COVER
(COVid iVERmectin)

Randomized, Double-blind, Multi Centre Phase II, Proof of Concept, Dose Finding Clinical Trial on Ivermectin for the early Treatment of COVID-19

CLINICAL STUDY PROTOCOL

PROTOCOL NUMBER: 2020-34 EUDRACT NUMBER: 2020-002283-32

VERSION NUMBER 21st May 2020, version 2.0

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INVESTIGATOR AGREEMENT

Randomized, Double-blind, Multi Centre Phase II, Proof of Concept, Dose Finding Clinical Trial on Ivermectin for the early Treatment of COVID-19

Sponsor and author approval:

This clinical study protocol has been reviewed and approved by the Sponsor Representative and the local Principal Investigator.

_____	_____	_____
Sponsor Representative	Signature	Date

_____	_____	_____
Principal Investigator	Signature	Date

Investigator signature:

I have read the contents of this protocol and agree to abide by all provisions set for therein.

I agree to personally conduct or supervise this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki and with the International Conference on Harmonisation guidelines on Good Clinical Practice and applicable local regulatory requirements.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. I agree to make available to sponsor personnel, their representatives and relevant regulatory authorities, study documents, office and clinical charts and records of the subjects recruited in the clinical site in order to verify the data that I have entered into the case report forms.

SYNOPSIS

Study Title

Randomized, Double-blind, Multi-centre, Proof of Concept, Dose Finding Phase 2 Clinical Trial on ivermectin for the treatment of Covid-19.

Design

Prospective, multi-centre, randomized, double-blind trial to assess safety and efficacy of ivermectin for the treatment of initial infection with SARS-CoV2 infection.

Study arms: A) placebo B) ivermectin 600 µg/kg daily for 5 consecutive days (I_600) + placebo. C) ivermectin 1200 µg/kg daily on an empty stomach with water for 5 consecutive days (I_1200). Patients will be randomized at emergency rooms of hospitals as well as at outpatient ambulatory care as well as at home, according to routine procedures of recruiting centres.

In arm A and B, the number of placebo tablets to be administered will be calculated by the study dedicated pharmacist considering the number of tablets that should be taken in case a patient with the same weight is assigned to arm C.

Sample size

A first analysis will be conducted after enrollment of the first 60 patients (20 per arm) for safety and efficacy purpose.

Thereafter, if both experimental treatments will be compared with control group, the total number of patients to be analyzed will be 102 (129 to be enrolled).

If only one experimental group is going to be compared with control arm, the total number of evaluable patients will be 84 (105 to be enrolled).

Inclusion Criteria

- Age (>=18 years)
- Positivity at RT-PCR for SARS_CoV2 (nasopharyngeal swabs)

- COVID-19 Severity[1] Score < 3
- Patient able to take oral drugs

Exclusion criteria:

- Pregnant or lactating women (pregnancy test not required, in case of doubt patient is excluded)
- Subjects suffering from known CNS diseases
- Lack of (or inability to provide) informed consent
- Patient under dialysis
- Any severe medical condition with a prognosis of < 6 months
- Patients under warfarin treatment
- Patients under antiviral treatment
- Patients under chloroquine phosphate or hydroxychloroquine

Trial duration

Overall trial duration is expected to be approximately 6 months.

Primary objectives

The study is aimed

1. at defining if ivermectin, administered at dosage of 600 mcg/kg or 1200 mcg/kg QD for five consecutive days is safe in patients with initial, asymptomatic or oligosymptomatic SARS_CoV2 infection, and:
2. at defining if ivermectin, administered at the dosage(s) found to be safe decreases the viral load of SARS-CoV2 at Day 7.

Secondary objectives

To assess

1. the temporal profile of viral load at baseline, day 7, 14 and 30
2. the time to clinical cure (for symptomatic patients)
3. the proportion of patients with virological clearance at day 14 and 30.
4. the hospitalization rate.
5. the COVID-19 Severity Score at day 14 and 30

[1] 1 is "no limitation of activities", 2 is "limitation of activities", 3 is "hospitalized, no oxygen therapy", 4 is " hospitalized, oxygen by mask or nasal prongs", 5 is "non-invasive ventilation or high-flow oxygen", 6 is "intubation and mechanical ventilation", 7 is "ventilation + additional organ support - pressors, RRT (renal replacement therapy), ECMO (extracorporeal membrane oxygenation)", and 8 is "death".

Analysis

The data will be analyzed according to the intention-to-treat principle for efficacy. All randomized subjects will be included in the analysis. For safety analysis, only patients receiving at least one dose of study treatment will be included.

Safety

Registration of all adverse events reported by the patients, once daily.

Routine visits and Follow-up

Patients will be followed with telephone calls, once daily until day 5; on day 7 when they will undergo a scheduled medical visit (at hospital or as outpatients or at home according to local procedures), plus laboratory exams. A second day scheduled medical visit plus laboratory exams will take place at day 14 and a follow-up visit will take place at day 30. Study investigators will be available by telephone call for any unscheduled contact.

TABLE OF CONTENT

ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
Cmax	Maximum (peak) plasma drug concentration
COVID-19	Coronavirus disease 2019
DD-PCR	Digital droplet quantitative PCR
eCRF	electronic case report form
EDC	Electronic data capture
HCQ	Hydroxychloroquine
ITT	Intention to treat
PP	Per-protocol
QD	once a day
RCT	Randomized clinical trial
RSI	Reference safety information
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SARS-CoV2	Severe Acute Respiratory Syndrome - Coronavirus – 2
SmPC	Summary of product caractherisctics
SUSAR	Suspected unexpected serious adverse reactions
TCR	Time to clinical resolution
Vd	Volum distribution
WBC	White blood cells
WHO	World Health Organization

INTRODUCTION

Rationale and background

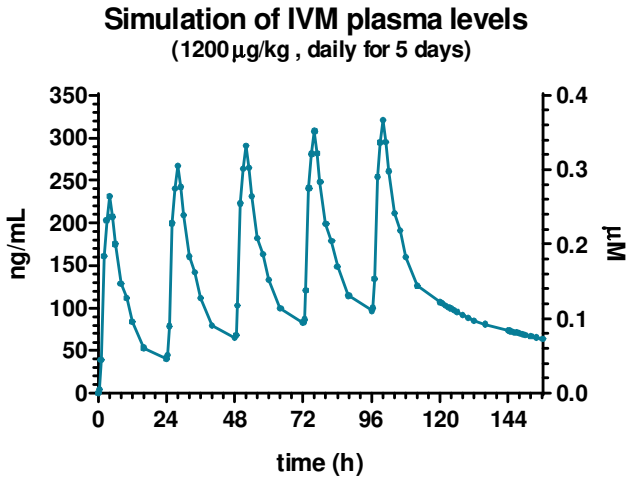
As of 23rd April 2020, the novel betacoronavirus SARS-CoV-2 has infected more than 2'160'000 individuals, killed over 175'000 people and has spread to more than 200 countries (WHO 23April 2020), virtually all countries of the globe. So far, despite the huge number of patients and the great number of clinical trials, either concluded or underway, no convincing proof of clinical efficacy has been obtained for any of the antiviral treatments used. Hydroxychloroquine (HCQ) has been claimed to reduce the viral load and to be clinically effective, but on the basis of methodologically questioned trials (Sanders et al. 2020). However, HCQ has become the standard of care in many COVID units and is authorized for off-label use in many countries, either alone or in association with other drugs such as anti retroviral drugs. It is reasonable to hope that some of the numerous trials currently underway will produce evidence in a relatively short time. Recently, the European Medicines Agency has warned against the inconsiderate use of HCQ, because of the risk of serious side effects, and stated that "In the context of COVID-19, these medicines should only be used as part of clinical trials or in line with nationally agreed protocols." (EMA 2020).

Recently, another drug, ivermectin, has been proven effective in vitro in reducing the viral load of SARS-CoV 2 infected Vero cells by 99.98% in 48 hours (Caly et al. 2020). Ivermectin is an "old drug"(Omura 2008) extensively used on hundred millions people for over 35 years for a wide range of parasitic infections, and with a broadening range of potential indications in recent years.

Caly et al. (Caly et al. 2020) hypothesized that the antiviral action against the SARS-CoV-2 in vitro was through the inhibition of the IMPα/β1 heterodimer-mediated nuclear import of viral proteins, as shown for other RNA viruses (Tay et al. 2013; Wagstaff et al. 2012; Yang et al. 2020). However, the IC-50 for this antiviral effect was approximately 2.5 µM, equivalent to 2,190 ng/mL, that is about 50-fold higher than the peak concentration (C_{max}) achieved in plasma after the single dose of 200 µg/kg, normally used as anti-parasitic drug in clinical practice (Muñoz et al. 2018; Buonfrate et al. 2019; Naquira et al. 1989). This difference raised concern on the likelihood of a successful use of ivermectin for the treatment of COVID-19 (Chaccour et al. 2020), even using doses 10-fold higher than the approved one (Schmith et al., 2020).

However, the following points suggest that five daily doses of 600 and 1200 µg/kg in a fasted state, i.e. the schedule envisaged in the present CT, might allow to reach clinically relevant drug concentrations at the target organ (lung):

i) The results of our simulation of the plasmatic concentrations expected in patients receiving the highest dose (1200 µg/kg) in fasted state. This simulation was based on the plasma values obtained by Guzzo et al., (Guzzo et al. 2002) after single injection of 500-2000 µg/kg in fasted state, using a half-life of elimination of 35h. This value is consistent with the terminal part of the PK profile shown in (Guzzo et al. 2002), corresponds to the value determined in a recent PBPK study (Duthaler et al. 2019), and is the same used by Schmith et al., (2020) for their simulation.



The Cmax value we predict after the first 1200 µg/kg dose (230 ng/mL, 0.26 µM) is proportional to the Cmax value measured after a single dose of 600 µg/kg (105-119 ng/mL, (Smit et al. 2019)), the value measured after a single dose of 200 µg/kg (46 ng/mL, (Muñoz et al. 2018)) and the value estimated by Schmith et al., 2020 for a single dose of 200 µg/kg (27 ng/mL) according to PBPK data (Duthaler et al. 2019).

Importantly, our simulation highlights that some accumulation occurs with the five daily doses (accumulation ratio calculated on the AUC: 2.25), and that Cmax values up to 320 ng/mL (0.37 µM) can be expected in plasma after the fifth dose.

Notably, these plasmatic levels are only slightly higher than the plasmatic levels observed with single administration of 2000 µg/kg in fasted state or 500 µg/kg in fed state (248 and 260 ng/mL), which were well tolerated (Guzzo et al. 2002). Moreover, a recent systematic review and meta-analysis showed no difference in the severity of the adverse events between standard (up to 400 µg/kg) and higher doses of ivermectin (Navarro et al. 2020).

ii) The possibility that concentrations in lung are higher than those in plasma. A large volume of distribution has been reported in different species including humans (Duthaler et al. 2019; Muñoz et al. 2018). A study in cattle (Lifschitz et al. 2000) showed that, after a single subcutaneous injection of avermectin, the drug availability in lung exceeds by 2.67-fold the one in plasma (calculations on the $AUC_{0-\infty}$); similarly, a study in goat (Lespine et

al. 2005), showed 3-fold higher ivermectin concentrations in lung than in plasma two days after a single subcutaneous or oral administration, a difference which persisted even 7 days after. Thus, lung concentrations of ~0.7 µM (0.26 µM x 2.67) could be reached in lung after a single dose of 1200 ug/kg in humans. Moreover, as seen above, a drug accumulation is expected after five daily doses, which could amount to 2.25-fold as estimated in plasma, up to 5.35-fold as estimated by Schmith et al., (2020) consistently with the longer elimination half-life found in cattle lung (~80h, (Lifschitz et al. 2000)). According to these calculations, after five 1200 µg/kg doses, ivermectin can reach lung concentrations of 1.6-3.7 µM, i.e. similar to the concentration needed to inhibit the replication of SARS-CoV-2 in cells (2.5 µM).

Another interesting observation came from the results of a trial with ivermectin for dengue virus infection (Yamasmith 2018). In this study, 400 µg/Kg ivermectine daily for three days showed no efficacy on clinical endpoints but it significantly affected the clearance of the NS1 antigen (a proxy of the viral load), although the active concentration on Vero cells infected with the Dengue virus was 25 µM, i.e. much higher than that reported in SARS-CoV2 – infected cells (Caly et al. 2020),

We believe that in the current pandemic situation several risks exist that pose serious ethical concerns, as it has been already pointed out (Kalil 2020). Anecdotal reports from observational series of clinical efficacy of ivermectin (at low, standard dose) in severely ill COVID-19 patients are already coming out (Patel 2020, unpublished). Already, several different treatments have become of widespread use despite very weak, if any, evidence of efficacy. This poses even a threat to the planning of rigorous RCTs, just because these treatments have often become accepted standards of care. The appearance of a new drug in the scenario has already induced expectations and reached the general press (Newsweek 2020). The risk is that the “new” drug might enter large, Phase 3 clinical trials, and/or even enter “compassionate” use, before any preliminary indication of efficacy comes out. We believe that a first, proof of concept, dose- finding trial on a limited number of patients with mild SARS-CoV2 infection is warranted before embarking on larger trials. Antiviral drugs can probably play a role in the first phase of the infection, by reducing the viral load before clinical complications arise. A viral load reduction is a pre-requisite for a possible clinical effect, and can be measured on a reasonably small group of patients, but seems very unlikely to be obtained with the doses of the drug that are normally used for parasitic infections. This is why we intend to try higher dose schedules, 600 and 1200 mcg/kg, though remaining at a much lower daily dosage compared with the maximum dose found to be safe

(Guzzo et al. 2002), and beginning with a first phase of the study that will assess the frequency of side effects, before the second phase on biological efficacy, that will only be started once safety will have been confirmed.

TRIAL OBJECTIVES

Primary objectives

The study is aimed:

1) at defining if ivermectin, administered at dosage of 600 µg/kg or 1200 µg/kg QD for five consecutive days, is safe in patients with initial, asymptomatic or oligosymptomatic SARS_CoV-2 infection,
2) at defining if ivermectin, administered at the dosage(s) found to be safe, decreases the viral load of SARS-CoV-2 at Day 7.

Secondary objectives

To assess

1. the temporal profile of viral load at baseline, day 7, 14 and 30
2. the time to clinical cure (for symptomatic patients)
3. the proportion of patients with virological clearance at day 14 and 30.
4. the hospitalization rate.
5. the COVID-19 Severity Score at day 14 and 30

STUDY DESIGN

This is a multicentre, prospective, randomized, double-blind, adaptive phase II dose finding study.

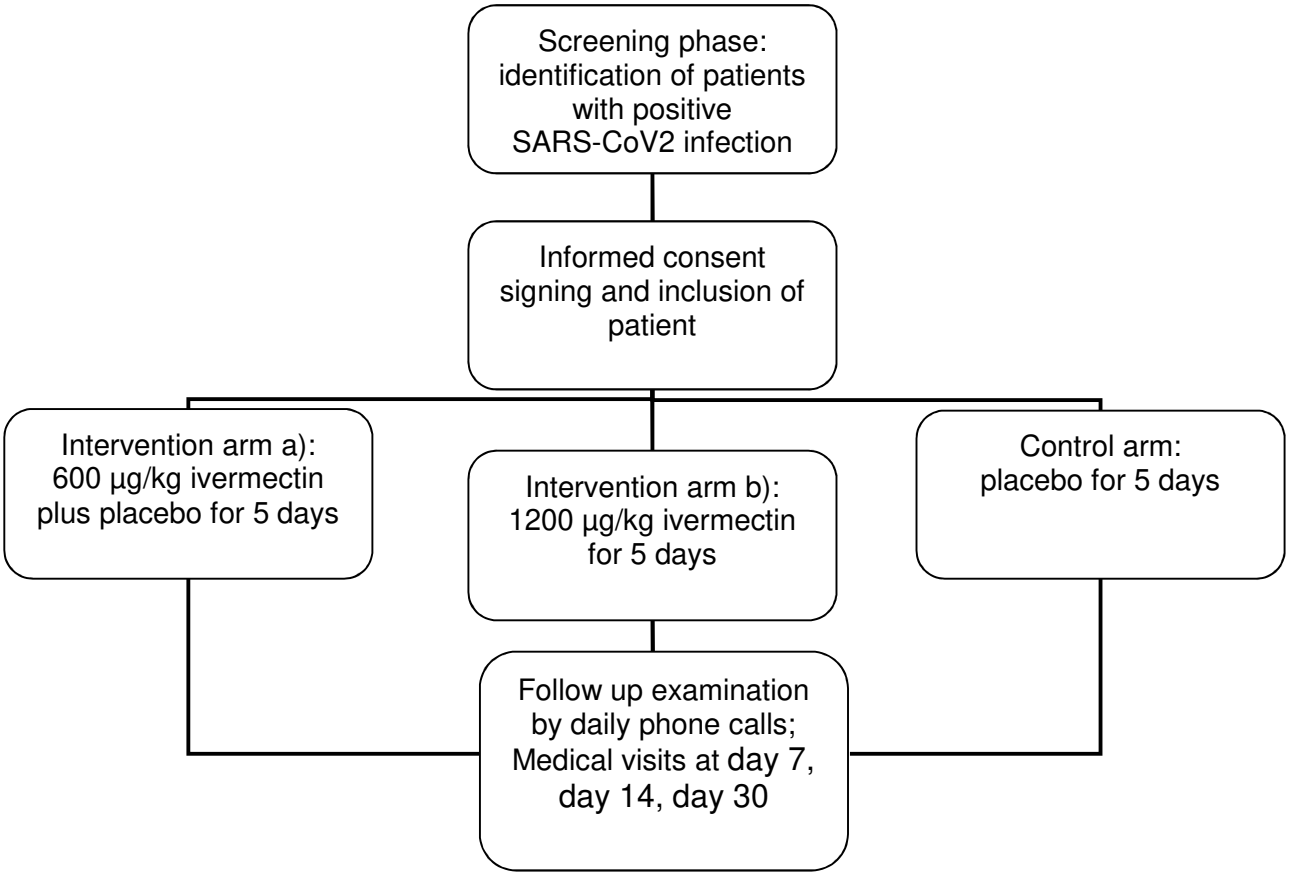
Patients meeting the inclusion criteria will be asked to participate to the study and randomized in a 1:1:1 ratio to either:

- Placebo arm (arm A): placebo will be identical in appearance to ivermectin in order to preserve blinding and will be administered p.o. at empty stomach with water once daily, for 5 days

- Intervention arms: a) Ivermectin, single dose 600 µg/kg, for 5 days (I_600) and placebo (arm B) ; b) Ivermectin, single dose 1200 µg/kg, for 5 days (I_1200) (arm C)); these drugs will be administered p.o. once daily, for 5 days.
In arm A and B, the number of placebo tablets to be administered will be calculated by the study dedicated pharmacist considering the number of tablets that should be taken in case a patient with the same weight is assigned to arm C.
Patients will be randomized by a centralized computer system. At randomization a treatment ID is assigned to the patient. Once a treatment ID is assigned this must not be re-assigned even in cases of errors.
Enrolled subjects will be identified by a unique subject number (patient code) that will remain consistent for the duration of the study.

Patients will be recruited at the emergency room of hospitals, and/or among asymptomatic hospital workers found positive for SARS-CoV-2 at routine screening and/or in outpatient ambulatory settings, and/or at home, if not meeting the clinical criteria for hospitalization, according to the routine procedure of each participating site. The expected duration of subjects inclusion in the study is of 3 months, or until the planned number of subjects to be enrolled will be reached.

Study flow chart



All phases of the trial will be recorded following the CONSORT statement.

Patient selection

Inclusion Criteria

- Age (>=18 years)
- Positivity at RT-PCR per SARS_CoV-2 (nasopharyngeal swabs)
- COVID-19 Severity[2] Score < 3
- Patient able to take oral drugs
- Informed consent to study participation and to personal data treatment

Exclusion criteria:

- Pregnant or lactating women (pregnancy test not required, in case of doubt patient is excluded)
- Subjects suffering from known CNS diseases
- Lack of (or inability to provide) informed consent
- Patient under dialysis
- Any severe medical condition with a prognosis of < 6 months
- Patients under warfarin treatment
- Patients under antiviral treatment
- Patients under chloroquine phosphate or hydroxychloroquine

Trial duration

Overall trial duration is expected to be approximately 6 months.

Primary outcomes

1. Number of serious adverse drug reaction (SADR).
2. Quantitative viral load at Day 7 as measured by quantitative, digital droplet PCR.

NB: The primary outcome no.2., as well as all secondary outcomes, will be measured only if the number of SADR is less than 4 in at least one of the treatment arms.

[2] 1 is "no limitation of activities", 2 is "limitation of activities", 3 is "hospitalized, no oxygen therapy", 4 is " hospitalized, oxygen by mask or nasal prongs", 5 is "non-invasive ventilation or high-flow oxygen", 6 is "intubation and mechanical ventilation", 7 is "ventilation + additional organ support - pressors, RRT (renal replacement therapy), ECMO (extracorporeal membrane oxygenation)", and 8 is "death".

Secondary outcomes

1. Trend over time of quantitative viral load at Day 7, 14 and Day 30 as measured by quantitative, digital droplet PCR.
2. Time to clinical resolution (for symptomatic patients).
3. Proportion of patients with virological clearance at day 14 and 30
4. Rate of hospitalization.
5. COVID-19 Severity Score at Day 14 and Day 30

Statistical design and sample size

The statistical study design is conceived in 2 steps.
The patients will be randomised to I_600 + placebo or I_1200 or placebo with an allocation ratio=1 :1 :1.

Step 1:
Safety analysis
After randomisation of the first 60 evaluable patients (20 per arm) a first analysis will be performed on the 2 experimental treatments for safety purpose. Safety endopoint will be the occurrence of a SADR. Definitions are reported in the paragraph «Definition and reporting of adverse events»
A'Hern single stage design (A'Hern 2001) will be adopted. For each experimental arm, the null hypothesis that the true toxicity rate is 30% will be tested against a one-sided alternative. The null hypothesis will be rejected if ≤4 SADRs are observed in 20 patients. This design yields a type I error rate of 10% and power of 80% when the true toxicity rate is 5%.
If ≥5 SADRs are observed in one of the experimental arms, the allocation of patients to that arm will be interrupted and the study will continue for efficacy analysis only for the control arm and the other treatment arm. In case that ≥5 SADRs will be experienced in both arms the study will be stopped.

Interim efficacy analyses
Two interim analyses are planned at the end of stage 1: the first for efficacy and the second for futility. For both analyses only the experimental treatments considered « safe » at first stage will be tested against the control arm. For the efficacy analysis the Haybittle–Peto boundary will be used as stopping rule (Haybittle 1971): if a probability ≤0.001 that a

difference as extreme or more as that observed at the interim analysis, between the treatments is found, given that the null hypothesis is true, then the trial should be stopped early for efficacy. In case of the probability will be greater than 0.001 the trial will continue with the stage 2 and the final analysis will be still evaluated at the level of significance without alpha error correction.The interim analysis for futility will be performed according to the conditional power analysis Lachin 2005). The experimental arm will be stopped if, under the assumption of the results distribution of future data, calculated assuming the current trend or the alternative hypothesis, the probability of detect a statistically significant results at the end of the trial will be <20%.

Step 2: final efficacy analysis.

Each experimental arm passing the step 1, will be compared with control arm at a statistical significant level of 0.025, one side. In this way, in case that both arms are considered for the efficacy comparison, the statistical significant level will be set to 0.025, 1 side, in order to preserve an overall family wise error of 0.05. Primary endpoint will be the difference in viral load decline from baseline to 7 days. Viral load will be measured as $\log_{10}$ of genome copies per mL, ascertained by Digital Droplet quantitative PCR (DD-PCR). In order to calculate the sample size, we refer to data recently published on Lancet Inf. Dis. (To 2020), showing that in a population with mild disease presentation, the difference in mean viral load from baseline to 7 days is 1.05 $\log_{10}$ copies per mL (from 0.77 to 1.33 $\log_{10}$ copies, calculated from the slope and its 95%CI), with an estimated SD=0.69 $\log_{10}$ copies per mL. The desired difference in decrease between each experimental group and control is at least 0.47 $\log_{10}$ copies per mL in order to detect an effect size Δ =0.68 (considered to be of moderate-large magnitude according to Cohen 1988). According to these hypotheses, with 34 pts per arm the study has a power=80% to detect a statistically significant difference between the experimental vs. control arm, at 0.025 alpha level, one side.

Therefore, if both experimental treatments will be compared with control group, the total number of patients to be analyzed will be 102. Considering a potential 20% loss to follow-up, it is planned to enroll 129 patients.

If only one experimental group is compared with control arm, the total number of evaluable patients will be 84 (105 to be enrolled).

Random allocation procedure

Patients will be randomly assigned to one of the three treatment groups with an equal probability of assignment to each treatment (allocation ratio 1:1:1). The study biostatistician will prepare the sequence of treatments according to a randomized permuted blocks procedure and the randomized list will be centralized. The randomization list will be generated using SAS 9.4 release. The randomised allocation of treatment ID will be centralised.

Upon recruitment of a patient meeting the inclusion criteria, the local investigator will follow an online procedure (detailed in the Manual of Procedures) to know the treatment ID of the patient. After randomization the treatment ID, along with patient's weight and patient code, will be transmitted to the hospital pharmacist who is in charge to prepare the study treatment according to randomization arm.

Blinding procedure

Ivermectin and placebo treatment will be double blinded, i.e. the treatment will be unknown to both the subject and the treating physician. The hospital pharmacist will be unblinded to study treatment because in charge to prepare the study treatment according to randomization arm.

The study medication will be labeled using a unique treatment ID, which is linked to the patient code. For each patient the treatment ID assigned at the time of randomization will be the same during the whole treatment period. The active and placebo kits will be presented in the same packaging to ensure blinding of the study medication.

The Investigator will receive sealed emergency envelopes allocated to his/her site. Each envelope is labeled with the protocol acronym and a treatment ID. Inside the envelope, the respective treatment arm is recorded. The Investigator is authorized to unseal the envelope only in case of a medical emergency when adequate treatment of the concerned patient requires immediate knowledge of the actual previous trial treatment.

If felt useful, the investigator may first discuss options with the other investigators and the scientific coordinator from Sponsor before unblinding the subject's treatment assignment.

Situations other than medical emergencies may require unblinding of a subject's treatment assignment. In these cases, a discussion with the Principal Investigator and with the Sponsor staff is recommended before the patient is unblinded.

If this is impractical, the investigator must notify to the Sponsor as soon as possible, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
Specific procedures for emergency unblinding of a subject's treatment are provided in the appropriate "Unblinding procedures".
The study pharmacovigilance dedicated staff retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to the investigational product and that potentially require expedited reporting to regulatory authorities. The subject who has been unblinded may continue on study treatment according to clinical judgement.
In case of code break, the Investigator must compete the "Unblinding Form" providing the date of and reason for unblinding and send it to the Sponsor and the Safety Desk of the Sponsor immediately and no later than 24 hours from the time of unblinding via email to the Sponsor (ricerca.clinica@sacrocuore.it) and the study safety desk (safetydesk@rc.marionegri.it), respectively. Thereafter, the Investigator should access the Electronic Data Capture (EDC) system as soon as possible and report this information in the electronic Case Report Form (eCRF). During each monitoring visit, the monitor will check whether the emergency envelopes are still intact.

Statistical Analysis

Data will be analyzed by the study biostatistician using the software SAS 9.4 release. A full Statistical Analysis Plan will be written prior to statistical analysis.
The primary safety analysis will be performed on safety analysis set, including patients who received at least one dose of study tratement.
The analysis of primary efficacy as well as secondary outcomes will be performed according to an Intention to Treat basis (ITT) considering all subject as originally assigned to the treatment arms.
Patients with missing values and patients lost during treatment or at follow-up will contribute to the analysis of the secondary outcomes only for the time during which data are available.
A per-protocol (PP) analysis will be also performed including only patients who took the allocated treatment as specified in the protocol, in order to check for consistency with the primary analysis.

Analysis of the primary outcome

The proportion of patients in each experimental group experiencing at least one SADRs will be described by means of frequency and percentages.
The mean of the differences in viral load decline from baseline to 7 days between each experimental group and the control group will be described by standard summary measures for continuous data and compared by mean of Student T test or the equivalent non parametric method (according to the Barlett's test for homogeneity of variances).

Analysis of the secondary outcomes

Binary outcomes will be described by frequencies and proportions and summarised by mean of absolute and relative difference, with their relative 95% CI. Mantel Haenzel test will be used for pairwise comparison between groups. For expectedly rarer outcomes (such as deaths, patients with blood test alterations during treatment), Fisher's exact test will be used if required.
Continuous variables will be first assessed with Barlett's test for homogeneity of variances. Then, the t-test for comparing two means or the Wilcoxon rank sum for non-normal populations, whichever the more appropriate, will be used.
The pattern of compliance to treatment will be explored and compliers/non compliers will be compared with respect to baseline demographic and clinical data.
Time to clinical resolution (TCR) will be calculated as the time from randomisation to clinical resolution or death. A competing risk model will be used to analyze TCR, since the death is considered as competing event.
The assessment of safety profile will be mainly based on adverse reactions (ARs) and the frequency and nature of SAEs.
For each patient and for each type of adverse event, the worst degree ever suffered during treatment will be used for the analysis. All safety parameters will be presented and analyzed in terms of listings and summary tables.
The proportion of patients in each group experiencing adverse events will be compared through the chi-square test (or the Fisher's exact test when appropriate).
SAEs will be summarized by presenting the number and percentage of patients having any SAE. Other information collected (e.g. severity or suspected relationship to study medication) will be listed as appropriate.
Generalized longitudinal mixed models will be used to analyze the trend over time of viral load ad different time points (baseline, 7 days, 14 days, 30 days).

Multiple regression will be used to study the variation of main random variables according to several potential predictor variables including among others: age; sex; continent of origin; recruiting centre; test results on recruitment.

STUDY PROCEDURES

Baseline

Suitable subjects will be identified through laboratory diagnosis of SARS-CoV-2 infection according to the reference standard (molecular) method of each participating site. Eligible patients will be directly asked (if still present at hospital at the moment of the positive test result) or by phone interview (if at home) their consent for study entry. The following procedures will be completed and recorded in each patient eCRF:

- Confirmation of eligibility
- Explanation of the study protocol according to the patient information sheet and request for consent to the patient
- Acquisition of Informed Consent for: participation to the study; use of personal data; donation of biological samples for study purpose.
- Demographics (i.e. age, gender, weight, height)
- Disease history, including information on concomitant medications
- Clinical assessment (by direct observation if recruited on site or by phone interview if recruited at home)

Once the inclusion and exclusion criteria are confirmed patients will be assigned to the control or intervention arms, according to the random selection.

The Investigators should register in the Subject Screening Log the age and the microbiology results for SARS-CoV-2 of all the patients who are asked to enter the study, irrespective of their subsequent enrolment. If the patient is not subsequently enrolled, the reason will be indicated in the form.

Routine visits

Patients will be followed with telephone calls, once daily until day 5. A scheduled medical visit plus lab exams will take place at day 7, 14 and 30. Study investigators will be on call for any unscheduled telephone contact or unscheduled hospital visit.

At routine visits the following procedures will be completed:

- Laboratory tests as per routine procedures of each participating site, plus (if not included in routine): FBC, ALT at Day 7, 14 after administration of the first dose.
- Collection of any adverse events to be recorded in the eCRF
- On Day 7 and 14 a second and a third nasopharyngeal swabs will be performed for molecular analysis of SARS-CoV-2 infection. If negative at day 14, the swab will be repeated once, or not, according with routine procedures. If still positive, it will be repeated at Day 30.

When the visit includes administration of therapy (Day 1), ivermectin (or placebo) will be administered according to the randomized arm.

A clinical examination and lab/imaging exams will be carried out for subjects present at the clinical site at the time of inclusion, according to local routine. Available, relevant findings will be recorded in the eCRF.

In case of worsening of symptoms, and in consultation with the doctor ordinarily caring for home patients, the patient will be taken again to the emergency room of the recruiting site (or visited at home, or at outpatient ambulatory setting, according to the procedures of each site) and fully re-assessed, including for the need of hospitalization. In case of hospitalization, the patient will be followed according to routine procedures of each site, and each day of hospitalization will be dealt with as an unscheduled visit.

Follow up visits

A follow-up visit will be carried out at Day 30, with a further clinical and laboratory assessment and all these findings will be recorded in the eCRF.

Unscheduled Visits

Study investigators will be on call for any unscheduled telephone contact.

On entering the study patients will be given a telephone number and instructed to contact that number immediately and arrange a clinic visit at the sign of any worsening clinical symptom, that will be dealt with as above.

Clinical management during the follow-up period will be carried out according to local standard protocols/practice.

Table 1. Summary of the Study Intervention

Assessment	Baseline, Enrolment	Routine visits			Unscheduled visits	Follow up visit (Day 30)
		Days 1 to 5	Day 7 (see text)	Day 14 (see text)		
Informed Consent	X					
Selection criteria	X					
Randomization	X					
Demographics	X					
Clinical data/symptoms	X	X	X	X	X	X
Administration of ivermectin or placebo		X				
Concomitant medications	X	X	X	X	X	X
Blood monitoring if applicable (see text)	X		X	X	X	X
Adverse events	X	X	X	X	X	X

Study treatments

The quantity of ivermectin and placebo required for completion of this study will be provided by the Sponsor. Study drug and placebo will be distributed to the sites by Sponsor's delegates. The drug distribution will take place at the study site or at home, according to local rules and procedures. Patients should take ivermectin or placebo orally on an empty stomach with water. Patients will be administered a single oral daily dose of approximately 600 µg/Kg (486-679 µg/Kg as rounded to a whole number of tablets), or 1200 µg/Kg (1098-1286 µg/Kg). The number of tablets to be administered will vary from five to fourteen according to the patient's weight, based on a dosage table (see table 2).

The corresponding placebo has the same excipient composition, tablets configuration, and dosage as the ivermectin drug product.

For all centers, ivermectin and matching placebo will be packed in blisters. The randomized study treatment will be dispensed to patients. Each dosing container will contain sufficient medication for the treatment period.

During the visit scheduled at day 7, patients will return all the unused tablets, so that compliance evaluation can be performed; the reasons why the tablets have not been taken completely should be registered.

Table 2. Number of tablets (9 mg ivermectin**) to be administered according to the patient's body weight and treatment arm.**

Body weight (kg)	ARM A:Placebo	ARM B: Single oral dose 600 µg/Kg			ARM C: Single oral dose 1200 µg/Kg	
	N. tablets (placebo)	N. tablets (ivermectin)	N. tablets (placebo)	Range of dose/weight	N. tablets (ivermectin)	Range of dose/weight
35-37	5	2	3	486-514	5	1216-1286
38-41	5	3	2	659-711	5	1098-1184
42-48	6	3	3	563-643	6	1125-1286
49-52	7	3	4	519-551	7	1235-1286
53-56	7	4	3	643-679	7	1125-1189
57-63	8	4	4	571-632	8	1143-1263
64-67	9	4	5	537-563	9	1209-1266
68-71	9	5	4	634-662	9	1141-1191
72-78	10	5	5	577-625	10	1154-1250
79-82	11	5	6	549-570	11	1207-1253
83-86	11	6	5	628-651	11	1151-1193
87-93	12	6	6	581-621	12	1161-1241
94-97	13	6	7	557-574	13	1206-1245
98-101	13	7	6	624-643	13	1158-1194

102-108	**14**	**7**	**7**	**583-618**	**14**	**1167-1235**

Formulation, Packaging and Handling

The composition of the ivermectin tablets is as reported in the attached IMPD (FILE NAME: Ivermectin 9mg IMPD.pdf). The composition of the placebo tablets is as reported in the attached IMPD (FILE NAME: IMPD PLACEBO Ivermectin 9mg.pdf).

Ivermectin and placebo can be stored at room temperature.

The Hospital Pharmacy (unblinded) will receive from the sponsor the tablets of ivermectin (9 mg of active substance) and placebo in bottles of 170 tablets each. After the patient's enrollment and once receiving the required information (unique randomization number and body weight), the pharmacist will be able to prepare the packages of ivermectin/placebo depending on the enrollment arm (A, B, C). The number of tablets per each subject depends on the body weight (Table 2).

The pharmacist will prepare the daily therapy in five packs, assigning to each the progressive number from 1 to 5 (referred to the days of therapy from 1 to 5) and the respective dates. Inside each pack the patient will find the number of tablets assigned for each day of therapy.

The type of packaging must guarantee the correct conservation of the tablets inside.

Each package must be appropriately labeled with the title of the study, the study code (e.g. EudraCT n°), the ID patient (patient's unique code), randomization code (MED.ID), the expiration date, the dispensing day, the name of the PI, the phone contact (preferably PI contact), IMP and number of tablets, the drug information , the conservation method and the number of tablets inside, the pharmaceutical company and the Sponsor details.

Patient Withdrawal

Patients may withdraw (or be withdrawn) from the study at any time. Withdrawals will not be replaced.

Reasons for patient withdrawal include:

- Adverse event that in the judgement of the Investigator requires study withdrawal.
- Patient wishes to withdraw from the study.
- Patient is lost to follow-up.

A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow up AEs outside the clinical study. The primary reason for withdrawal from the study should be documented on the appropriate

section of the eCRF. Patients withdrawing from the study will be encouraged to complete the safety evaluation.

Concomitant Medication

The investigator will record in the eCRF any medication taken by the patient during the course of the study. Warfarin, antiviral drugs, chloroquine phosphate or hydroxychloroquine are not allowed for patients in the study (see Exclusion criteria).
Any changes during the study will be documented.
In addition any medications given to treat an adverse event will also be recorded.

End of Study

The end of the study is defined as the last follow-up visit of the last patient. The Ethics Committees will be notified within 90 days of the end of the study.
Recruitment will be stopped once the required number of patients is reached or in case of (unexpected and most unlikely) severe adverse events in the treatment arm or if the analysis of the first step will show an unfavorable safety profile of both experimental arms.

Data lock

Data lock will occur at the date of 2 months after recruitment of the last patient.
Codes will be broken after all the planned analyses will have been achieved and blinded conclusions drawn.

DEFINITION AND REPORTING OF ADVERSE EVENTS

The collection, assessment and presentation of safety reports will be carried out in accordance with the detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (‘CT-3’).
Patients will be carefully monitored for any AE occurring during the trial conduct. Such monitoring also includes clinical laboratory tests. AEs will be assessed in terms of their seriousness, severity, and causal relation to the study treatment. Safety reporting to study investigators, ECs, competent authorities will then follow in accordance with the results of such assessment.

Definitions

Adverse event

An AE is any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with the study treatment. Any clinical manifestation of progression of the disease under study (including signs, symptoms or abnormal laboratory values) is not recorded as an AE. Likewise, a failure of expected pharmacological action is not considered an AE.

With the exception of the above, an AE can therefore be any of the following:

- Any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease observed during the course of a clinical trial and the use of a medicinal product, whether or not considered related to the study drug;
- Any new disease or exacerbation of an existing disease that is different from the disease under study. Therefore a worsening in the character, frequency, or severity of a known condition should be classified as an AE;
- Recurrence of an intermittent medical condition (e.g., migraine) not present at baseline;
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug;
- Any symptom or medical complication related to a protocol-mandated intervention, including screening invasive procedures such as biopsies, placement of catheters and administration of contrast media.

Surgical procedures are not AEs because they are therapeutic measures. The condition for which the surgery is required is an AE, if it is different from the disease under investigation and occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the condition leading to these measures are not AEs, if the condition was known before the start of study treatment. In the latter case, the condition should be reported as medical history. Nonetheless, adverse events occurred during or after planned surgical measures should be considered as reportable events.

Adverse drug reaction

An Adverse drug reaction (ADR) is defined as any untoward and unintended response to an investigational medicinal product related to any dose administered.

Serious adverse event or serious adverse reaction

The ICH guidance, “Clinical Safety Data Management: definitions and Standards for Expedited Reporting” (ICH E2A), defines a serious adverse event or reaction (SAE/SAR) as any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening - an event in which the participant was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe;
- Requires inpatient hospitalization - any patient admission to a health care facility, even if for less than 24 hours. Hospitalizations also include transfer within the hospital to a different inpatient unit that are due to the occurrence of an AE. A planned hospitalization required by the protocol or programmed prior to study initiation does not constitute a SAE;
- Prolongation of existing hospitalization - any extension of hospitalization beyond the anticipated;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect. A pregnancy during the study meets the seriousness criteria in the following cases: miscarriage, congenital anomaly, neonatal death, infant death.
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above; examples of such events are intensive treatment in an emergency room or at home

for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse;

The terms “severe” and “serious” are not synonymous. The term “severe” is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as severe headache). On the other hand, the term “serious”, describes patient/event outcome or action criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. For example, a headache that significantly interferes with the participant’s usual functions might be assessed as “severe” in the clinical study documentation, but would NOT require reporting unless it meets one of the criteria for a SAE. Alternatively, a heart attack requiring admission to hospital may be assessed as mild, but would still be classified as serious because it meets the criteria for a SAE.

Severity and seriousness will be independently assessed for each AE and recorded on the e-CRF.

Suspected Unexpected Serious Adverse Reactions (SUSARs)

A SUSAR is a serious adverse reaction, the nature or severity of which is not consistent with the reference safety information (RSI) for the medicinal product.
The RSI for ivermectin/placebo is contained in the Summary of product characteristics (‘SmPC’).

Standard definitions for safety events are summarized in **Table** 3.

Table 3 Standard definitions of safety events

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable

	suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: - results in death - is life-threatening - requires inpatient hospitalisation or prolongation of existing hospitalisation - results in persistent or significant disability/incapacity - consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature or severity of which is not consistent with the Reference Safety Information for the medicinal product. The RSI for ivermectine/placebo is contained in the Summary of product characteristics ('SmPC').

Adverse Events

Adverse event management

The occurrence of AEs should be sought at each visit from the moment of performance of the first trial related procedure, including screening examinations and, subsequently at each study visit. AEs may be spontaneously reported by the patient during the screening process or during study visits, investigated through non-directive questioning of the patient regarding periods between visits, or directly observed through physical examination, laboratory tests, or any other relevant assessment.

All AEs should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded in the patient file and on the eCRF.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent: assessment of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it and the outcome should be made at each visit (or more frequently, if necessary).

Adverse event notification

AEs notification will be carried out completing the relative page on the study eCRF. It is recommended that notification is done once the information regarding each AE is complete. Any time new information becomes available or when one or more of the AE characteristics is modified (i.e. severity, seriousness and/or outcome), such new information should be entered onto the same AE record.

Vice versa, the repetition of the same AE after its resolution should be reported as two separate events. For example, liver enzyme alterations that are present in two consecutive visits will be reported as a single AE, and the worst severity recorded. On the contrary, a second transaminase elevation that appears after normalization of the blood picture will be reported as a second hepatic event.

Adverse event assessment and reporting

All AEs will be recorded by the investigator. Detailed information on all AEs will be recorded in the patient's clinical chart and the required information entered onto the relevant page of the eCRF.

In particular, all information concerning the following AE characteristics should be minutely and timely registered and updated as necessary:

- Diagnosis
- Seriousness
- Severity
- Causal relation to study treatments
- Start date
- End date
- Action taken with Study Drug
- Outcome

In addition, the following variables will be collected for SAEs as applicable:

- Date of awareness of the SAE
- Seriousness criteria
- Causality assessment in relation to Study procedure(s), concomitant treatments and medical history
- For fatal SAEs:
    a. Date of death
    b. Probable cause of death
    c. Autopsy performed
- Treatments and examinations for SAE management
- Narrative Description

Diagnosis

Whenever possible, AEs (including laboratory abnormalities that constitute AE) should be described using a diagnosis, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

All AEs should be classified according to the NCI-CTCAE (version 4.03) criteria. Classification should include the NCI-CTCAE official clinical or laboratory categories, followed by the specific clinical parameters as listed in the relevant severity grading table.

Seriousness

Any AE which fulfils one or more of the seriousness criteria listed above should be treated as SAE and the clinician observing the event should complete the SAE form and follow the expedited SAE notification procedures indicated below.

The initial seriousness and severity of the event should be recorded. If a new serious criterion is met this should be recorded as a follow-up.

Severity

Severity of AEs will be assessed according to the NCI-CTCAE, version 4.03.

Anyway, in the case where NCI-CTCAE grading does not exist for an AE, the severity will be assessed according to the general guideline provided by NCI-CTCAE (**Table 4**).

Table 4 NCI-CTCAE grading

Grade 1: Mild	Asymptomatic or mild symptom causing no or minimal interference with usual social and functional activities; clinical or diagnostic observations only; intervention not indicated
Grade 2: Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL) like preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
Grade 3: Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL like bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden
Grade 4: Potentially Life-threatening	Life-threatening consequences; urgent intervention indicated
Grade 5: Fatal	Death related to AE

The severity of the event should be recorded and in case the severity changes only the worst grade should be reported.

Relationship to study agents

The site investigator is responsible for assessing the relationship between the AE and the study drugs. Site investigators must determine whether there is a reasonable possibility that the study drugs caused or contributed to an AE/SAE.

The relationship assessment should be based on clinical judgment and should involve the evaluation of the following criteria:

- The temporal relationship between the event and administration of the study treatment;
- A plausible biological mechanism for the agent to cause the AE;
- All other possible etiologies for the AE;
- Previous reports of similar AEs associated with the study treatment or other agents in the same class;
- Recurrence of the AE after re-challenge or resolution after de-challenge, if applicable;

Investigators shall use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an

AE is considered to be related to the study drug, using the standard available attribution categories.

The investigator should express his/her level of confidence in the assessment of the causal relationship of an event to study treatment using the terms reported in **Table 5.**

Table 5 Assessment of causality

Attribution categories	Description
Certain	AE has a plausible time relationship to study drug(s) intake; the event cannot be explained by disease or other concomitant drugs; Response to drug(s) withdrawal plausible, rechallenge satisfactory (if necessary)
Probable	AE has a reasonable time relationship to study drug(s) intake; the event can be unlikely attributed to disease or other concomitant drugs; Response to drug(s) withdrawal clinically reasonable, rechallenge not required
Possible	AE has reasonable time relationship to study drug intake; the event could also be explained by disease or other concomitant drugs; information on drug withdrawal may be lacking or unclear
Unlikely	AE with a time to drug intake that makes a relationship improbable (but not impossible); other plausible explanations exist
Unrelated	AE with a time to drug intake that makes a relationship impossible; other plausible explanations exist
Conditional/Unclassified	Event or laboratory test abnormality; more data for proper assessment needed or additional data under examination
Unassessable/ Unclassifiable	Report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory; data cannot be supplemented or verified

Expectedness

Expectedness will be classified by the Sponsor on the basis of the RSI of study drug, included in the ivermectin SmPC.

Assessment of cases with multiple SAEs

Whenever possible, SAEs (including laboratory abnormalities that constitute SAEs) should be described using a diagnosis, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified or when more diagnoses occur at the same

time, each sign/symptom or diagnosis should be reported in a single SAE form and the main SAE should be listed as first. Each SAE should be independently assessed for causality, seriousness, severity, onset date and outcome by Investigators and for expectedness by the Sponsor.

Reporting

AE

AEs notification will be carried out completing the relative page on the study eCRF.

SAE

To ensure patient safety, every SAE, regardless of suspected causality, occurring from the acquisition of the informed consent until the date of last visit must be immediately reported to Sponsor and always within 24 hours of learning of its occurrence.
The investigator will notify the Study safety desk all SAEs occurring during the treatment period.

To notify the Sponsor, the identified SAEs should be recorded and described on the appropriate SAE form of the eCRF, which should be dated and signed electronically. By clicking on a specific link in the form, an automatic email will be sent to Study Safety Desk and to all Investigators with EDC system access.

In case the EDC system is malfunctioning, the SAE should be notified by completing an editable pdf SAE form provided during the site activation and sending it by email or fax within 24 hours of the initial observation of the event to the Study safety desk:

Laboratory of Methodology for Clinical Research
Istituto di Ricerche Farmacologiche Mario Negri IRCCS
Study Safety Desk
email: safetydesk.rc@marionegri.it
Fax: + 39 023571800

Once EDC system functionality is restored, all the cases reported through the pdf SAE form must be entered in the electronic SAE form of the EDC system.

Any new or additional information regarding the SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. Once

a SAE is detected, it should be followed until its resolution or until it is judged to be permanent. Follow-up information is sent to the same contact(s) to whom the original SAE report form was sent, using a new SAE report form stating that this is a follow-up to the previously reported SAE.

The repetition of the same SAE after its resolution should be reported as a second separate event.

Suspected Unexpected Serious Adverse Reactions (SUSARs)

The management of suspected unexpected serious adverse reactions (SUSARs) will be done according to the guideline 2011/C 172/01 "Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3')" based on Article 18 of directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

According to the CT-3, the SUSARs will be notified via EudraVigilance to Competent Authorities:

- within 7 days if the SUSAR results in death or is life-threatening
- within 15 days if the SUSAR is not fatal and not life-threatening

For this purpose, the Sponsor is registered to EudraVigilance as Sponsor of not-for-profit clinical trials.

All SUSARs will be notified to the Coordinating Ethics Committee and to the trial Investigators.

Deaths

All deaths that occur from date of acquisition of informed consent to the end of the safety follow-up period (25 days after the last study drug administration), must be reported as follows:

- Death which is clearly the result of COVID- 19 disease progression should be documented in the eCRF but should not be reported as an SAE.

- Death not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported as an SAE within 24 hours. The SAE form should report the main and contributory causes of death. This information can be captured also in the eCRF.

- Death with an unknown cause should always be reported as an SAE. If the cause of death later becomes available (e.g. after autopsy), the cause of death should be replaced by the established cause of death.

The term “sudden death” should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death later becomes available (e.g. after autopsy), “sudden death” should be replaced by the established cause of death.

Overdose, misuse, abuse, medication errors

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug (e.g. misuse, abuse, medication errors etc.) is not an AE unless it results in untoward medical effects.

Cases of accidental overdose with ivermectin have been reported, but none have resulted in fatalities. In cases of accidental intoxication with unknown doses of products destined for veterinary use (oral use, as an injection, cutaneous use), the symptoms described were: rash, contact dermatitis, oedema, headache, vertigo, asthenia, nausea, vomiting, diarrhoea and abdominal pain. Other effects have also been observed, including: seizures, ataxia, dyspnoea, paraesthesia and urticaria.

Management in case of accidental intoxication:

- Symptomatic treatment and surveillance in a medical care setting with fluid replacement and hypertensive treatment, if necessary. Although there are no specific

studies available, it is advisable to avoid combination of GABA agonists in the treatment of accidental intoxication due to ivermectin.

Ivermectin must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose.

All AEs associated with an overdose or incorrect administration of study drug should be recorded on the AE form. If the associated AE fulfills seriousness criteria, the event should be reported using SAE form to the Sponsor within 24 h from learning of the event.

Study recording period and follow-up for adverse events and serious adverse events

Adverse events and serious adverse events will be recorded from time of acquisitionof informed consent, throughout the treatment period and including the safety follow-up period (25 days after the last study drug administration). During the course of the study all AEs and SAEs should be proactively followed up for each participant. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

The investigator is responsible for following all SAEs until resolution, until the participant returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

Follow-up of unresolved adverse events

Any AEs that are unresolved up to the end of safety follow up period (25 days after the last study treatment administration) are followed up by the investigator for as long as medically indicated. After 25 days, only subjects with ongoing investigational product-related SAEs will continue to be followed for safety.

Reporting requirements for pregnancies

National regulations require that clinical trial Sponsors collect information on pregnancies occurring during clinical trials, in which exposure to the study drug at any time during pregnancy, is suspected. Therefore, pregnancy and suspected pregnancy (including a positive pregnancy test) occurring while the patient is on study drug, or within 25 days after the last study drug administration, are considered reportable events.

Maternal exposure

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drugs may have interfered with the effectiveness of a contraceptive medication. Any pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Study safety desk immediately and always within 24 hours from its first knowledge.

Immediately after detecting a case of suspected pregnancy in a clinical trial patient, a decision to continue the pregnancy will require immediate withdrawal from the trial.

The Investigator will follow the pregnancy until its outcome, and must notify the Study safety desk the outcome of the pregnancy as a follow-up to the initial report. For any event during the pregnancy, which meets a seriousness criterion, the Investigator will also follow the procedures for reporting SAEs (complete and send the SAE form to the study safety desk within 24 hours of the Investigator's knowledge of the event). All spontaneous miscarriages, congenital abnormalities or birth defects and neonatal deaths that occur within 30 days from birth without regard to causality and any infant death that the Investigator suspects to be related to exposure to the study drug should be immediately reported and always within 24 hours from the Investigators' knowledge of the event as SAE. The outcome of all pregnancies should be followed up and documented even if the patient was discontinued from the study.

PHARMACOKYNETICS STUDY

A pharmacokynetics study aimed at evaluating the association between plasma drug concentration and clinical endpoints is planned.
The study will be conduted on a subgroup of patients, according the detailes in Appendix 1.
For patients included in the study an additional informed consent will be required.

ETHICAL ASPECTS

This study is to be conducted according to globally accepted standards of good clinical practice (as defined in the ICH E6 Guideline for Good Clinical Practice, 1 May 1996), in agreement with the Declaration of Helsinki and in keeping with local regulations.

Written approval of the protocol and the associated study documentation will be obtained from the Competent Ethics Committees and from the National regulatory authority, according to local regulations.

Approval letters must contain the following information:

- Date of the meeting
- Information that identifies the version of both the protocol and the subject information/informed consent
- Details of any other documents reviewed

All protocol amendments will be submitted to the Ethics Committees for approval prior to implementation, except for any urgent amendments to ensure patient safety, which will be immediately implemented and then notified as soon as possible to the Ethics Committees and competent Authorities. In addition the Ethics Committees will be informed of any administrative changes.
Raw anonymized data sets will be available to the scientific community upon legitimate request, once the trial is completed.

Informed consent

It is an Investigator responsibility to inform and obtain the patient Informed Consent.
In accordance with the AIFA communication «*Clinical trials' management in Italy during the COVID-19 (coronavirus disease 19) emergency (March 12th 2020)* », eligible patients will be directly asked (if still present at hospital at the moment of the positive test result) or by phone interview (if at home) their consent for study entry. For patients directly enrolled at hospital or other study site by the investigator, informed consent will be collected orally and certified by the investigator himself and by a witness, given the impossibility of keeping potentially infected material. Patients enrolled at home, after an initial telephone conversation, will receive the information and consent forms by email and send them back signed in digital format (pdf scan). In both cases, the patient will be asked to re-sign the original consents for the conservation in the trial master file at the first useful occasion after the sample has become negative.

The Informed consent procedure will be in accordance with the European Regulation n. 679/2016 on the Protection of Personal Data, the Personal Data Protection Code (Legislative Decree 196/03) and subsequent amendments and additions, and to the provisions, guidelines and general authorizations of the National Guarantor for Personal Data Protection.

Participant confidentiality

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number.

This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IEC for each study site, as appropriate.

Data handling and record keeping

Records and documents pertaining to the conduct of this study, including eCRFs, ICFs, Investigator Site Files (ISFs) must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, participant to local regulations.

No records may be disposed without the written approval of the Sponsor.

Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

DATA MANAGEMENT

Source Data

Source documents are where data is first recorded, and from which participants' eCRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the eCRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

eCRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions.

On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code.

Collection of Data, Direct Entry

All data obtained during this clinical trial will be captured electronically in a project specific programmed EDC application. The eCRFs were specifically designed for the collection of the clinical data detailed in this trial protocol.

All data entered into the eCRF will have to be verified by the original patient's file.

For each patient enrolled after allocation of a Patient ID, all trial-related visits will be recorded in the eCRF. This eCRF must be completed by the Investigator for all patients, whether they completed the trial according to protocol or dropped out prematurely.

In particular, a web-based Clinical Data Management System (CDMS/eCRF) supported by REDCap, a secure web platform for building and managing online databases and surveys (https://redcap.marionegri.it/) will be used for collecting information for all patients. Each user has their own account, and their user account will only have access to REDCap projects which other users have granted them access. eCRF administrator will organize users in different roles groups. There are user controls to limit access to various functionality and modules, such as being able to export data, to enter data, to add or modify database fields or survey questions, to build or run reports, to modify user privileges, to view the logging records, and so on.

Monitoring

Due to pandemic situation and in accordance with the AIFA communication «*Clinical trials' management in Italy during the COVID-19 (coronavirus disease 19) emergency (March 12th 2020)* », the monitoring activities will be performed remotely. Remote monitoring visit will be performed through periodic, comprehensive connections through the web or the telephone with all participating centres by Sponsor personnel or representatives in order to perform, if applicable, the source data verification (SDV).

More details of the monitoring procedures will be specified in the Monitoring Plan.

In accordance with applicable regulations including Good Clinical Practice (GCP), monitors will contact the sites prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory and ethical requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of the source document for all data items.

Site activities will be monitored to verify that:

- Data are authentic, accurate and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

PROCEDURE FOR THE CONCLUSION OF THE TRIAL

The trial will be concluded when the expected number of patients to be enrolled will be reached, or before if unexpectedly serious/frequent adverse events should be recorded in oneor in both the treatment groups. In case this only happens in the arm b) of the treatment group, this arm will be immediately stopped and the trial will continue witih the comparator group and the arm a) of the treatment group.

FUNDING

This work is partly supported by the Italian Ministry of Health (Ricerca corrente).

INSURANCE

Being a non-profit study pursuant to Ministerial Decree of 17.12.04, specific study insurance coverage is not required, in accordance with the Italian regulatory provisions contained in Legislative Decree n. 23 of 08.04.2020.

REGISTRATION

The trial will be registered with the Osservatorio Nazionale sulla sperimentazione clinica dei farmaci and with EudraCT. The trial will be also registered with ClinicalTrials.gov.

PUBLICATION POLICY

The results will be submitted for publication irrespective of the findings. Their interpretation will be independent of the sponsor and of the funding sources.

The publication policy will respect the general principles and recommendations for publication and dissemination of resulting data.

Upon completion of the study, the P.I. and co-P.I.s will prepare a manuscript that will be presented to the Coordinating Board (who shall represent all partners), who will discuss the issue and provide the lead author with opinions and recommendations as rapidly as possible.

The Coordinating Board will also analyze the request of ancillary publications and ensure that individual publication requests do not conflict with each other. Investigators will be free to publish individual results only after publication of the overall results.

All the site Investigators will be entitled to authorship, provided they have contributed an agreed minimum number of patients to the trial, and they will be listed in order of contribution (proportionally to the number of patients who concluded follow up). Centres contributing more than 20% of cases that qualify for analysis will be permitted a second author. The first cited author will be the Investigator who writes the article. The last author will be the one who proposed the study. The trial biostatistician(s) will also be included among the principal authors of the manuscript.

The remaining team members of all the sites will be cited in the acknowledgements as the COVER Study Group.

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Appendix 1

Pharmacokynetics study

Exploratory endpoint:

Association between plasma drug concentration and clinical endpoints

Plasma ivermectin concentration

The measurement of the drug concentrations in the plasma is included in the project, as ancillary study, to assess inter-individual differences in drug bioavailability which can underlie either no or poor efficacy (insufficient blood concentrations) or adverse events (too high blood concentrations). In fact, a high variability in absorption has been described (Guzzo et al., 2002).
In order to avoid too much distress to the patients, together with considerations on feasibility, blood samples will be collected in a subset of patients (≥ 10 per dose), at three time-points (just before, four and 72 hours after the fifth dose) chosen according to pharmacokinetic considerations (see below).

Ivermectin will be administered orally at doses of 600 or 1200 ug/kg, once daily for five days.
Following oral administration of ivermectin in humans, the peak plasma concentrations (tmax) are observed at approximately four hours after dosing, and the apparent half-life is approximately 18 hours (Guzzo et al., 2002). With this PK profile, repeated daily administrations are expected to result in some accumulation of the drug. For these reasons and for feasibility considerations, blood levels of ivermectin will be measured at the following three time points: just before, and 4 and 48 hours after, the fifth dose. These data will inform on the maximal drug levels and the drug accumulation following repeated doses, on the inter-individual variability and, possibly, on association between blood drug dose and clinical endpoints.

Ivermectin will be measured in plasma samples by HPLC-MS/MS at the laboratory of the IRCCS-Sacro Cuore Don Calabria hospital. The method of analysis for ivermectin concentrations in plasma has already been validated according to the EMA guidelines.

Blood samples are withdrawn at protocol-defined times in 2x7 mL EDTA tubes (lavender top). Tubes are gently inverted for 6-8 times. The sample collection date and time must be entered.
The tubes are centrifuged at 2000 g for 10 minutes at room temperature within 2 hours from withdrawal. The supernatant is splitted in 1.0 ml aliquots in 2.0 mL polypropylene tubes. Aliquots (analysis samples) are then stored at -20°C (or lower T) until analysis.

Stored analysis samples from the subject will be sent from participating clinical sites, in controlled temperature conditions, to the Laboratory of the IRCCS Sacro Cuore Don Calabria Hospital at the end of the study.

Further details on sample collection, numbering, processing and shipment will be provided in the Laboratory Manual provided to the sites.