3 contacts in each cluster)
Allocation:	Cluster-randomized
Masking:	Open-label
Contacts:	As defined by the current protocol of the Catalan epidemiological surveillance system
Intervention:	Pharmacological (Hydroxychloroquine in index cases and in contacts)
Primary Purpose:	Prevention at population level
Actual Study Start Date:	March 16, 2020
Estimated Primary Completion Date:	May 13, 2020
Estimated Study Completion Date:	May 13, 2020
Site:	Catalonia

Design considerations

The design intervention is based on the design used during the vaccination trial developed for Ebola in 2015 (ref1). This was a cluster randomized controlled trial with the aim of evaluating vaccines against the disease in Guinea, West Africa. In the ring vaccination trial, a person newly diagnosed with the disease becomes the index case around whom an epidemiologically defined ring is formed. This ring is then randomized to either immediate vaccination (intervention) or delayed vaccination (control) in a 1:1 ratio on an open label basis. The incidence of disease is compared between the two arms over equivalent time periods measured from the time of randomization of each ring. Comparing the hazard ratio in those enrolled in the study allows estimation of vaccine efficacy, while overall vaccine effectiveness can be estimated by comparing incidence across all members of the rings, including those not eligible for vaccination in the study. This design permits to track the epidemic, recruiting individuals at increased risk of infection due to their connection to a case and thus, may both contribute to transmission interruption and have a higher power to detect vaccine efficacy than other study designs.

In our scenario, after the Catalan epidemiological surveillance system detects a person newly diagnosed with the COVID-19, this individual will be considered the index case and an epidemiological ring of contacts will be formed. These rings of contacts will include all the index case contacts on day 1, as are defined in the Catalan/Spanish protocol and eventually new cases that could be also linked with the index case a posteriori taking into account the incubation period. In our intervention, the index case will be randomized (experimental arm vs control arm). The ring assigned to the index case receiving experimental intervention will be treated too.

If the index case is identified but he/she does not meet the inclusion criteria (for example, due to hospital admission), we will recruit and randomize his/her ring of contacts in the clinical trial. The ring will receive the experimental intervention or not according to the group assigned to the index case.

Additionally, we will enhance passive recruitment by conducting an Information, Education, Communication (IEC) campaign in the social media (Twitter, etc.). The material posted will explain information about the study (describing the aims, details, risks and benefits), describe the criteria for inclusion, and provide contact information with the research team for those people who meet the criteria and are willing to participate. This procedure will allow to reach the estimated sample in the contacts group.

*[Ref1]: Ebola ça Suffit Ring Vaccination Trial Consortium. The ring vaccination trial: a novel cluster randomized controlled trial design to evaluate vaccine efficacy and effectiveness during outbreaks, with special reference to Ebola. BMJ. 2015 Jul 27;351:h3740. doi: 10.1136/bmj.h3740.

4.2 INTERVENTIONS

Arm	Intervention/treatment
CONTROL ARM	**No treatment. Standard surveillance** Contacts will complete a survey collecting demographic, epidemiological and clinical data and provides a swab for RT-PCR testing at baseline and day 14.
EXPERIMENTAL ARM	**Prophylaxis of contacts** Contacts receive Hydroxychloroquine prophylaxis. Contacts will complete a survey collecting demographic, epidemiological and clinical and provides a swab for RT-PCR testing at baseline and day 14. Follow-up symptom diaries will be collected for 14 days. Prophylactic regimen: Hydroxychloroquine 800 mg (620 mg base) followed by 400 mg daily for 6 days [OHCQ 800mg d1, 400mg d2-7 (total dose 3,2g)].

Supply, packaging, and storage

All treatments will be stored at and administered by the Pharmacy Department of Hospital Universitari Germans Trias i Pujol (HUGTIP). Hydroxychloroquine will be stored in a safe place during the study, in accordance with conditions defined in its Summary of Products Characteristics (SmPC). Being marketed medication, specific temperature control for the study will not be performed. The medication will be supplied in blister packs and the primary packaging will not be altered by the Pharmacy office. An information sheet with the relevant information on instructions for use, pharmaceutical form, dosage and safety aspects will be attached. The distribution of the treatments will be performed through field teams consisting of health care workers. The treatments will be prepared for each participant. To check compliance with study treatment, the investigators will ask the subject about treatment adherence and this data is to be written in the database. Pills will not be counted to assess compliance.

4.3 AIM AND OUTCOME MEASURES

Hypothesis: Our primary hypothesis is that implementation of an antiviral prophylaxis among contacts of confirmed Covid-19 cases, detected by the Catalan epidemiological surveillance system will reduce the transmissibility of SARS-CoV-2 within the study population over the course of the outbreak.

4.3.1 Objectives and Endpoints

Objectives:

- Evaluate the transmissibility of SARS-CoV-2 and reduction of disease progression within the study population over the course of the outbreak.

Outcome Measures

1. Incidence of secondary Covid-19 cases among contacts of a case [Time Frame: Up to 14 days after start of treatment]
2. Incidence of new infections measured by PCR conversion to positive of contacts that are negative at baseline [Time Frame: Up to 14 days after start of treatment]

Other outcomes

1. Incidence of new infections measured by SARS-CoV-2 IgM/IgG positivity at day 14 [Time Frame: Up to 14 days after start of treatment]

4.4 ELIGIBILITY CRITERIA

4.4.1 Inclusion Criteria:

1. Asymptomatic individuals exposed to a PCR confirmed COVID19 case within 7 days as either a healthcare worker or household contact
2. Aged ≥18 years male or female;
3. In women of childbearing potential, negative pregnancy test and commitment to use contraceptive method throughout the study.
4. Willing to take study medication;
5. Willing to comply with all study procedures;
6. Able to provide oral, informed consent and/or assent.

4.4.2 Exclusion Criteria:

1. With known history of cardiac arrhythmia (or QT prolongation syndrome);
2. Unable to take drugs by mouth;
3. With significantly abnormal liver function (Child Pugh C)
4. Need of dialysis treatment, or GFR≤30 mL/min/1.73 m2;
5. Participants with psoriasis, myasthenia, hematopoietic and retinal diseases, CNS-related hearing loss or glucose-6-phosphate dehydrogenase deficit; 6. Persons already treated with any of the study drugs during the last 30 days;
7. Pregnant or lactating women;
8. Any contraindications as per the Data Sheet of Hydroxychloroquine.

If a contact is symptomatic at the time of the baseline visit, he/she will be classified as a co-primary case, and we will collect epidemiological information but will not be enrolled in the study as a contact participant.

4.5 RANDOMIZATION AND STATISTICAL ANALYSIS

Sample size calculation: Approximately 750 rings of size 3 contacts per ring (total 2250 contacts) are required to have 80% power to reject the null hypothesis (10% difference in incidence of secondary cases among contacts, expected 15% in control arm, and 5% in intervention arm) The final sample size achieved will depend on the number of new index cases accumulating during the study period.

Stratified randomization: Random allocation of intervention (the ring includes the index case plus its contacts) is done remotely, by a member of the study team not involved in the definition of rings. We will use block randomization to achieve balanced sample size in each group.

Allocation: The study is open label. Oral pre-informed consent is obtained before randomization in order to ask willingness to participate in the trial. With a positive answer to participate, informed consent and eligibility are done after randomization. Communicable disease control measures other than ring treatment are identical in the two groups.

Population: Considering the open-label design and the possibility of side effects caused by the study medication, the primary efficacy analysis was performed on the intention-to-treat (ITT) population. Sensitivity analyses were performed with the per-protocol (PP) population, which included all randomized individuals who completed the study procedures to day 14 with no major protocol deviations. Safety was assessed in the safety population, which included all participants who received any therapy, including usual care.

Analyses: Variables will be described at the individual level using the frequency and percentage (categorical variables) and the mean and standard deviation (SD) or median and interquartile range (IQR) (continuous variables). The cumulative incidence in primary, secondary, and safety outcomes will be compared at the individual level using a binomial regression model with robust standard errors to account for clustering within rings. We will define a generalized linear model with a binomial distribution and a logarithm link function to estimate the relative risk (RR) as a measure of effect. The individual-level variables adjusted for are age, gender, region, and time of exposure. Survival curves by study groups on time-to-event outcomes will be compared using a Cox proportional hazards model with a cluster-level frailty term to adjust for clustering. We will do additional pre-specified analyses to assess the consistency of treatment effects in subgroups defined according to the viral load of the contact at baseline, viral load of the index case, place of exposure, time of exposure to the index case.

Planned interim analysis: We plan an interim analysis for possible early trial termination for superiority or futility of the experimental therapy. The trial is open-label and does not need unblinding. The interim analysis will be performed by an independent statistician. The analysis will be performed on the primary endpoint when 25% (n=48) of patients have been randomized and have completed 14 days follow-up. Randomization will be done by blocks, so we expect similar numbers in each group at interim analysis. We will look at the 95% CI for the difference

between groups. The Peto approach will be used: the trial will be ended using symmetric stopping boundaries at P<0.01, both in case of superiority or futility.

Interruption criteria: Incidence of secondary cases among contacts of a case is < 2% (stop for futility) or >8% (stop for superiority).

4.6 PROCEDURES AND STUDY VISITS

- Active surveillance, laboratory confirmation of cases of COVID-19, and the list of contacts is independently undertaken by Catalan epidemiological surveillance system (SUVEC).
- After notification of the disease the SUVEC will process the data and notify the researchers team.
- The researcher's team will call the positive cases to offer people diagnosed with coronavirus to participate in a clinical trial.
- An oral inform consent will be obtained by phone. The researcher will inform about the trial to individuals that fulfil inclusion criteria (based on online medical records and clinical history taken by phone) and the randomization process will start (for index cases and their contacts).
- Dedicated outbreak field-teams will visit candidates and verify the inclusion criteria eligibility on day 1.
-The SUVEC or researcher's team will provide the list of contacts. Oral inform consent and inclusion criteria verification) will be done for each contact.
-Kits will be numbered to ease traceability

1. Baseline visit

- Nasopharyngeal swab (or sputum if possible) will be collected and sent to the microbiology department for testing.
- Everyone will be asked and examined when needed for signs of COVID-19 infection:
  - Symptoms of acute respiratory infections (cough, odynophagia, rhinorrhea, myalgia, headache). Severe (any duration) or mild (lasting at least 48h - two nights)
  - Dyspnea of any duration
  - Fever (> 37.5) of any duration
  - Diarrhea accompanied by 1, 2, or 3

- Epidemiological investigation will include questions about:
  - number of days that has been in contact with the index case,
  - place of contact (home, work, nursing care facility, hospital),
  - use of mask (both case and contact)
- Contacts on the experimental arm will be offered prophylactic treatment as per regimen in Fig 1.

Fig 1. Treatment schedule for contacts of a COVID-19 case

Days	1	2	3	4	5	6	7	14
AM	♣♣♣♣ †	♣♣	♣♣*	♣♣	♣♣	♣♣	♣♣*	†

♣ Hydroxychloroquine 200 mg; *Telephone check; † Home visit

2. Follow up day-3 (by telephone call)

- Everyone will be examined for signs of COVID-19 infection and will be asked about Adverse Events and Compliance to treatment.

3. Follow up day-7 (by telephone call)

- Evaluation of health status, adverse events, and compliance to treatment

4. Follow up day-14 (home visit)
- Evaluation of health status, adverse events, and compliance to treatment
- A nasopharyngeal swab will be collected from the contact.
- A SARS-CoV-2 rapid test IgM/IgG/Ag will be conducted by fingerprick (contacts)

5. Unscheduled follow up due to symptom presentation (home visit)
At any follow visit, if a participant presents with a clinical condition that might need a detailed medical evaluation (including, but not only respiratory distress with respiratory rate >=30 breaths/min; Temperature >38ºC, Blood pressure <90/60mmHg) will be referred to the reference hospital for further management. In a less severe symptomatic situation not requiring hospitalization we will take a nasopharyngeal swab at this time from contacts at home.

6. Evaluation of primary outcome - health status of contacts for 14 days follow-up-
- The research team will initiate active surveillance of any asymptomatic person who meets the definition of contact, following the protocols of the Catalan epidemiological surveillance system (SUVEC).
- If during the 14 days after the exposure the contact develop symptoms, he/she is asked to immediately contact the research team.
- The research team will investigate that contact to rule out infection by SARS-CoV-2 including:
- Clinical examination
    - Symptoms of acute respiratory infections (cough, odynophagia, rhinorrhea, myalgia, headache). Severe (any duration) or mild (lasting at least 48h - two nights)
    - Dyspnea of any duration
    - Fever (> 37.5) of any duration
    - Diarrhea accompanied by 1, 2, or 3
- Nasopharyngeal swab

7. Evaluation of Adverse Events
Safety outcomes will include the frequency and severity of adverse events (AE), serious AE (SAE), and AE of special interest (e.g., cardiac) up to 28 days from treatment start
See definitions and procedures below.

8. Evaluation of Compliance to treatment
We will use a self-reported questionnaire for assessment of adherence to treatment (Brief Medication Questionnaire – BMQ).
The tool includes a 5-item Regimen Screen that asks patients how they took each medication in the past week, a 2-item Belief Screen that asks about drug effects and bothersome features,

Fig 2. Workplan timeline for a contact

	Baseline	**Day 3**	**Day 7**	**Day 14**
Written Informed Consent	X			
Pregnancy test	X			
Clinical examination	X			
Inclusion criteria checks	X			
Nasopharyngeal Swab	X			X
Blood sample (Rapid Test)				X
Adverse events assessment		X	X	X
Compliance assessment		X	X	
Follow up assessment			X	X

5. SUBSTUDY 2- EARLY TREATMENT OF OUTPATIENT CASES WITH COVID-19

5.1 STUDY DESIGN

Study Type:	Interventional
Estimated Enrolment:	280 COVID-19 cases
Allocation:	Randomized
Masking:	Open-label
Index Cases	Those individuals diagnosed of mild COVID-19 (SARS-CoV-2 PCR positive plus symptoms)
Intervention:	Pharmacological (Hydroxychloroquine in index cases)
Primary Purpose:	Prevention of disease progression
Actual Study Start Date:	March 16, 2020
Estimated Primary Completion Date:	May 13, 2020
Estimated Study Completion Date:	May 13, 2020
Site:	Catalonia

5.2 INTERVENTIONS

Arm	Intervention/treatment
CONTROL ARM	**No treatment. Standard surveillance.** Index case completes a survey collecting demographic, epidemiological and clinical data and provides a swab for RT-PCR testing at baseline and on days 3 and 7. Symptom or disease progression, safety, and self-reported treatment compliance will be monitored at days 3, 7, 14 and 28 Isolation of patient and contact tracing as per national guidelines.
EXPERIMENTAL ARM	**Treatment of COVID-19 (index case).** Index case receives Hydroxychloroquine*. Index case completes a survey collecting demographic, epidemiological and clinical data and provides a swab for RT-PCR testing at baseline and on days 3 and 7. Eligible individuals will be offered with hydroxychloroquine 800 mg (620 mg base) followed by 400 mg daily for 6 days (total dose 3.2 g)] Symptom or disease progression, safety, and self-reported treatment compliance will be monitored at days 3, 7, 14, and 28. Isolation of patient and contact tracing as per national guidelines ***Amendment:** Co-administered Darunavir-cobicistat 800mg/150mg once daily for seven days was stopped on 04th April (substantial amendment).

5.2.1 Supply, packaging, and storage

All treatments will be stored at and administered by the Pharmacy Department of Hospital Universitari Germans Trias i Pujol (HUGTIP). Hydroxychloroquine and will be stored in a safe

place during the study, in accordance with conditions defined in its Summary of Products Characteristics (SmPC). Being marketed medication, specific temperature control for the study will not be performed. The medication will be supplied in blister packs and the primary packaging will not be altered by the Pharmacy office. An information sheet with the relevant information on instructions for use, pharmaceutical form, dosage and safety aspects will be attached. The distribution of the treatments will be performed through field teams consisting of health care workers. The treatments will be prepared for each participant. To check compliance with study treatment, the investigators will ask the subject about treatment adherence and this data is to be written in the database. Pills will not be counted to assess compliance.

5.3 AIM AND OUTCOME MEASURES

Hypothesis: Our primary hypothesis is that implementation of an early antiviral treatment intervention among confirmed cases with COVID-19 presenting mild symptoms will improve virological and clinical outcomes.

5.3.1 Objectives and endpoints

Objectives:

- Determine the virological and clinical outcome in SARS-CoV-2 positive cases.

Outcome Measures

Ring prophylaxis effectiveness to reduce development of disease assessed by Incidence Endpoints

- Viral load reduction in nasopharyngeal swabs at days 3, and 7 after treatment start [Time Frame: Up to 7 days after start of treatment]
- Time to complete resolution of symptoms [Time Frame: Up to 28 days after start of treatment]

Other outcomes

- Hospitalization and death rate at day 28 after treatment start [Time Frame: Up to 28 days after start of treatment]

5.4 ELIGIBILITY CRITERIA

5.4.1 Inclusion Criteria

1. Patients who meet the requirements of the New Coronavirus Infection Diagnosis (Acute—≤5 days—respiratory infection symptoms, fever, cough, shortness of breath, acute olfactory loss, and positive PCR)
2. Aged ≥18 years male or female
3. In women of childbearing potential[1], negative pregnancy test and commitment to use contraceptive method[2] throughout the study.
4. Willing to take study medication
5. Willing to comply with all study procedures, including repeat nasal swab at day 3
6. Able to provide oral and written informed consent

[1]A woman will be considered of childbearing potential if not permanently sterilized nor postmenopausal. Permanent sterilization methods include tubal ligation, hysterectomy and bilateral oophorectomy. Postmenopausal is defined as 12 months with no menses without an alternative medical cause.

[2]Contraceptive methods: male or female condom with or without spermicide, cap, diaphragm or sponge with or without spermicide, intrauterine device, bilateral tubal occlusion, vasectomized partner, sexual abstinence during the study.

5.4.2 Exclusion Criteria

1. Hospital admission
2. Serious condition meeting one of the following: (1) respiratory distress with respiratory rate ≥30 breaths/min; (2) oxygen saturation ≤93% on quiet status; (3) Arterial partial pressure of oxygen (PaO2)/oxygen concentration ≤300mmHg;
3. Critically ill patients meeting one of the following: (1) Experience respiratory failure and need to receive mechanical ventilation; (2) Experience shock; (3) Complicated with other organs failure and need intensive care and therapy in ICU;
4. Participants under treatment with medications likely to interfere with experimental drugs
5. Unable to take drugs by mouth;
6. With significantly abnormal liver function (Child Pugh C)
7. Need of dialysis treatment, or GFR ≤30 mL/min/1.73 m^2;
8. Participants with psoriasis, myasthenia, hematopoietic and retinal diseases, CNS-related hearing loss or glucose-6-phosphate dehydrogenase deficit
9. Participants with severe neurological and mental illness;
10. Pregnant or lactating women;
11. Inability to consent and/or comply with study protocol;
12. Individuals with known hypersensitivity to the study drugs
13. Persons already treated with any of the study drugs during the last 30 days.
14. Any contraindications as per the Data Sheet of Hydroxychloroquine.

5.5 RANDOMIZATION AND STATISTICAL ANALYSIS

Sample size calculation: We estimated that a sample size of 280 patients would provide the trial with 80% power to detect a difference of 0.5 $\log_{10}$ in the mean reduction of SARS-CoV-2 viral load at a two-sided significance level of $\alpha = 0.05$, assuming an expected standard deviation of 1.5. A 0.5 $\log_{10}$ copies/mL difference in reduction was chosen to represent the minimal threshold for a biologically relevant change for our analyses.

Stratified randomization: Random allocation of intervention is done remotely, by a member of the study team not involved in the definition of rings. For the purpose of Study-2 only cases meeting the eligibility criteria above will be included. We will use block randomization to achieve balanced sample size in each group.

Allocation: The study is open label.

Populations: Considering the open-label design and the possibility of side effects caused by the study medication, the primary efficacy analysis will be performed on the intention-to-treat (ITT) population. Sensitivity analyses will be performed with the per-protocol (PP) population. Safety will be assessed in the safety population, which included all participants who received any therapy, including usual care.

Statistical analyses: Efficacy will be determined by comparing the mean reduction of the viral load from baseline to days 3 and 7, with the use of a mixed effects regression model taking into account the randomization group and repeated measures within each individual. The viral load will be provided in logarithmic scale; specimens with undetectable viral load at a given follow-up assessment were assigned a value of 3 $\log_{10}$ copies per mL (i.e., lower limit of detection) for the purpose of statistical analysis. The secondary clinical outcome regarding between-group differences in disease progression will be assessed using risk ratio (RR) for the predefined events. The time to clinical improvement will be analyzed using Kaplan-Meier survival functions and hazard ratios (HRs), calculated using a Cox proportional hazards regression model based on the assumptions of proportional risks. Kaplan-Meier estimates will be compared using the log-rank test.

5.6 PROCEDURES AND STUDY VISITS

- Active surveillance, laboratory confirmation of cases of COVID-19.
- After notification of the disease the SUVEC will process the data and notify the researchers team.
- The researcher's team will call the positive cases in order to offer people diagnosed with coronavirus to participate in a clinical trial.
-Test and treatment Kits will be numbered to ease traceability
- Dedicated outbreak field-teams will visit candidates and verify the inclusion criteria eligibility on day 1.

1. Baseline visit

- Nasopharyngeal swab (or sputum for patients with productive cough) will be collected and sent to the microbiology department for testing.
    - Nasopharyngeal: Use only synthetic fiber swabs with plastic shafts. Insert a swab into the nostril parallel to the palate. Leave the swab in place for a few seconds to absorb secretions. Place swabs immediately into sterile tubes containing 2-3 ml of viral transport media.
    - Sputum: Have the patient rinse the mouth with water and then expectorate deep cough sputum directly into a sterile, leak-proof, screw-cap sputum collection cup or sterile dry container.
- Everyone will be asked and examined when needed for signs of COVID-19 infection to identify the severity signs (Temperature, Oxygen saturation, Respiratory rate, Blood Pressure) Patients on the experimental arm will be offered treatment according to regimen in Fig 3.

Fig 3. Treatment schedule for a COVID-19 mild case

Days	1	2	3	4	5	6	7	14	28
AM	♣♣♣♣ †	♣♣	♣♣ †	♣♣	♣♣	♣♣	♣♣ †	*	*

♣ Hydroxychloroquine 200 mg; † Home visit
* Telephone check
Amendment: DRVc was stopped as of 4th April 2020

5.6.1 Study visits

2. Follow up day-3 (home visit)
- A nasopharyngeal swab will be collected at home by the outbreak team

- Everyone will be examined for signs of COVID-19 infection and will be asked about Adverse Events and Compliance to treatment.

3. Follow up day-7 (home visit)
- A nasopharyngeal swab will be collected at home by the outbreak team.
- Evaluation of health status, adverse events, and compliance to treatment

4. Follow up day-14 (telephone call to assess disease progression)
- Evaluation of health status

5. Follow up day-28 (telephone call to assess disease progression)
- Evaluation of health status

Fig. 4 Workplan timeline for a case.

	Baseline	**Day 3**	**Day 7**	**Day 14**	**Day 28**
Written Informed Consent	X				
Pregnancy test	X				
Inclusion criteria checks	X				
Clinical examination	X	X			
Nasopharyngeal Swab	X	X	X		
Adverse events assessment		X	X	X	X
Compliance assessment		X	X		
Follow up assessment			X	X	X

6. ADVERSE EVENTS

6.1 DEFINITIONS:

Adverse event (AE): Medical event presented by a patient or clinical research subject administered a pharmaceutical product, and which does not necessarily have a causal relation to the treatment.

Serious adverse event (SAE): Medical event classified as such and which, regardless of the dose involved:

- Causes patient death.
- Produces a life-threatening situation for the patient.
- Requires or prolongs in hospital admission.
- Produces important or persistent incapacitation/handicap or constitutes a congenital defect or anomaly.
- Needs action to prevent any of above situations.
- Is considered medically significant (examples of such events are intensive care in an Emergency Service or at home in a patient with allergic bronchospasm; blood dyscrasias or seizures not giving rise to hospital admission, or the development of drug dependency or abuse).

Adverse event of special interest (AESI): AE thought to be [potentially] associated with the investigational compound or disease under study. An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. AEs of special interest include the following:

Common AEs observed with Hydroxychloroquine:

- Skin rash
- Diarrhea
- Nausea/Vomiting
- Headache
- Asthenia
- Drowsiness

AEs of special interest:

- Dizziness
- Syncope
- Cardiovascular events

Unexpected adverse event (UAE): AE related to the product in investigation the nature or intensity of which does not coincide with the information available on the product administered (IB or SmPC).

Serious Unexpected Adverse Reaction (SUSAR): SAE related to the product in investigation the nature or intensity of which does not coincide with the information available on the product administered (IB or SmPC).

6.2 ADVERSE EVENTS ASSESSMENT

6.2.1 Seriousness

An SAE is any medical event that meets the criteria of SAE
Events not considered to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency out participant treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

6.2.2 Intensity

The following scale will be used:

- Grade 1 (mild): Symptoms causing no or minimal interference with usual social and functional activities.
- Grade 2 (moderate): Symptoms causing greater than minimal interference with usual social and functional activities.
- Grade 3 (severe): Symptoms causing inability to perform usual social & functional activities.
- Grade 4 (potentially life-threatening): Symptoms causing inability to perform basic self-care functions or medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death.
- Grade 5 (death): Any AE where the outcome is death.

6.2.3 Causality

All AEs must have their relationship to study intervention assessed by the physician who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- Related – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

6.2.4 Expectedness

An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention. Risk information of study interventions may be found in the SmPC of each study drug.

The assessment of the expectedness between an AE and the administration of treatment is a decision to be made by the principal investigator OM or co-investigator MV, who are qualified physicians.

Expectedness will be assessed in relation to the AE being previously documented as per attached Technical Data Sheet – Ficha técnica point 4.8-). A serious unexpected adverse reaction (SUSAR) is a suspected adverse reaction (AR) whose nature, severity or outcome is not consistent with the Technical Data Sheet.

All unexpected serious ARs will be notified through Eudravigilance. For a suspicion of AR considered to be expected only for one of the two treatments (darunavir-cobicistat or hydroxychloroquine, we will consider question 7.25 (The rules governing medicinal products in the European Union VOLUME 10 - Guidance documents applying to clinical trials) on how should SUSARs of combination IMPs be reported? The question and answer document, section 7 of which includes relevant aspects of AR assessment to be considered.

6.2.5 Duration

For both AEs and SAEs, the Investigator will provide a record of start and stop dates of the event (expressed in the shortest time unit possible). Changes in the severity of an AE or SAE will be documented in the clinical record.

6.2.6 Action taken

The Investigator will report the action taken with study intervention as a result of an AE or SAE, as applicable (e.g., discontinuation or reduction of dose, as appropriate) and report whether concomitant and/or additional treatments were given for the event.

6.2.7 Outcome

Any AE or SAE will be followed preferably until:

- Resolution of the event;
- Stabilization of the event; or
- Resetting the baseline situation of the event, in case baseline situation is available.

Otherwise, they will continue until:

- The event can be attributed to products other than the study medication or factors unrelated to the study; or
- It is unlikely to obtain further information

In the event that the subject dies from a SAE, the rest of AE or SAE that are active will be recorded as "not recovered".

6.3 TIME FRAME FOR ADVERSE EVENTS COLLECTION

The investigator must collect all the AE and SAE that occur from the moment the subject signs the informed consent until the last study visit. Follow up will be assessed up to 28 days after start of treatment.

6.4 DOCUMENTATION RELATED TO ADVERSE EVENTS

Each AE and SAE to take place during the study should be documented in the medical records of the participant in accordance with standard clinical practice of the investigator. For each SAE, an independent set of SAE form will be used independently. Only if there are multiple SAE at the time of the initial report and these are temporary and / or clinically interrelated can be registered on the same set of SAE form.

The investigator should try to make a diagnosis of the event based on the signs, symptoms and / or other clinical information. An AE diagnosis must be recorded per line, or a sign/symptom if the diagnosis is not available. If a diagnosis subsequently becomes available, this then should be entered, and the sign/symptom crossed out.

SAE pages found in the investigator's file shall be completed as precisely as possible and shall be signed by the investigator before being sent to the sponsor. In the initial page of the SAE form, the investigator must provide his/her opinion in regard to the relationship of the event to the study intervention.

6.5 PREGNANCY

Cases of pregnancy shall be recorded as AE and should only be considered as SAE only if they meet any seriousness criteria. Pregnancy is also a protocol deviation requiring premature termination of the subject. The investigator will provide medical support to the pregnant subject.

No special measures are required in relation to the pregnancy of a partner of a male participant.

6.6 PROCEDURE FOR ADVERSE EVENT REPORTING

6.6.1 Investigator

All AEs and SAEs will be recorded, regardless of the causality, in the corresponding AE form.
The investigator will immediately notify the study sponsor of any SAE. The notification will be performed within 24 hours of first knowledge by the investigator.

6.6.2 Contact details for Sponsor

safety@fls-rs.com
The recording of AEs and SAEs is the responsibility of the trial investigator team, which should indicate the time of appearance of the event (expressed in the shortest time unit possible), its serious / not serious status, and in case it is considered related to investigational products, whether it was expected or unexpected. The intensity of the event (grade 1 to 5) is to be specified, along with the measures adopted (none, treatment, temporal or permanent discontinuation of investigational product), course (complete remission, partial remission, persistence) and causality based on the criteria indicated in section 6.2.3.

6.6.3 Sponsor

A group of researchers designated by the sponsor, will review the list of AEs, SAEs and SUSARs reported by the investigators in the CRF. The objective of this revision is the proper adjudication and notification, if needed, to the Spanish Agency of Medicines and Medical Devices (AEMPS) through the notification to Eudravigilance database, competent authorities of the autonomous region and the Ethics Committee implicated in the clinical trial.

The sponsor will inform the AEMPS, the competent authorities of the autonomous region and the Ethics Committee implicated in the clinical trial about any important information of security of the investigational medicinal product.

The sponsor will inform the Spanish AEMPS of any SUSAR which may be related to the study treatment.

The sponsor will inform competent authorities of the involved autonomous region of any SUSAR which may be related to the study treatment, and that have been happened in subjects in its autonomous region.

The deadlines to notify a SUSAR is, from the first knowledge by the investigator:

- 15 days
- 7 days if the SUSAR has resolved in death or has been life-threatening. Relevant follow-up information for these cases will be subsequently be submitted within an additional 8 days.

If the notification is sent in electronic form, it will not necessary to notify the competent authorities of the autonomous region.

The sponsor will keep a detailed register of all the AE notified by the investigators.

All AE will be notified in table form in the final report of the clinical trial.

7. DATA COLLECTION

The CRF will be administered to all selected participants. Data will be collected using face-to-face questionnaires (paper CRF) by the field clinical teams and data will be entered in a standardized electronic questionnaire (digital CRF) to be accessed online, and which will be merged in a secured web site that uploads data in real time. The chief investigator will be responsible for keeping a subject identification log of all subjects enrolled into the study, their corresponding study number and sample IDs. This information will be kept on a secure server in a password protected file and will only be available to the chief investigator and the study personnel who are directly obtaining clinical data. Identifying information of a SARS-CoV-2 PCR result of some participants will be extracted from the Epidemiological Repository of Catalonia (REC), which is the data platform that aggregates and manages data of Catalan surveillance systems of notifiable diseases including epidemic outbreaks like SUVEC (all are of mandatory declaration), and which is coordinated by the general sub-directorate for public health emergencies surveillance and response of the Public Health Agency of Catalonia, Health Department, Government of Catalonia. Subjects will be assigned a linked-anonymized study number to ensure subject confidentiality throughout the duration of the study.

8. DATA MANAGEMENT

The clinical trial has created a data management system and procedures to warrant homogenization, traceability, and data quality. Paper CRF will be used to collect the CRF's data during home visits, and electronic CRF for telephone visits. Data will be entered in a digital CRF. Quality control procedures will be put in place for data checking by an external data management group. Rigorous consistency checks will be created in order to reduce errors during data entry. The data management group and statisticians will be responsible for the final

analysis of the data. Study data will be sent from paper CRF to a central FLS database. This database will enter and store the final data and will be on a server hosted at a secure Data Center with appropriate series of protocols to test and maintain network security, and to provide access management policies for network drives, databases and remote access.

For data safety purposes each person entering data in the digital CRF will be required to define clear data access. Data management team and researchers will be the only ones to access the database. The backup of the data will be done on a timely basis. The final stored data will be placed on the FLS server and will be anonymous; the tools used to identify individuals may have individual identifiers, but this information will only be associated to a numerical identification number. This information will uniquely identify project participants will be associated with the rest of the captured sensitive information. If information that could enable to identify individuals has to be stored, used or shared, it will be encrypted. Consequently, those receiving the final data for analysis will not have access to any information that might help to physically identify individuals.

Data cleaning process will be conducted by consultancy TRF: detecting and correcting (or removing) corrupt or inaccurate records from the database. The inconsistencies detected or removed originally caused by user entry errors, by corruption in transmission or storage will be confirmed with the site research team and will be recorded.

9. DATA QUALITY INSPECTION TEAM

People from FLS will be selected to constitute a data quality inspection team in order to undertake periodic quality reviews of the entered data. The Data Quality inspection team will identify potential data entry errors, inconsistencies and missing data.

9.1 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

Data will be stored in accordance with the Data Protection Law (LOPD, the organic Law 3/2018 of 5 December on the Protection of Personal Data and the Guarantee of Digital Rights complementary to the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data). The chief investigator will have overall control of, and act as the custodian for all data for the full duration of the study. The data will be available for internal monitoring (verification of data using paper CRF validate by research team against the information recorded in the CRF).

10. MONITORING AND GOOD CLINICAL PRACTICE

We will carry out risk-adjusted monitoring since the trial is performed in a clinical care practice setting, with follow-up of the subjects treated in the community or primary care setting.

Data will be entered directly into the application, and it will be considered source data, as the contacts do not have a care episode opened.

Data monitoring tasks defined:

- Verification of the study master file (authorizations, protocol, drug information and other essential documents, pursuant to section 8 of ICH Guide E3),
- Verification of signature of informed consent,
- Checking the dates of visit and verification of absent data not entered in the application
- Verification of the values of serological results
- Detection of unreported adverse effects from the review of data from the medical records with open episodes during the course of the study

11. ETHICS

11.1 GENERAL CONSIDERATIONS

The clinical trial will be conducted according to the principles of the Declaration of Helsinki, (amended Fortaleza, Brazil, October 2013).

This study will be conducted according to Spanish regulations regarding clinical trials (Royal Decree 1090/2015) and biomedical investigations (Organic Law 14/2007 of biomedical investigation and the Royal Decree 1716/2011), which develop the European Directive on clinical trials (Regulation EU No 536/2014). The required documentation prior to the start will be:

- Protocol acceptance by the Sponsor and the Coordinating Investigator
- Protocol approval by the Ethics Committee
- Protocol authorization from the Spanish Drug Agency (Ministry of Health)

All subjects will be guaranteed continued medical and nursing supervision throughout the duration of the study.

This study will conform to the standards of GCP published by ICH (E6 R2).

11.2 DATA HANDLING

The processing of the data will be subject to current legislation as regards data protection (LOPD, The Organic Law 3/2018 of 5 December on the Protection of Personal Data and the Guarantee of Digital Rights complementary to the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data).

Cases are registered by the Epidemiological Surveillance Emergency Service of Catalonia (SUVEC). The SUVEC is under the Public Health Agency of Catalonia (ASPCAT), which is within the Departament de Salut (Public Health Secretariat).

The sponsor and the Departament de Salut have signed a collaboration agreement where, among other points, the access of the study investigators to COVID-19 patient data is specified for the conduct of this clinical trial, preserving the confidentiality of personal data, through the Sub-direcció General de Vigilància i Resposta a Emergències de Salut Pública. So, the study team will contact with participants after to review the SUVEC's register of COVID-19 data.

The participant will be identified in the records by the corresponding unique code number. The participant is to be guaranteed anonymity and is to be informed that all communication will take place between him/her and the investigator and not the sponsor of the study.

The SUVEC aim is to respond quickly to the diseases of urgent declaration and epidemic outbreaks declared by doctors in the healthcare network of Catalonia through research and control of urgent declaration diseases, outbreaks and public health alerts, as well as the application of prevention and control measures (chemoprophylaxis, vaccination, detection of risk contacts, isolation measures).

On the other hand, the ASPCAT is regulated by Law 5/2019, July 31, of the Public Health Agency of Catalonia and modification of the Law 18/2009, October 22, on public health. Its functions are expressly attributed to "Fostering research in public health and promoting the training of professionals engaged in it, in collaboration with other competent bodies, universities and research centers."

According to the data protection regulations, the ASPCAT, and therefore the SUVEC can process the data of patients (and their contacts) diagnosed with SARS-CoV-2 coronavirus to invite them to participate in the clinical trial. In this sense, Organic Law 3/2018, on the Protection of Personal Data, establishes through its Additional Provision seventeenth in section 2. B that "b) the health authorities and public institutions with powers to monitor the public health can carry out scientific studies without the consent of those affected in situations of exceptional relevance and seriousness to public health. "

Therefore, and understanding that given the current situation of coronavirus, and that ASPCAT, and therefore SUVEC, is a public institution with powers in public health surveillance, and that it specifically has the function of promoting health research public, would be enabled to process the data in order to offer people diagnosed with coronavirus to participate in a clinical trial, without prejudice to the need to sign the subsequent informed consent document to participate in the trial.

11.3 ORAL INFORMED CONSENT AND PARTICIPANT INFORMATION SHEET AND WRITTEN INFORMED CONSENT

The investigator will inform the candidates of the nature, duration and purpose of this study and, in addition, of all the inconveniences and obstacles that, if any, can be expected. In addition, information will be provided to the participant. Subjects must have the legal capacity to give their consent and exercise their freedom of decision. If the subject wishes to participate in the study, his/her oral consent will be obtained by phone.

The consent will be given orally during the enrolment telephone call and will be obtained before starting the participation in the study. The investigator will keep a call recording of the informed consent process.

At the Baseline home-visit, a Written Informed Consent will be obtained.

11.4 INSURANCE POLICY

In accordance with the Royal Decree 1090/2015, of 4th December, the trial sponsor has a policy of liability insurance. The sponsor shall extend this policy or another with equivalent coverage until the end of the trial. This policy also covers the responsibilities of the sponsor, the principal and his/her collaborators, as well as the hospital or site where they carry out the clinical trial.

12. RISK MITIGATION

After analysis of the safety of drugs and the current evidence of the efficacy, we do not consider choosing another drug. As of March 26, 2020, the Catalan Infectious Diseases Departments involved in the treatment of COVID-19 have agreed to withdraw LPVr, DRVc from the treatment protocol. DRV has been shown to exert no activity on the SARS-CoV-2 clinical studies and is therefore withdrawn for futility. Although LPVr shows in vitro efficacy against SARS-CoV-2 at elevated total drug concentrations, human clinical trials have not demonstrated superiority of LPVr vs Placebo. It has been considered that the magnitude of the possible clinical benefit of LPVr if it is started in the early stages of the disease is small and does not compensate for the gastrointestinal and renal toxicity of the drug. The same applies to azithromycin in line with AEMPS that has questioned the use of azithromycin in patients with COVID-19 based on the limitations of a single trial. And after in vitro studies with azithromycin no activity against the virus is detected

We have considered that a reduction in the glomerular filtration rate can alter the safety profile of hydroxychloroquine and might be an appropriate reason to exclude patients from participation in trials. We have also decided to exclude patients with a positive history of arrythmia or QT prolongation or use of QTc prolonging medication.

We will advise patients to call the investigator team if they present any adverse event. The patients will be advised of frequent adverse events related to study drugs including those of hydroxychloroquine (blurred vision, nausea, vomiting, abdominal cramps, headache) and darunavir (gastrointestinal).

13. NON-BACKGROUND REFERENCES

1) The Janssen UK team. Lack of evidence to support use of darunavir-based treatments for SARS-CoV-2. 2020 March.

2) Cao B, Wang Y, Wen D et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020 Mar 18. doi: 10.1056/NEJMoa2001282.

3) AEMPS (https://www.aemps.gob.es/la-aemps/ultimainformacion-de-la-aemps-acerca - del-covid% e2% 80% 9119 / treatments-available-for-the-management-of-respiratory-infection-by-sars-cov-2 /)

APPENDIX. LIST OF INVESTIGATORS AND KEY ROLES:

PARTNER/PRINCIPAL INVESTIGATOR (PI) /INVESTIGATOR (I)	KEY ROLE
Hospital Universitari Germans Trias i Pujol	
Oriol Mitja, **(PI)** Infectious Diseases Department,	Conceptualizing a research idea Creating a research design Selection of statistical tests/analyses Performing statistical analyses and computations (including computer work) Interpretation of statistical analyses Laboratory analyses
Marti Vall, (I) Infectious Diseases Department,	
Roger Paredes, (I) Infectious Diseases Department,	
Jordi Ara, (I) Nephrology Department,	
Lurdes Matas, (I) Microbiology Department,	
Ventura Clotet, (I) Infectious Diseases Department,	
Maria Ubals, (I) Infectious Diseases Department	
Carles Quiñones (I), Pharmacy Department	
Departament de Salut	
César Velasco, **(PI)** Agencia de Qualitat i Avaluació Sanitàries de Catalunya (AQuAs), Barcelona.	Patient identification and enrolment Patient examination, randomization, treatment and follow-up Data collection Creating research design
Rosa M Vivanco Hidalgo, (I) Agencia de Qualitat i Avaluació Sanitàries de Catalunya (AQuAs), Barcelona	
Servei d'Urgències de vigilancia epidemiológica de Catalunya (SUVEC),	
Joan Guix, (I) Secretaria de Salut Pública del Departament de Salut, Generalitat de Catalunya	
Robert Fabregat, (I) Director General de Recerca i Innovacio del Departament de Salut, Generalitat de Catalunya	
Josep Ma Argimon, (I) Institut Català de la Salut, Departament de Salut, Generalitat de Catalunya	
Centre for Epidemiological Studies on Sexually Transmitted Diseases and HIV/AIDS of Catalonia (CEEISCAT)	
Jordi Casabona**, (PI)**	Building an online survey supervision of data entry Data cleaning and coding Participating in the research design
Alexis Sentís, (I)	

Summary of Changes

Version	Date	Description of protocol changes
v11	06.03.2020	First version approved
v12	17.03.2020	Includes substantial amendment No.1 v1 (17.03.2020) **Sub-studies 1 and 2- Treatment schedule with HCQ (cases, contacts):** Increase of HCQ total dose- Hydroxychloroquine 800 mg (620 mg base) followed by 400 mg daily for 6 days (total dose 3.2g). **Data handling considerations:** The sponsor and the Departament de Salut have signed a collaboration agreement where the access of the study investigators to COVID-19 patient data is specified for the conduct of this clinical trial, through the Sub-direcció General de Vigilància i Resposta a Emergències de Salut Pública.
v13	30.03.2020	Includes substantial amendment No.2 v1 (17.03.2020) **Sub-study 1- Randomization considerations:** If the index case does not meet the inclusion criteria, we recruit and randomize his/her ring of contacts. **Sub-study 1- Recruitment considerations:** We enhance passive recruitment by conducting an Information, Education, Communication (IEC) campaign in the social media. **Sub-study 1- Outcome measures:** Owing to the availability of rapid test, a secondary outcome has been added to investigate serological profile of contacts - SARS-CoV-2 rapid test IgM/IgG/Ag will be conducted by fingerprick. **Sub-study 1- Outcome measures:** If during the 14 days after the exposure the contact develops symptoms, he/she is asked to immediately contact the research team (passive vigilance). We will make a follow visit and take a nasopharyngeal swab. If the symptoms are detected during a follow up visit (phone) we will rule out infection by SARS-CoV-2 and take a nasopharyngeal swab (active vigilance). **Sub-study 2- Drug regimen:** DRV no longer included because of cumulative evidence on inefficacy for SARS-CoV-2. Coadministered Darunavir-cobicistat 800mg/150mg once daily for seven days was stopped on 04th April. **Sub-study 2- Outcome measures:** Viral load assessment extended timeframe to day 7. Also, follow-up to resolution of symptoms and disease progression extended timeframe to day 28.
v14	30.03.2020	Includes additional information requested by the AEMPS on amendment No. 2
V15	12.05.2020	Includes substantial amendment No. 3 v1 (13.05.2020) **Sub-studies 1 and 2-** Data management and cleaning process will be conducted by consultancy TRF **Sub-studies 1 and 2- Sample size considerations:** We consider rings of size 3.5 -320 cluster of contacts per ring (total 2250 contacts) are required to have 80% power to reject the null hypothesis (reduction of incidence from 6% to 3%. **Sub-studies 1 and 2- Statistical analyses:** Change of primary population from per-protocol to Intention-to-treat due to the open label nature of the study. **Sub-studies 1 and 2: Statistical analyses:** Change of SAP, from cluster level to individual level analyses because size of clusters is unexpectedly small (median 2) due to lockdown and cluster show little intra-cluster variability for the primary outcome (interim analysis)

Statistical Analysis Plan

Protocol Title:	Treatment of non-severe confirmed cases of COVID-19 and chemoprophylaxis of their contacts as prevention strategy: a Cluster Randomized Clinical Trial (PEP CoV-2 Study)
Protocol:	CQ4COV19 version 1.0 (March 13, 2020)
EudraCT:	2020-001031-27
Compound:	Hydroxychloroquine
Phase:	Phase III
Sponsor:	FUNDACIÓN FLS DE LUCHA CONTRA EL SIDA, LAS ENFERMEDADES INFECCIOSAS Y LA PROMOCIÓN DE LA SALUD Y LA CIENCIA
Principal Investigator	Oriol Mitja Associate Professor, Infectious Diseases and Global Health Hospital Universitari Germans Trias i Pujol, Badalona
SAP Author:	Cristian Tebé
SAP Version:	Version 1.0
SAP Date:	June 6 2020

Table of Contents

1. ANALYSIS AND REPORTING

○ SAFETY INTERIM ANALYSIS

An interim analysis for possible early trial termination for superiority or futility of the experimental therapy was planned. The interim analysis was performed by an independent statistician. The analysis was performed on the primary endpoint when 25% of patients were randomized and have completed 28 days follow-up.

○ FINAL ANALYSIS

All final, planned analyses identified in the protocol and in this SAP will be done after the last subject has completed 14 days follow-up (adverse events and time from randomization to complete alleviation of symptoms extended up to 28-days), and all relevant study data have been processed and integrated into the analysis data base, data have been reviewed at a data review meeting, and the database has been locked. Any post-hoc, exploratory analysis that were not identified in this SAP to support planned study analyses will be documented and reported in appendices to the CSR. Any results from unplanned analyses (post-hoc) will also be clearly identified in the text of the CSR.

2. ANALYSIS SETS

The following analysis sets are planned for this study:

- **Safety Set:** The safety set includes all subjects who receive at least 1 dose of study medication
- **Intention to Treat (ITT):** The ITT set includes all randomized subjects that have an outcome measurement.
- **Per Protocol Analysis Set (PPAS):** The PPAS set includes all subjects in the FAS with no major protocol deviations

Inclusion in the analysis sets will be determined at a data review meeting before database lock. The following protocol deviations may be considered as major and will lead to an exclusion of subjects form the PPAS:

- Not receiving any dose of study medication
- Lack of any efficacy assessment following randomization
- Age < 18 years
- Use of prohibited concomitant medication or non-pharmacological therapies
- Known history of any prohibited concomitant disease
- If a contact is symptomatic at the time of the baseline visit, he/she will be classified as a co-primary case, and we will collect epidemiological information but will not be enrolled in the study as a contact participant.
- Treatment compliance under 80%.

Additional protocol deviations may be considered major at the data review meeting and will be documented appropriately.
If a subject is randomized incorrectly or is administered the incorrect study medication, analyses of the ITT will be based on the assigned intervention, whereas all other analyses will be based on the actual intervention received.
Primary efficacy analyses will be based on the ITT. The PPAS will be used for sensitivity analysis for some efficacy endpoints. Safety analyses will be based on the safety set.
All subjects who signed informed consent will be considered as study participants.

3. GENERAL ISSUES FOR STATISTICAL ANALYSIS

3.1 GENERAL STATISTICAL METHODOLOGY

- Descriptive summaries will be provided where appropriate for each of the primary and secondary variables. In general, tables will summarize data by intervention group.
- Continuous, quantitative, variable summaries will include the number of subjects (N) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum, unless otherwise specified.
- Categorical, qualitative, variable summaries will include the frequency and percentage of subjects in the category. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the analysis set for the intervention groups, unless otherwise specified.
- Cumulative incidence in primary outcome will be compared at individual level (contacts) using a general linear model accounting for clustering within rings (with a binomial function and log as the link function). The robust standard errors within cluster will be derived using Sandwich estimator. The relative risk for response will be presented for Hydroxychloroquine versus control group, together with its 95% confidence interval and p value. We will provide estimates of the marginal effects. Model fit will be assessed using the usual goodness of fit test for binary regression. Analysis will be replicated using a generalized estimating equation model accounting for clustering within rings (with a binomial function and log as the link function).[4]
- Cumulative incidence in secondary outcomes will be compared at individual level (contacts) using a general linear model accounting for clustering (with a binomial function and log as the link function). The relative risk for response will be presented for Hydroxychloroquine versus control group, together with its 95% confidence interval.[4]
- There is no plan to adjust for multiplicity.
- Survival curves will be shown by study group on time to event outcomes and compared by means of a Cox proportional hazards model using a cluster-level frailty term to adjust for clustering.[4]
- We will conduct secondary analysis on previous estimated models, adjusted for baseline values of delay between symptom onset, viral load at baseline and isolation/treatment.
- All statistical tests will be based on a 2-sided test at the significance level of 0.05 and 95% confidence intervals, unless otherwise specified.
- Graphical presentations will be employed to illustrate results from the statistical analyses.
- R version 3.6.2 or superior will be used for the analysis.

3.2 HANDLING OF MISSING DATA

No imputation will be done for missing data on efficacy assessments.

3.3 VISIT WINDOWS

As the subjects are confined at home for the duration of the efficacy assessment period, the question of visit windows is not relevant. However, for visits, is acceptable +/-3 day.

4. STUDY SUBJECTS AND DEMOGRAPHICS

4.1 DISPOSITION OF SUBJECTS AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study. Descriptive summaries of analysis set data will be presented for all subjects unless otherwise specified and will include the following:

- The frequency and percent of subjects in each analysis set, overall and by intervention group.

- The disposition of subjects (including number of study participants, screening failures, number of subjects randomized, number of subjects treated, and number of completers), overall and by intervention group.
- Patients who discontinue study medication by reason for discontinuation, overall and by intervention group.
- Study withdrawals by reason for withdrawal, overall and by intervention group

In addition, all study withdrawals will be listed.

4.2 PROTOCOL VIOLATIONS AND DEVIATIONS

Protocol violations and deviations will be categorized as major or minor at the data review meeting before defining the analysis sets as described in Section.
Major protocol violations (i.e. those leading to exclusion from the PPAS) will be summarized by type of violation, overall and by intervention group. Individual major and minor protocol violations will be listed by subject.

4.3 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Descriptive summaries of the demographic and other baseline characteristics will be presented for the safety set. All demographic and baseline characteristics will be presented on cases and contacts both overall and by intervention group.
The following demographic and baseline data will be presented:

- Demographics (age and sex)
- Epidemiological data.
- Clinical data
- Symptoms data.

Demographic and other baseline data will be presented using descriptive statistics only; no hypotheses will be tested.

5. EFFICACY ANALYSIS

This study will examine the efficacy of a preventative strategy on reducing transmission and consequently, the COVID-19 incidence in the target population during an outbreak.
It may be necessary to complete additional exploratory analyses after the planned analyses are completed. Full details of additional analyses will be presented in the CSR, and any such analyses will be clearly identified as post-hoc.
All statistical tests will be based on a 2-sided test at the significance level of 0.05, unless otherwise specified.
All efficacy variables will be presented with descriptive statistics, broken down by intervention group. In addition, statistical analyses will be presented as described below.

5.1 PRIMARY EFFICACY VARIABLE ANALYSIS

In the primary efficacy analysis, the incidence of Covid-19 will be compared between study groups. The null hypotheses will be tested:

- The percentage of confirmed Covid-19 episodes among healthy contacts during the 14-day study period in the Hydroxychloroquine group is lower than the percentage of confirmed Covid-19 episodes among healthy contacts during the 14-day study period in the control group.

A Covid-19 episode will be confirmed if there is a consistent clinical history and a positive SARS-CoV-2 PCR. Cumulative incidence in the primary outcome will be compared at individual level by study group using general linear model accounting for clustering within rings (with a binomial function and log as the link function). The relative risk for response will be presented for Hydroxychloroquine versus control group, together with its 95% confidence interval and p value.

Analysis will be replicated using a generalized estimating equation model accounting for clustering within rings.
The primary efficacy analysis will be done in the ITT population.

5.2 SECONDARY EFFICACY VARIABLE ANALYSIS

No formal statistical inferences will be drawn from secondary efficacy analyses. Any P values presented from secondary efficacy analyses will be interpreted in an exploratory sense only.
The following efficacy variables will be analyzed in the same manner as the primary analysis, but without any sensitivity analyses:

- The percentage of positive PCR episodes among healthy contacts during the 14-day study period.
- The percentage of serological positivity (IgM/IgG) episodes among healthy contacts during the 14-day study period.
- Time to Covid-19 event
- Adverse events leading to treatment discontinuation and mortality for any cause.

The following time-to-event variables will be compared between the study groups using a Cox proportional hazards model using a cluster-level frailty term to adjust for clustering. The hazard ratio for response will be presented for Hydroxychloroquine versus control group, together with its 95% confidence interval. The median and first and third quartiles of the time to event will also be estimated, and the times to event will be shown graphically with Kaplan-Meier graphs.

- Time to Covid-19 confirmation among healthy contacts

5.3 SUBGROUP ANALYSIS OF EFFICACY VARIABLES

For assessing consistency of efficacy results, the primary and key secondary efficacy analyses will be repeated separately for subgroups of subjects defined by:

- Place of contact: healthcare workers, household contacts, and residents in a nursing home.
- Cases viral load at baseline
- Contacts viral load at baseline
- Delay between contact with case and isolation/treatment
- By study site.

For all of these subgroups, primary and key secondary endpoint analysis models will be repeated.

6. SAFETY AND TOLERABILITY ANALYSIS

The analysis of safety assessments in this study will include summaries of the following categories of safety and tolerability data collected for each subject:

- Adverse events
    - Adverse events (AEs), treatment-emergent AEs (TEAEs), and serious adverse events (SAEs)
    - AEs leading to withdrawal
    - Any deaths

All safety analyses will use the safety analysis set.

6.1 ADVERSE EVENTS

All Adverse Events (AEs), Treatment-emergent Adverse events (TEAEs), and Severe Adverse Event (SAEs) will be coded using the MedDRA dictionary (the most recent version before starting the trial will be used).

An AE is defined as treatment emergent if the first onset or worsening is after the first administration of study medication and not more than 7 days after the last administration of study medication.
If the start date and time of an AE are partially or completely missing, the AE will be assumed to be treatment-emergent if it cannot be definitely shown that the AE did not occur or worsen during the treatment-emergent period (worst case approach). Missing dates and times will not be replaced.
The following are used for guidance for programmers.

- If the start time of an AE is missing, but the start date is complete, an AE will only be excluded from TEAEs if the start day is before the day of first dose of study medication or the start day is after the last day of the treatment-emergent period.
- If the start time and day are missing but the start month is complete, an AE will only be excluded from TEAEs if the start month is before the month of the first dose of study medication, or the start month is after last month of the treatment-emergent period, or if the stop date/time is before the first dose of study medication.
- If the start day and months are missing but the start year is complete, an AE will only be excluded from TEAEs if the start year is before the year of the first dose of study medication, or if the start year is after the last year of the treatment-emergent period, or if the stop date/time is before the first dose of study medication.

If the start date is completely missing, an AE will not be excluded from TEAEs unless the stop date/time is before the first dose of study medication.
All AEs will be summarized in a table whose rows give the number and percentage of subjects reporting at least one AE and the number of reported AEs for each of the following:

- Any AE
- Any TEAE
- Any serious TEAE
- Any drug related serious TEAE
- Any serious TEAE leading to death
- Any drug related TEAE
- Any severe TEAE
- Any TEAEs leading to discontinuation of study medication
- Any TEAEs of special interest

Summaries of incidence rates (frequencies and percentages of subjects reporting at least one AE) and the number of reported AEs of individual TEAEs by MedDRA SOC and preferred term will be prepared. Such summaries will be displayed for all TEAEs, TEAEs by maximum intensity, and TEAEs by strongest relationship to study medication.
Each subject will be counted only once within each preferred term. If a subject experience more than 1 TEAE within a preferred term, only the TEAE with the strongest relationship or the maximum intensity, as appropriate, will be included in the summaries of relationship and intensity.
The most frequent TEAEs, defined as PTs reported in more than 5% of subjects in any intervention group will also be summarized.
Cumulative incidence in safety outcomes will be compared using a general linear model accounting for clustering (with a binomial function and logit as the link function). Absolute and percentage differences will be reported accompanied by 95% confidence intervals.

In the AE data listings, all AEs will be displayed. Adverse events that are not treatment-emergent will be flagged.

6.1.1 Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages of subjects) and number of episodes of TEAEs leading to withdrawal of study medication, by intervention group, SOC, and preferred term, will be prepared.
A data listing of AEs leading to withdrawal of study medication will also be provided, displaying details of the event(s) captured on the CRF.

6.1.2 Serious Adverse Events

A summary of incidence rates (frequencies and percentages of subjects) and number of episodes of SAEs by intervention group, SOC, and preferred term will be prepared.
A data listing of SAEs will also be provided, displaying details of the event(s) captured on the CRF.

6.1.3 TEAEs of special interest

As specified in the protocol, TEAEs of special interest include the following:

- Common AEs observed with Hydroxychloroquine:
  - Skin rash
  - Diarrhea
  - Nausea/Vomiting
  - Headache
  - Asthenia
  - Drowsiness
- AEs of special interest:
  - Pneumonia
  - Dyspnea/ Respiratory failure.
  - Dizziness
  - Syncope
  - Cardiovascular events

A summary of incidence rates (frequencies and percentages of subjects) and number of episodes of TEAEs of special interest, by intervention group, SOC, and preferred term, will be prepared.
These lists of preferred terms considered to be of special interest will be checked at the data review meeting, which will be held before database lock.

6.2 EXPOSURE AND COMPLIANCE

Investigational product administration will be summarized in terms of the number of doses received, and in terms of duration of exposure, from first dose to last dose of the study treatment. Descriptive statistics for these quantities, including the mean, median, SD, minimum, maximum, and quartiles, will be provided by intervention group.
Compliance will be calculated as the number of doses the subject actually received as a percentage of the number of doses the subject would have received if the study were completed.

7. REFERENCES

1. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.

2. ASA. (1999) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, August 7, 1999. http://www.amstat.org/about/ethicalguidelines.cfm
3. RSS (1993) The Royal Statistical Society: Code of Conduct, April 1993. http://www.rss.org.uk/main.asp?page=1875.
4. Campbell MJ and Walters SJ. How to Design, Analyze and Report Cluster Randomized Trials in Medicine and Health Related Research. Chichester, Wiley, (2014).

8. TABLES, LISTINGS, AND FIGURES

8.1 PLANNED TABLE DESCRIPTIONS

The following are planned summary tables for the study. The numbering is intended to be compatible with the format of clinical study reports as per ICH E3 (ICH, 1995), so tables are included in section 14 of the report.

Table Number	Population(s)	Table Title / Summary
14.1 Demographic and baseline tables		
14.1.1	ALL	Analysis populations
14.1.2	SAS	Summary of reasons for discontinuation of study medication
14.1.3	SAS	Summary of reasons for withdrawal
14.1.4	FAS	Summary of major protocol violations
14.1.5	SAS	Summary of demographic data of index cases: age, sex, time onset of symptoms, symptoms, viral load and type of case.
14.1.7	SAS	Summary of demographic data of contacts: age, sex, PCR, symptoms and type of contact.
14.2 Efficacy tables		
14.2.1	FAS, PPAS, ITT	primary summary statistics
14.2.2	FAS, PPAS, ITT	primary raw and adjusted analysis (protocol definition)
14.2.2.1	FAS	subgroup analysis by type of contact
14.2.2.2	FAS	subgroup analysis by contacts viral load
14.2.2.3	FAS	subgroup analysis by cases viral load
14.2.2.4	FAS	subgroup analysis by index case time onset of symptoms
14.2.2.5	FAS	subgroup analysis by study site
14.2.3.1	FAS, PPAS, ITT	The percentage of positive PCR episodes among healthy contacts: summary statistics
14.2.3.2	FAS, PPAS, ITT	The percentage of positive PCR episodes among healthy contacts: GEE model
14.2.4.1	FAS, PPAS, ITT	The percentage of serological positivity (IgM/IgG) episodes among healthy contacts: summary statistics
14.2.4.2	FAS, PPAS, ITT	The percentage of serological positivity (IgM/IgG) episodes among healthy contacts: GEE model
14.2.5.1	FAS, PPAS, ITT	Time to Covid-19 confirmation among healthy contacts: summary statistics
14.2.5.2	FAS, PPAS, ITT	Time to Covid-19 confirmation among healthy contacts: : Cox regression analysis
14.2.6.1	FAS, PPAS, ITT	Time to positive PCR: summary statistics
14.2.6.2	FAS, PPAS, ITT	Time to positive PCR : Cox regression analysis
14.2.7.1	FAS, PPAS, ITT	Time to serological positivity (IgM/IgG) : summary statistics

Table Number	Population(s)	Table Title / Summary
14.2.7.2	FAS, PPAS, ITT	Time to serological positivity (IgM/IgG) : Cox regression analysis
14.2.8.1	FAS, PPAS, ITT	Time to hospital admission : summary statistics
14.2.8.2	FAS, PPAS, ITT	Time to hospital admission Cox regression analysis
14.2.9.1	FAS, PPAS, ITT	Time to death : summary statistics
14.2.9.2	FAS, PPAS, ITT	Time to death Cox regression analysis
14.2.10.1	FAS, PPAS, ITT	Time to hospital admission (index cases) : summary statistics
14.2.10.2	FAS, PPAS, ITT	Time to hospital admission (index cases) Cox regression analysis
14.2.11.1	FAS, PPAS, ITT	Time to death (index cases) : summary statistics
14.2.11.2	FAS, PPAS, ITT	Time to death (index cases) Cox regression analysis
14.2.12.1	FAS, PPAS, ITT	Virological clearance (index cases) : summary statistics
14.2.12.2	FAS, PPAS, ITT	Virological clearance (index cases) mixed model
14.3 Safety and tolerability tables		
14.3.1 Displays of adverse events		
14.3.1.1	SAS	Summary of all AEs
14.3.1.2	SAS	TEAEs by SOC and preferred term
14.3.1.3	SAS	TEAEs by severity
14.3.1.4	SAS	TEAEs by relationship to study medication
14.3.2 Displays of serious and other significant adverse events		
14.3.2.1	SAS	SAEs by SOC and preferred term
14.3.2.2	SAS	AEs leading to withdrawal from the study by SOC and preferred term
14.3.2.3	SAS	TEAEs of special interest by SOC and preferred term

8.2 PLANNED FIGURE DESCRIPTIONS

The following are planned summary figures for the study. Figures will be numbered according to the ICH E3 guidelines CSRs (ICH, 1993), and so will be included in section 14, after the tables.

Figure Number	Population	Figure Title / Summary
14.4 Efficacy figures		
14.4.1	FAS, PPAS, ITT	Kaplan–Meier graph of time to Covid-19 confirmation by treatment
14.4.2	FAS, PPAS, ITT	Kaplan–Meier graph of time to positive PCR by treatment
14.4.7	FAS, PPAS, ITT	Kaplan–Meier graph of time to hospital admission
14.4.8	FAS, PPAS, ITT	Kaplan–Meier graph of time to death
14.4.9	FAS, PPAS, ITT	Kaplan–Meier graph of time to hospital admission (index cases)
14.4.10	FAS, PPAS, ITT	Kaplan–Meier graph of time to death (index cases)
14.4.11	FAS, PPAS, ITT	Virological clearance by timepoint (index cases)
14.4.12	FAS, PPAS, ITT	Forest plot of subgroup analyses efficacy
14.4.13	FAS, PPAS, ITT	Forest plot of secondary outcomes

Changes to the Statistical Analysis Plan

Protocol Title: Treatment of non-severe confirmed cases of COVID-19 and chemoprophylaxis of their contacts as prevention strategy: a Cluster Randomized Clinical Trial (PEP CoV-2 Study)

SAP Author: Cristian Tebé

SAP Version: Version 1.0 with changes

SAP Date: October 8 2020

The final statistical analysis plan (SAP) incorporates updates resulting from statistical reviewer comments and suggestions though the peer review process. Major updates are the variation of the definition of the ITT population and the adjustment of the primary analysis to address missing data.

1. ANALYSIS SETS

The Intention to treat analysis set has been adjusted to include participants with missing outcome data.

2. HANDLING OF MISSING DATA

Multiple imputation by chained equations is applied to account for missing data. The assumption that unobserved values are missing at random is assessed looking at the lack of relationships in missingness patterns.

3. EFFICACY ANALYSIS

The primary efficacy analysis is performed on the intention-to-treat population with multiple imputation to account for missing data.

Complete case and per-protocol population analyses are conducted as sensitivity analyses.