MASTER CLINICAL STUDY PROTOCOL

An open-label, multicentre, randomised, adaptive platform trial of the safety and efficacy of several therapies, including antiviral therapies, versus control in mild / moderate cases of COVID-19

Protocol Number	01-COV
Short title	ANTICOV
Name of products	Information provided in Appendix
Drug Class	Antimalarials, antivirals
Phase	Phase III
Indication	Mild / Moderate infection with SARS-CoV-2
Sponsors	Bernhard-Nocht-Institut für Tropenmedizin – Ghana Centre Pasteur du Cameroun – Cameroon Centre Suisse de Recherches Scientifiques – Ivory Coast DNDI – Kenya, Democratic Republic of Congo, Sudan Epicentre – Niger, Uganda, Ifakara Health Institute – Equatorial Guinea, Inserm /ARNS – Burkina Faso, Guinea Institute of Tropical Medicine – Ethiopia ISGlobal – Mozambique
Study Protocol Version/Date	Version 5.0 dated 09 July 2020

STUDY SPONSOR

Sponsor name

- **Sponsor's Medical Expert**

  To be added

- **Clinical Project Manager**

  To be added

- **Serious Adverse Event (SAE) Reporting**

Sponsor contact details for SAE reporting to be added

Sponsor Signatures

I have read and approved this protocol. My signature, in conjunction with the signatures of the Investigators, confirms the agreement of the Sponsor and Investigator that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations, including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the ethical principles that have their origins in the Declaration of Helsinki and applicable privacy laws.

Signature of the Sponsor's Medically Responsible Person

The signatory agrees to the content of the final clinical study protocol as presented.

Name:	*To be added*	Role:	
Date:	.....	Signature:	.....

Signature of the Sponsor's Statistician

The signatory agrees to the content of the final clinical study protocol as presented.

Name:	Roger J. Lewis, MD, PhD	Role:	Statistician
Date:	.....	Signature:	.....

Signature of Principal Investigator

I have read this protocol and agree that it contains all information necessary to carry out the study. I will conduct the study as described herein.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of the study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.

I will use only the Informed Consent Form approved by the Sponsor or its representative and will fulfil all responsibilities for submitting pertinent information to the Ethics Committee (EC) responsible for the study if required by national law.

I agree that the Sponsor or its representatives shall have access to any source documents from which case report form information may have been generated.

I agree that the study will be conducted in accordance with all applicable laws and regulations, including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

Name:

Affiliation:

Date: ..... Signature: .....

Signed copies of this signature page are stored in the Sponsor's study file and in the Investigator Site File at the investigational centre.

In the protocol document, this page may remain unsigned.

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Synopsis

Title	An open-label, multicentre, randomised, adaptive platform trial of the safety and efficacy of several therapies, including antiviral therapies, versus control in mild / moderate cases of COVID-19
Short Title	ANTICOV
Study Number	01-COV
Clinical Study Phase	III
Primary Objective	The primary objective is to compare the efficacy of alternative treatment strategies versus control on the risk of progression to severe respiratory disease
Secondary Objectives	The secondary objectives are: • To compare the safety of each study arm to control, up to Day 21 of follow-up • To compare the rate of hospitalisations due to COVID-19 in each study arm versus control • To compare the time to hospitalisation due to COVID-19 in each study arm versus control • To compare the disease-free rate in each study arm versus control • To compare the death rate in each study arm versus control • To compare time to worsening of SpO2 $\leq$ 93in each study arm versus control • To compare the capacity to prevent severe progression between study arms • To identify risk factors for severe progression • To assess efficacy in sub-groups of patients e.g. with pre-existing conditions/co-morbidities, by age group, sex, BMI, timeframe between onset of symptoms and randomisation
Investigational Products (IPs)	Several marketed products including antiviral therapies
Dose	Doses used are within those for the registered indications of the IPs
Route of Administration	Oral
Duration of Treatment	Up to 14 days depending on the treatment arm
Study Duration	Patient participation in the master study will be 22 days.
Indication	Mild / Moderate COVID-19
Inclusion and Exclusion Criteria	*Inclusion Criteria* 1. Male or female patients,

	2. Adults ≥ 18 years of age at the time of screening. Children > 12 years of age may be included if recommended by the DSMB after the first analysis. 3. COVID-19 confirmed by molecular biology for SARS-Cov2 according to national guidelines, based on result within 24 hours prior to screening. 4. Viral syndrome with or without uncomplicated pneumonia, defined as blood oxygen saturation level (SpO2) ≥ 94%. 5. Corrected QT interval (QTc – Bazett and Fridericia) < 480 msec on ECG 6. Signed written consent from the patient or his/her representative. 7. Accepting and having the ability to be reached by telephone throughout the study. 8. Having designated a contact person who can be contacted in case of emergency. *Non-inclusion Criteria* 1. Abnormal physical examination findings: a) respiratory rate ≥ 25 per minute. b) blood pressure < 90/60 mmHg or > 160/100 mmHg. c) body weight < 45 kg for patients ≥ 18 years of age and age-adapted for children > 12 years of age if inclusion is recommended by the DSMB after the first analysis. d) recurrent diarrhoea or vomiting episodes (> 3 in the last 24 hours) or hypokalaemia (< 3.5 mmol/L). 2. Known glucose-6-phosphate dehydrogenase (G6PD) deficiency. 3. Feeling unwell for more than 7 days prior to screening. 4. Severe cardiopathy or history of arrhythmia, renal or liver insufficiency. 5. History of congenital or acquired long QT-interval, family history of long QT arrythmia, cardiac disease such as heart failure, myocardial infarction, family history of sudden cardiac death, sudden cardiac death, bradycardia < 50 bpm. 6. Past history of retinopathy, such as spots or dark strings floating in the field of vision (floaters), blurred or fluctuating vision, impaired colour vision, dark or empty areas in vision. 7. History of severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis 8. End-organ compromise requiring admission to a resuscitation or continuous care unit or short-term life-threatening comorbidity with life expectancy < 3 months.

	9. Pregnancy based on urine pregnancy test at screening or breast-feeding, unless recommended by the Data and Safety Monitoring Board after the first interim analysis. 10. Prior treatment with. lopinavir/ritonavir within 29 days prior to screening except if patients are receiving the same regimen as planned in this study. Patients randomised to lopinavir/ ritonavir will stop their current treatment and switch to the IP lopinavir / ritonavir. If randomised to other arms, patients will continue their current treatment with lopinavir/ritonavir. 11. Prior treatment with hydroxychloroquine within 29 days prior to screening or on-going at screening. 12. Use of concomitant medications that are contraindicated with hydroxychloroquine, known hypersensitivity to 4-aminoquinoline compounds (Amodiaquine, Chloroquine, Hydroxychloroquine) or quinine, concomitant treatment carrying risk of torsade de pointes, concomitant use of tamoxifen. 13. Use of concomitant medications that are contraindicated with lopinavir/ritonavir, known hypersensitivity, drugs with metabolism highly dependent on the isoform CYP3A with narrow therapeutic range, e.g. amiodarone, colchicine, simvastatin. 14. On-going treatment at screening with: • chronic systemic glucocorticosteroid > 40 mg daily; • immunosuppressive treatment; • azithromycin; • anti-arrhythmic agent. 15. For any new antiviral included in the study, prior treatment with the antiviral, presence of contraindication to its use or intake of concomitant medication proscribed with its use. 16. Unwilling or unable to comply with the requirements of the study protocol at any time during the study, e.g. no access to or not comfortable with use of a smartphone or with answering questions using a telephone, in the opinion of the Investigator. 17. Any other reason that makes it impossible to monitor the patient during the study. 18. Enrolled in other clinical trials with unregistered drugs or with registered drug which could interact with any of the study IPs or contra-indicated as concomitant treatment within the past 3 months prior screening
Study Design	Multicentre, randomised, open-label, adaptative master protocol / platform study

Data and Safety Monitoring Board	The DSMB will be composed of 5 members independent of the Investigators and Sponsors and having expertise in COVID-19 or respiratory viruses, antiviral therapies and viral shedding, emerging epidemics and adaptive platform trial design. The DSMB will review the study at pre-determined intervals and issue recommendations concerning ongoing study conduct in order to ensure that risks are minimised and benefits are maximised for patients.
Number of Patients	Between 2000 and 3000 patients will be included, although the trial may be extended with the investigation of additional IPs
Primary Endpoint	The primary endpoint is SpO2 $\leq$ 93% within 21 days after randomisation to treatment, including death for any reason
Secondary Endpoints	The secondary endpoints are: • Mean number and incidence rate of serious adverse events (SAEs) • Mean number and incidence rate of severe adverse events • Mean number of discontinuations or temporary suspensions of IP • Number of hospitalisations due to severe progression • Time to hospitalisation • Disease-free status: disease-free based on normalisation of pre-existing symptoms (based on mMRC scale, scale of Clinical Improvement and clinical symptoms) and SpO2 $\geq$ 94% at Day 21 and no hospitalisation for COVID-19 • Occurrence of death • Time to worsening of SpO2 $\leq$ 93% within 21 days • Failure rate for each study arm • Occurrence of SpO2 $\leq$ 93% or death or hospitalisation due to COVID-19 • Sub-group analysis of failure rate for each study arm
Sample Size Calculation	To verify the adequacy of the planned sample size, expressed per treatment arm,, an analogous Bayesian adaptive study was simulated using Fixed and Adaptive Clinical Trial Simulator software from Berry Consultants, LLC. The simulation was carried out for a study evaluating fours arms, namely one control arm and three active treatment arms to anticipate the addition of a treatment arm with a sample size of 625 patients per arm for a total of 2500 patients. The simulated trial design began with an initial "burn-in" period, during which patients were allocated in a fixed ratio of 4:2:2:2 among the four treatment arms, until 300 patients had been randomised. From that point on, a fixed 40% of all patients were randomised to the control arm, while the remaining patients were adaptively randomised among the active treatment arms proportionally to the probability that each arm was the best performing arm. Interim analyses were conducted after every 300 patients were enrolled and,

	at each interim analysis, study design included early stopping rules for futility or success, or the randomisation ratios could be adjusted for the next 300 patients. The criterion for stopping early and declaring early for futility was that no IP had a probability > 0.1 of decreasing the rate of severe progression by at least 2.5% absolute difference. Similarly, the criterion for stopping early and declaring, and an IP superior to control if there was > 0.95 probability that the most effective IP reduced the proportion of patients with severe progression by 5% or greater absolute difference (super-superiority). If the study continued until the maximum sample size of 2500 patients (a per-arm sample size of 625), then one or more IPs were declared effective if there was a probability of at least 0.992 that the IP is superior to control. Using this design and specific criteria for demonstrating efficacy, simulations demonstrated control of the type I error rate at 0.024 and the trial design achieved a power of 0.85 to demonstrate a decrease in the rate of progression to severe disease in one of the active arms from the control rate off 10% to 5%. Under the null hypothesis of no treatment effect with any of the three active IPs, the study will stop early for futility 67.0% of the time, limiting the exposure of patients to ineffective treatments. Under an alternative hypothesis in which a single IP is extremely effective, reducing the proportion of patients who deteriorate from 10% to 2.5%, the study will identify that effective therapy early, before the full sample size is enrolled, 79.8% of the time. In addition, the simulations show that if one of the active IP arms is beneficial then patients will be selectively assigned the effective therapy and, if any of the active arms is harmful, the study will effectively randomise patients away from the harmful arm(s), to minimise the risk to patients. The simulation of the analogous design demonstrated that a sample size of 625 patients will yield a power of approximately 85% to detect a decrease in the rate of severe progression at 21 days from 10% to 5%. The simulation assumed a drop-out/lost to follow-up rate of 5%. The final analysis model will include an adjustment for time of enrollment to account for secular changes over time in the effectiveness of the standard of care (SOC), either because the approach to SOC changes or the affected patient population changes over time. The defined constant allocation to the control therapy over time ensures that the acquired data will be sufficient to estimate and adjust for changes in outcomes over time. Thus, the proposed perpetual, platform study will have suitable power and control of the type I error risk for the evaluation of pharmacological interventions for the prevention of severe progression of ambulatory patients with COVID-19 in Africa.
Statistical Analyses	The following populations will be used in the statistical analyses.

	• Intent-to-treat (ITT): all patients who received at least one dose of IP, including • Per protocol (PP): all patients in the ITT population who were free from major protocol violations that could lead to bias • Safety: all patients who received at least one intake of IP *Efficacy Analyses* Interim analyses and the primary analysis of a treatment arm when it is declared either effective, ineffective or is dropped for futility will be based on the ITT population. The primary analysis will be a Bayesian comparison of the proportions experiencing progression to severe disease with the treatment versus control, with adjustments for site and temporal effects. Prior to the first interim analysis, a limited number of additional covariates may be specified for inclusion in the primary analysis, as predictors of outcome in ambulatory patients with COVID-19 become better understood. Traditional frequentist statistical methods will be used to summarise and analyse secondary endpoints, once a treatment is declared effective, ineffective, or is removed from the study due to futility in further evaluation. Both continuous and dichotomous outcomes will be analysed with terms used to account for country of enrollment, either by including country as a fixed effect in regression models or using generalised estimating equations to account for clustering within country. A logit link function will be used for dichotomous outcomes and a constant link function will be used for continuous outcomes. Generalised estimating equations models will include site effects and time as prespecified covariates. As above, a limited set of additional covariates may be prespecified, prior to the first interim analysis, based on emerging information regarding predictors of outcomes in patients with COVID-19. As the analysis of the secondary outcomes is descriptive, no correction will be made for multiple comparisons and a nominal one-tailed alpha of 0.025 will be used for comparisons between the active treatment arms and control; a two-tailed alpha of 0.05 will be used for comparisons between pairs of active IP arms. *Safety Analysis* AEs will be analysed both by ITT and by treatment received, in the Safety Population. Comparisons of rates of AEs will be presented descriptively. Descriptive statistics for each scheduled time-point and for changes from baseline to selected time-points will be provided for vital signs and optional assessments. For height, weight and BMI, descriptive statistics will be calculated by sequence and overall, while for blood pressure, heart rate and temperature descriptive statistics will be calculated by treatment and occurrence

List of Abbreviations

AE	adverse event
BP	blood pressure
COVID-19	coronavirus disease 2019
CT	computed tomography (scan)
CYP3A	cytochrome P450 3A4
DRC	Democratic Republic of the Congo
DSMB	Data and Safety Monitoring Board
EC	Ethic Committee
ECG	electrocardiogram
eCRF	electronic case report form
FACTS	fixed and adaptive clinical trial simulator
G6PD	glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
GEE	generalised estimating equations
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IDDO	Infectious Diseases Data Observatory
IP	investigational product
ITT	intent-to-treat (population)
MERS-CoV	Middle East respiratory syndrome-related coronavirus
MedDRA	Medical Dictionary for Regulatory Activities
MRC	Medical Research Council
PAR	paracetamol
PCR	polymerase chain reaction
PP	per protocol
QTc	corrected QT interval
RAR	response-adaptive randomisation
SAE	serious adverse event
SARS-CoV-2	severe acquired respiratory syndrome - coronavirus 2
SpO2	blood oxygen saturation level
SOC	system-organ class
SUSAR	suspected unexpected serious adverse reaction
WHO	World Health Organisation

1 Introduction

1.1 Background Information

In December 2019, a new human coronavirus with respiratory tropism, SARS-CoV-2, emerged in China and rapidly spread to other parts of the world.[1,2] Coronavirus disease 2019 (COVID-19), the disease caused by the virus, has a highly polymorphic clinical presentation, ranging from isolated upper airway involvement to acute respiratory distress syndrome.[3,4] The clinical picture may be initially severe, or progress in two stages, with worsening 7 to 10 days after the first clinical signs, possibly linked to a cytokine storm as part of the immune response and accompanied by a high risk of thrombosis.[5–10] In high or upper-middle income countries, the overall case-fatality rate of COVID-19 has been between 3 and 4%, with more severe forms correlated to increasing age, male sex, hypertension, diabetes and obesity.[11] Currently, management of COVID-19 is essentially symptomatic, as no antiviral treatment has, to date, demonstrated a clinical benefit in this setting.[12]

At present, it seems that approximately 80% of patients infected with SARS-CoV-2 remain asymptomatic while 20% develop mild to severe symptoms. Once patients progress towards severe pneumonia, i.e. in approximately 10% of cases, sophisticated supportive treatment is required including oxygen, ventilation, vasopressors and antibacterial treatment. Significant healthcare resources are therefore needed to manage and care for these patients. To date, no treatment has shown confirmed efficacy in treating severe cases. It is therefore crucial to avoid, as far as possible, progression to severe disease.

From a public health perspective, the primary objective of disease management is therefore to limit the number of COVID-19-related hospitalisations for oxygen therapy and/or intensive care to a number that is practicable, i.e. to treat patients before they become critically ill and require intensive care especially in low and middle income countries. It is also likely that early treatment in the most at-risk ones will also be the best way to reduce mortality.

Another issue to consider is the duration of shedding of the virus as this has been found to occur in stools and via respiratory aspirates and droplets. It is likely that the potential treatment will reduce the duration of virus shedding, which could have additional benefits in preventing transmission.

1.2 Study Rationale

1.2.1 Rationale for Study Design

This is a multicentre, randomised, open-label, adaptive clinical study on the safety and efficacy of treatments for COVID-19 in patients treated on an out-patient basis.

As there is no validated animal model for COVID-19, the efficacy of any potential treatment remains speculative beyond what is known about their pharmacokinetic and in-vitro data. Several repurposed drugs are currently being tested in severe cases or as prophylaxis, and the results may become available by the time the present study is initiated. At the same time, a number of other drug candidates are being evaluated for in-vitro efficacy or in small proof-of-concept studies.[13] In view of the rapidly evolving landscape in Africa, it was decided to select an adaptive design for the study in order to allow for the flexibility of adding or dropping arms or adjusting the randomisation ratio based on the data as it becomes available.

Additionally, given that the control arm in the study may not be acceptable in some countries, it was decided to adopt a master platform-based approach to be allow for integration of data

from all sites in the interim analyses, irrespective of their ability to have randomised patients in all treatment arms..

In the context of COVID-19, and at the time of protocol development, patients may spontaneously present to hospital for diagnosis in various clinical contexts (see Figure 1):

- asymptomatic, but perceived as at risk;
- with viral syndrome without uncomplicated pneumonia, i.e. presence of fatigue, irregular fever, chills, muscle pain, sore throat, rhinitis, etc.;
- with uncomplicated pneumonia, i.e. SpO2 $\geq$ 94%, crackles on auscultation, irregular breathing difficulties but respiratory rate < 25/min;
- moderate to severe pneumonia with SpO2 $\leq$ 93%, with our without mental confusion, with our without respiratory rate $\geq$ 25/min, with our without BP < 90/60mm Hg.

All patients will be tested for the presence of SARS-CoV-2 using the available molecular assay.

Different strategies will apply among the afore-mentioned four categories of patients who test positive for SARS-CoV-2:

- asymptomatic patients will not be randomised but will be monitored by the medical team for disease progression based on national guidelines;
- patients with viral syndrome, without uncomplicated pneumonia will be randomised in the study;
- patients with uncomplicated pneumonia will be randomised in the study; and
- patients with moderate to severe pneumonia will be hospitalised and potentially referred to other studies such as SOLIDARITY*.

Figure 1. Flowchart for Patient Recruitment

Based on predictions, it is assumed that patients, both children and adults with mild / moderate forms of COVID-19 will be sent back home. Patients will be provided with national recommendation for home care or WHO recommendations is national ones are not available. However, in some countries, all patients, irrespective of severity, maybe be confined in a

* SOLIDARITY is an international clinical trial to help find an effective treatment for COVID-19, launched by the WHO and partners.

COVID-19-specific hospital area. This will not, however, be considered to be "hospitalisation for management of COVID-19" in the context of the study.

In summary the **case definition** will be as follow: RT-PCR SARS-CoV2 positive and symptomatic patients presenting with either a mild / moderate unspecific viral disease or an uncomplicated pneumonia as defined is the inclusion / exclusion criteria, not requiring oxygen and antibiotics..

1.2.2 Rationale for IP Selection

The IPs selected for the study are all affordable, commercially-available medicinal products that are registered for use in other indications in the countries where the study is being conducted. The safety and efficacy profiles of the IPs are well known, and they have been selected for use in the study based on their known safety and efficacy profiles (see Appendix 1 for information on IPs).

To date, there are a number of ongoing clinical trials that are either evaluating other other potential antiviral for mild COVID or testing HCQ and/or lopinavir/ritonavir in either mild or severe COVID. Recently SOLIDARITY, DISCOVERY and RECOVERY studies'results have shown that HCQ or lopinavir/ritonavir are not suitable options for hospitalised patients who present with a more advanced and severe phase of the disease, requiring more an immunosuppressive effect rather than an antiviral one. WHO therefore decided to stop enrollment with those 2 compounds for hospitalised patients whilts stating that "This decision applies only to the conduct of the Solidarity trial in hospitalized patients and does not affect the possible evaluation in other studies of hydroxychloroquine or lopinavir/ritonavir in non-hospitalized patients or as pre- or post-exposure prophylaxis for COVID-19." (https://www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19)

The sponsors will continuously monitor emerging results from ongoing trials. Any strong evidence will be assessed by the DSMB who may provide recommendation about the study arms, especially in the case of evidence of futility coming from other well designed Randomized Clinical Trials.

In addition, the sponsors will include new treatment arms selected from other repurposed drugs, either as monotherapy or combination. Selection will be supported by evidence or SARS-CoV-2 antiviral efficacy from in vitro analyses and understanding of the PK/PD or directly from PoC studies, evidence of good safety, and perpective of affordable access. All proposed new IPs will be submitted for approval by ECs, and National Regulatory Authorities prior to implementation, together with potential adjustment to existing inclusion/exclusion criteria.

1.2.3 Rationale for Selection of Doses and Route of Administration

The IPs will be administered at the doses defined in Appendix 1, which are within the recommended doses for the registered indications of the products. The IPs will be administered by the oral route (see Appendix 1 for additional information on IPs).

1.2.4 Benefit-to-risk Assessment

There is currently no specific treatment appropriate for the outpatient setting with demonstrated efficacy against COVID-19. The safety profiles of the IPs are well known in their approved indications. Information regarding the risks related to the IPs is provided in Appendix 1.

2 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the efficacy of alternative treatment strategies versus control on the risk of progression to severe respiratory disease	• SpO2 ≤ 93% on repeated measurement within 21 days after randomisation of treatment, which will be considered as failure. Death for any reasons occurring within 21 days after randomisation of treatment will be considered as failure.
Secondary	
• To compare the safety of each study arm to control, up to Day 21 of follow-up	• Mean number and incidence rate of serious adverse events (SAEs) • Mean number and incidence rate of severe adverse events • Mean number of discontinuations or temporary suspensions of IP
• To compare the rate of hospitalisations due to COVID-19 in each study arm versus control	• Number of hospitalisations due to severe progression
• To compare the time to hospitalisation due to COVID-19 in each study arm versus control	• Time to hospitalisation
• To compare the disease-free rate in each study arm versus control	• Disease-free status: disease-free based on normalisation of pre-existing symptoms (based on mMRC scale, scale of Clinical progression and clinical symptoms) and SpO2 ≥ 94 at Day 21 and no hospitalisation for COVID-19
• To compare the death rate in each study arm versus control	• Occurrence of death
• To compare time to worsening of SpO2 ≤ 93 in each study arm versus control	• Time to worsening of SpO2 ≤ 93 within 21 days
• To compare the capacity to prevent severe progression between study arms	• Failure rate for each study arm (see Primary Endpoint)
• To identify risk factors for severe progression	• Occurrence of SpO2 < 93 or death or hospitalisation due to COVID-19
• To assess efficacy in sub-groups of patients e.g. with pre-existing conditions/co-morbidities, by age group, sex, BMI, timeframe between onset of symptoms and randomisation	• Sub-group analysis of failure rate for each study arm

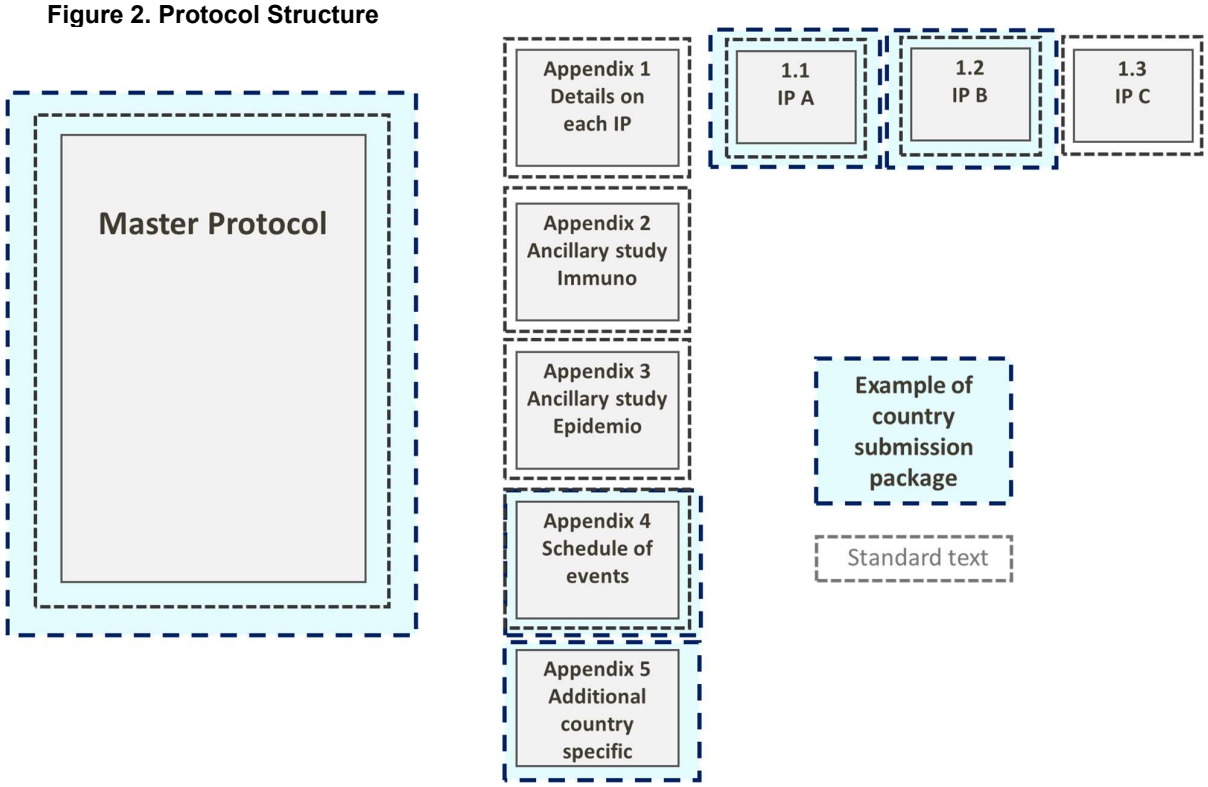
3 Study Design

3.1 Description of Study Design

This is a large, multicentre, multiple country, randomised, open-label, adaptive, platform clinical study aiming to determine the efficacy and safety of various treatment regimens for prevention of the need for hospitalisation for specialised care due to severe progression of COVID-19.

The study is designed as a master protocol/platform study with the ability to incorporate the adding or dropping of treatment arms and that will include similar inclusion and non-inclusion criteria, the same primary and secondary endpoints, common data entry procedures, a shared database and a single statistical methodology for analysis of the primary endpoint (see Figure 2). Treatment arms may be added in some countries and not in others.

Figure 2. Protocol Structure



The flexible platform design will allow the treatment modalities to be adapted as new data emerge during the study. Based on regular interim analyses, recommendations may be made by the independent Data and Safety Monitoring Board (see Section 8) to stop a treatment arm for futility or success. New treatment arms may be added if promising new drug candidates or treatment combinations are identified during the study.

The study will begin with unbalanced randomisation of participants 3:2:2 to a control arm, paracetamol alone, and to two test arms (see Study Flowchart in Figure 3). If paracetamol cannot be administered as a control arm in some countries, patients will only be randomised (with equal probability) to test arms. Randomisation may then be adapted after the first interim analysis, i.e. once at least 100 patients have been randomised in each study arm, or after the

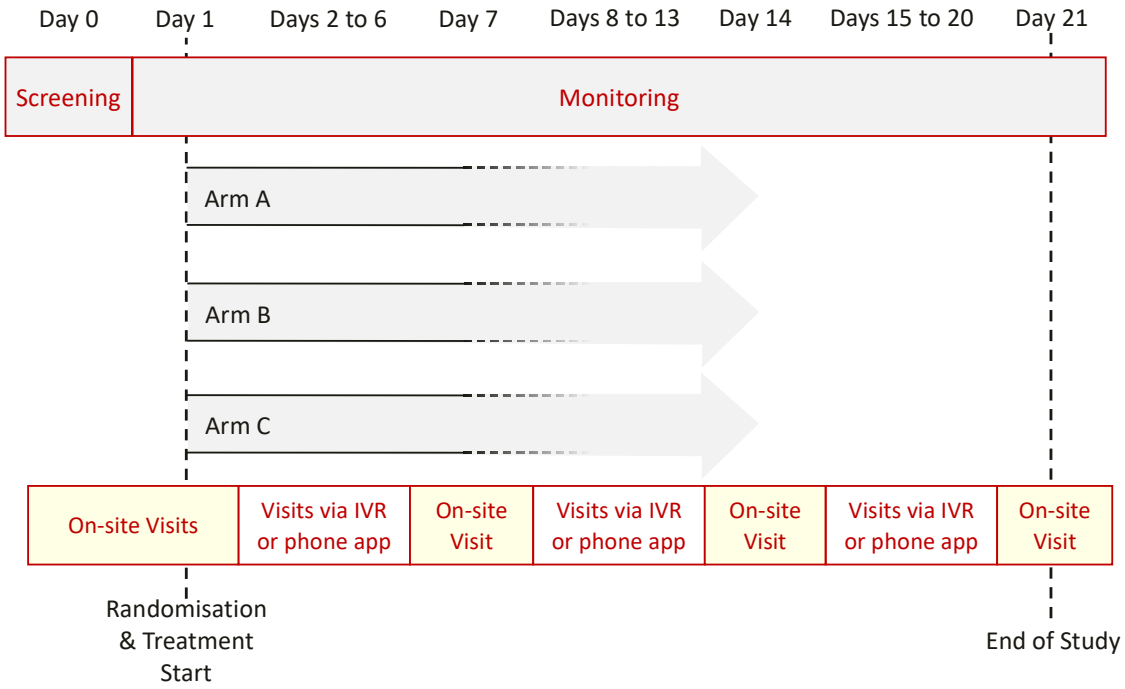
subsequent interim analyses (see Section 7.1). The IPs on the various treatment arms, the doses and treatment durations are presented in Appendix 1. Patient follow-up visits will be conducted as on-site visits alternating with daily questionaires using an electronical Patient Reporting Outcome application or patient will be called by the sites.

At some sites, paracetamol will not be included as a treatment option and a fourth (active) arm will be included. The initial randomization among these three arms will be in the ratio 1:1:1 (see details below).

It is planned to include between 2000 and 3000 patients in the master protocol, however, the sample size may be increased with the addition of additional IPs, with a maximum sample size.

For details on the arm adaptation, see Section 7 Statistical Methods.

Figure 3. Study Flowchart



3.2 Study Duration

First patient first visit is planned Q3 2020.

The duration of recruitment should not exceed 6 months based on the current epidemiology, however it is predicted to increase in the coming weeks.

The duration of participation for each individual patients will be 22 days.

Ancillary studies may be conducted in some countries, which may extend patient follow-up. The studies are described in Appendix 2 and Appendix 3.

4 Study Population

4.1 Inclusion Criteria

To be eligible for the study, patients must satisfy all the following inclusion criteria.

1. Male or female patients,
2. Adults ≥ 18 years of age at the time of screening. Children > 12 years of age may be included if recommended by the DSMB after the first analysis.
3. COVID-19 confirmed by molecular biology for SARS-Cov2 according to national guidelines, based on result within 24 hours prior to screening.
4. Viral syndrome with or without uncomplicated pneumonia, defined as blood oxygen saturation level (SpO2) ≥ 94%.
5. Corrected QT interval (QTc – Bazett and Fridericia) < 480 msec on ECG.
6. Signed written consent from the patient or his/her representative.
7. Accepting and having the ability to be reached by telephone throughout the study.
8. Having designated a contact person who can be contacted in case of emergency.

4.2 Exclusion Criteria

To be eligible for the study, patients must not satisfy any of the following non-inclusion criteria.

1. Abnormal physical examination findings:
   - respiratory rate ≥ 25 per minute;
   - blood pressure < 90/60 mmHg or > 160/100 mmHg;
   - body weight < 45 kg for patients ≥ 18 years of age and age-adapted for children > 12 years of age if inclusion is recommended by the DSMB after the first analysis;
   - recurrent diarrhoea or vomiting episodes (> 3 in the last 24 hours) or hypokalaemia (< 3.5 mmol/L).
2. Known glucose-6-phosphate dehydrogenase (G6PD) deficiency.
3. Feeling unwell for more than 7 days prior to screening.
4. Severe cardiopathy or history of arrhythmia, renal or liver insufficiency.
5. History of congenital or acquired long QT-interval, family history of long QT arrythmia, cardiac disease such as heart failure, myocardial infarction, family history of sudden cardiac death, sudden cardiac death, bradycardia < 50 bpm.
6. Past history of retinopathy, such as spots or dark strings floating in the field of vision (floaters), blurred or fluctuating vision, impaired colour vision, dark or empty areas in vision.
7. History of severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis.
8. End-organ compromise requiring admission to a resuscitation or continuous care unit or short-term life-threatening comorbidity with life expectancy < 3 months.
9. Pregnancy based on urine pregnancy test at screening or breast-feeding, unless recommended by the Data and Safety Monitoring Board after the first interim analysis.

10. Prior treatment with. lopinavir/ritonavir within 29 days prior to screening except if patients are receiving the same regimen as planned in this study. Patients randomised to lopinavir/ritonavir will stop their current treatment and switch to the IP lopinavir/ ritonavir. If randomised to other arms, patients will continue their current treatment with lopinavir/ritonavir.
11. Prior treatment with hydroxychloroquine within 29 days prior to screening or on-going at screening.
12. Use of concomitant medications that are contraindicated with hydroxychloroquine, known hypersensitivity to 4-aminoquinoline compounds (Amodiaquine, Chloroquine, Hydroxychloroquine) or quinine, concomitant treatment carrying risk of torsade de pointes, concomitant use of tamoxifen (Appendix 1).
13. Use of concomitant medications that are contraindicated with lopinavir/ritonavir, known hypersensitivity, drugs with metabolism highly dependent on the isoform CYP3A with narrow therapeutic range e.g. amiodarone, colchicine, simvastatin (Appendix 1).
14. On-going treatment at screening with:
    - systemic glucocorticosteroid > 40 mg daily;
    - immunosuppressive treatment;
    - azithromycin;
    - anti-arrhythmic agent.
15. For any new antiviral included in the study, prior treatment with the antiviral, presence of contraindication to its use or intake of concomitant medication proscribed with its use.
16. Unwilling or unable to comply with the requirements of the study protocol at any time during the study, e.g. no access to or not comfortable with use of a smartphone or with answering questions using a telephone, in the opinion of the Investigator.
17. Any other reason that makes it impossible to monitor the patient during the study.
18. Enrolled in other clinical trials with unregistered drugs or with registered drug which could interact with any of the study IPs or contra-indicated as concomitant treatment within the past 3 months prior screening

4.3 Patient Identification

Patients will be identified by an identification number during the screening period, i.e. after receiving information on the study and signing the informed consent. The patient identification number will be used to identify the patient throughout his/her participation in the study and will be composed by concatenation of the study number, the country code in two digits, the site code in two characters (ISO 3166 – 1 alpha 2) and the patient code in four digits.

4.4 Discontinuation/Withdrawal Criteria

4.4.1 Screening Failure

A patient who discontinues study participation prematurely for any reason after signing the informed consent form and undertaking the screening assessments, but before randomisation, is regarded as a “screening failure”. Information on screening failures will be collected and retained in accordance with Section 9.4.

Patients regarded as screening failures are permitted to re-enter the screening process at a later time-point, under the following circumstances:

- The inclusion and/or non-inclusion criteria preventing the patient's initial attempt to participate have been changed via protocol amendment;

Patients who re-enter the screening process under the circumstances listed above must sign a new informed consent form, will receive a new patient identification number and, if included, a new randomisation number.

4.4.2 Discontinuation of IP

The IP will be discontinued in the following situations:

- If the patient requests discontinuation of treatment with IP
- If the patient is admitted to hospital due to COVID-19: symptomatic rescue treatment should be made available.
- If the patient requires treatment with a prohibited concomitant medication (see Section 5.7.2)
- If the patient develops contraindications to any of the IPs
- If clinical reasons arise that are considered life-threatening by the Investigator.

The reason for IP discontinuation will be recorded in the electronic case report form (eCRF). Patients who discontinue the IP should continue participating in the study, off the IP, with continued assessments as per the Schedule of Events, including an end-of-study visit (see Schedule of Events, Appendix 4).

4.4.3 Withdrawal from Study

A participant may withdraw from the study at any time at his/her own request or must be withdrawn at any time for the following reasons:

- At the request of the Investigator if s/he thinks that study participation is no longer in the best interest of the patient
- At the request of the Investigator if s/he thinks that the patient is at significant risk of failing to comply with the provisions of the protocol so as to cause harm to her/himself or seriously interfere with the validity of the study results
- At the request of the ethics committee or regulatory authorities in the exercise of their duties, or of the Sponsor.
- At the request of the Investigator if the patients is hospitalised due to COVID-19: symptomatic rescue treatment should be made available.
- At the request of the Investigator if the patient requires treatment with a prohibited concomitant medication (see Section 5.7.2).

If a patient wishes to withdraw from the study, every effort should be made to ensure that s/he undergoes an early withdrawal study visit as soon as possible and a final follow-up visit at Day 21 for patient status if possible. See the Schedule of Events (Appendix 4) for assessments to be performed in the event of early withdrawal from study.

If a patient withdraws his/her consent for future collection of information, the Sponsor may retain and continue to use any data collected before consent was withdrawn.

If a patient withdraws from the study, s/he may request destruction of any samples collected and not tested, and this must be documented in the Investigator Site File.

4.4.4 Lost to Follow-up

A patient will be considered lost to follow-up if s/he can no longer be contacted by the study personnel.

Before the patient can be considered as lost to follow-up, the study personnel must make every effort to re-establish contact with the patient or relatives as soon as possible to advise him/her of the importance of continuing in the study and to ascertain whether or not s/he wishes to and/or should continue in the study. During the patient's planned study period, patients will be contacted by phone or visited at home if either not completing the questionnaire or not attending a planned visit, at least 3 times on different days. These contact attempts will be documented in a note in the Investigator Site File. Information on patient status, i.e. alive or dead, hospitalised, should be collected.

If all attempts to re-establish contact with the patient are unsuccessful, s/he will be considered to have withdrawn from the study and the primary reason for loss to follow-up will be recorded in the eCRF.

5 Study Treatments

5.1 Investigational Products

See Appendix 1,for information on the Investigational Products (IP).

5.2 IP Labelling

All IPs will be prepared and labelled in accordance with local regulations and laws in the countries where the study is conducted.

The labelling of the IP will include the following information:

- Name of Sponsor
- Drug name, dosage form, dosage strength and quantity
- Route of administration
- Study protocol number and/or code
- Instructions for use
- The statement "For clinical trial use only"
- Storage conditions
- Expiry date

The labelling will be provided in English, French, Portuguese or other languages depending on the country.

5.3 IP Supply and Storage

At the investigational centre the IPs will be stored in a locked cabinet, inaccessible to unauthorised personnel.

The supplies of the IPs for the study must not be used for purposes other than the present protocol. The Investigator and the study personnel staff may not, under any circumstances,

provide other healthcare workers or services with the IPs, or allow the IPs to be used other than as described in this protocol without prior written approval from the Sponsor.

A complete record of batch numbers and expiry dates of all IPs as well as the labels will be maintained in the Sponsor's study file. After completion of each IP arms, remaining products will be donated according to local law and requirement, to the site for use in the registered indication.

5.4 IP Assignment

Patients will be randomly assigned to one of the treatment arms via a centralised on-line system in order to accommodate the adaptive design of the study.

See Appendix 1 for additional information on IP assignment.

5.5 IP Logistics and Accountability

All IPs will be stored at the investigational centres in accordance with GCP and GMP requirements and the instructions given by the clinical supplies department of the Sponsor (or its affiliate/contract research organisation [CRO]) and will be inaccessible to unauthorised personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the Sponsor's study file; the centre-specific elements of this information will be available in the Investigator Site File. On the day of receipt, the responsible study personnel will confirm receipt of the IPs per the instructions supplied. The personnel will use the IPs only within the framework of this clinical study and in accordance with this protocol.

The Investigator or designee must maintain appropriate documentation on IP accountability, including the following information:

- IPs delivered to the centre
- IP inventory at the centre
- IP use by each patient
- IP returned to the Investigator of designee

The documentation should include dates, quantities, batch and/or serial numbers, and the code numbers (if any) assigned to the IP and study patients. On completion of the study, the Investigator or designee will oversee shipment of any remaining IP drug back to the Sponsor or Sponsor's designee according to the Sponsor's standard operating procedures. The documentation of IP accountability will be archived by the centre.

5.6 Treatment Compliance

For patients who are quarantined in hospitals or governmental facilities, the IP administered by study personnel, who will ensure and record compliance with treatment. For patients quarantined as out-patients, treatment compliance will be assessed at the time-points indicated in the Schedule of Events (Appendix 4) by questioning the patients as to whether they have been taking treatment.

5.7 Non-study Treatment

5.7.1 Prior and Concomitant Treatment

Patients will be allowed to continue their concomitant treatment or therapy during the study. Patients who are receiving medication or therapy that cannot be used in combination with the IPs, will not be included in the study (see Section 4.2 and Appendix 1).

Patients will be instructed to report any concomitant treatment, i.e. medication or medical procedures, to the Investigator. All concomitant treatment will be recorded in the source documents and eCRF.

5.7.2 Prohibited Treatment

Prohibited treatments, i.e. products contraindicated with the IPs are listed in Appendix 1.

6 Study Procedures and Assessments

6.1 Conduct of Study Procedures and Assessments

The current COVID-19 pandemic has placed a significant burden on the healthcare system. For this reason, specimen and data collection in the study will be conducted in such a way as to minimise the potential impact on non COVID-19 participants within the healthcare system.

Patients participating on an out-patient basis will be instructed to seek clinical care if they develop any signs or symptoms of severe progression requiring medical intervention and to inform the physician that they are taking part in the study.

6.2 Schedule of Procedures and Assessments

Study visits on Day 0, Day 1, Day 7, Day 14 and Day 21 will be conducted at the investigational centre. On Days 2 to 6, Days 8 to 13 and Days 15 to 20 data will be collected from the patients using a telephone application or patients will be called by the site.

Unless otherwise specified, the procedures and assessments listed in the following sections will be performed by or under the supervision of the Investigator.

6.2.1 Day 0 - Baseline Assessments

The following procedures and data collection will be performed at Day 0 or Screening.

- Provision of patient information and signature of Informed Consent Form
- Check Inclusion and Non-inclusion Criteria, including result of COVID-19 screening test
- Collection of demographic data:
  - sex
  - race
  - year of birth or age at consent
  - Pregnancy test (urine)
  - pregnancy status (and assessment of gestational weeks if the DSMB allows inclusion of pregnant women after first interim analysis)
- Collection of medical history, including contact with a person with confirmed or

suspected COVID-19 (if known), as well as co-morbidities with focus on:
- asthma or cystic fibrosis or any chronic respiratory disease likely to decompensate due to viral infection;
- cardiovascular history: high blood pressure, history of stroke or coronary artery disease, heart surgery;
- Diabetes or complications secondary to diabetes, e.g. micro- or macro-angiopathy;
- Immunodepression, including:
  - Medication, i.e. cancer chemotherapy, immunosuppressive treatment, i.e. biotherapy and/or corticosteroid therapy at immunosuppressive doses;
  - Uncontrolled HIV infection or known CD4 < 200/mm^3;
  - Solid organ or haematopoietic stem cell transplantation;
  - Metastatic cancer

- Collection of height and weight (body-mass index automatically calculated)
- Blood oxygen saturation level (SpO2) (see Section 6.3.1.1)
- ECG (see Section 6.3.3.3)
- Blood sample collection for laboratory tests (optional unless if blood sample will be collected at follow-up visits) - see Section 6.3.2.2)
- Chest x-ray may be performed if pneumonia is suspected (optional unless if chest X-ray will be performed at follow-up visits - see Section 6.3.3.4)
- CT-scan (optional unless if CT-scan will be performed at follow-up visits - see Section 6.3.3.5)
- Collection of vital signs (see Section 6.3.3.2)
- Collection of symptoms compatible with COVID-19 (see Section 6.3.1.4)
- Collection of adverse events
- Collection of concomitant treatments

6.2.2 Day 1 (can be perfomed same day as Day 0)

The following procedures and data collection will be performed on Day 1. All assessments will have to be performed before randomization to confirm eligibility.

- Physical examination (see Section 6.3.3.1)
- Collection of vital signs (see Section 6.3.2.1.7)
- Blood oxygen saturation level (SpO2) (see Section 6.3.1.1)
- mMRC Dyspnoea Scale (see Section 6.3.1.2)
- WHO Clinical progression scale (see Section **Error! Reference source not found.**)
- Collection of concomitant treatments
- Collection of adverse events
- Randomisation
- Start of IP administration

6.2.3 Days 2 to 6, Days 8 to 13, Days 15 to 20

The following data items will be collected from patients by telephone application or phone or direct interview on Days 2 to 6, Days 8 to 13 and Days 15 to 20.

- Warning signs for severe progression (see Section 6.3.1.5)

6.2.4 Days 7 and 14

The following procedures and data collection will be performed:

- Physical examination (see Section 6.3.3.1)
- Hospitalisation due to aggravation of COVID-19
- Collection of vital signs (see Section 6.3.3.2)
- Collection of symptoms compatible with COVID-19 (see Section 6.3.1.4)
- Blood oxygen saturation level (SpO2) (see Section 6.3.1.1)
- mMRC Dyspnoea Scale (see Section 6.3.1.2)
- WHO Clinical progression scale (see Section **Error! Reference source not found.**)
- Blood sample collection for laboratory tests (optional - see Section 6.3.2.2)
- Chest x-ray (optional - see Section 6.3.3.4)
- CT-scan (optional - see Section 6.3.3.5)
- ECG (optional - see Section 6.3.3.3)
- Check treatment compliance
- Collection of adverse events
- Collection of concomitant treatments

6.2.5 Day 21 - End of Study or Early Withdrawal

The following procedures and data collection will be performed on Day 21 and are to be performed in patients who discontinue the IP or withdraw from the study prematurely:

- Physical examination
- Hospitalisation due to aggravation of COVID-19
- Collection of vital signs (see Section 6.3.3.2)
- Blood oxygen saturation level (SpO2) (see Section 6.3.1.1)
- Collection of symptoms compatible with COVID-19 (see Section 6.3.1.4)
- mMRC Dyspnoea Scale (see Section 6.3.1.2)
- WHO Clinical progression scale (see Section **Error! Reference source not found.**)
- Blood sample collection for laboratory tests (optional - see Section 6.3.2.2)
- Chest x-ray (optional - see Section 6.3.3.4)
- CT-scan (optional - see Section 6.3.3.5)
- ECG (optional - see Section 6.3.3.3)
- Check treatment compliance
- Collection of adverse events
- Collection of concomitant treatments/procedures

For patients who discontinue the IP or withdraw early, in addition to the assessments above, a visit is to be performed on-site or by telephone on Day 21 to check patient status, i.e. hospitalised, not hospitalised, death.

6.3 Description of Study Assessments

6.3.1 Efficacy Assessments

6.3.1.1 Blood Oxygen Saturation Level (SpO2)

Resting blood oxygen saturation level (SpO2) will be collected using a finger pulse oximeter

SpO2 will be measured twice at 5 minutes intervals. If one value is above and the other is below the threshold of 94%, a third measurement will be performed to categorise the patient at inclusion and for failure. All values will be recorded in the eCRF.

6.3.1.2 Modified MRC Dyspnoea Scale

The modified Medical Research Council (mMRC) Dyspnoea Scale will be used to assess respiratory status. [adapted from 14] The grading scale is shown in Table 1.

Table 1. Modified MRC Dyspnoea Scale

Grade	Dyspnoea Symptoms
Grade 0	I only get breathless on strenuous exercise
Grade 1	I get short of breath when hurrying on level ground or walking up a slight hill
Grade 2	On level ground, I walk slower than other people the same age because of breathlessness or I have to stop for breath when walking at my own pace
Grade 3	I stop for breath after walking 100 m or after a few minutes on level ground
Grade 4	I am too breathless to leave the house or I am breathless when dressing

6.3.1.3 WHO Clinical progression scale

The WHO Clinical progression scale will be used to assess improvement in the patients' clinical status. The grading scale is shown in Table 2.

Table 2. WHO Clinical progression scale

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation pO_2/FIO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

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ECMO: extracorporeal membrane oxygenation, FiO_2: Fraction of inspired oxygen, NIV: non-invasive ventilation, PO2 : partial pressure of oxygen, SpO2: oxygen saturation, *if hospitalized for isolation only, record status as for ambulatory patient

6.3.1.4 Questionnaire on Symptoms of COVID-19

The presence of symptoms of COVID-19 will be assessed using a set of structured questions, as shown in Table 3.

Table 3. Questionnaire on Symptoms Compatible with COVID-19

Symptoms	Status	Start date of symptom
Fever	☐ No ☐ Yes	..... / ..... / 2020
Cough	☐ No ☐ Yes	..... / ..... / 2020
Shortness of breath	☐ No ☐ Yes	..... / ..... / 2020
Sore throat	☐ No ☐ Yes	..... / ..... / 2020
Runny nose (rhinorrhoea)	☐ No ☐ Yes	..... / ..... / 2020
Loss of smell (Anosmia)	☐ No ☐ Yes	..... / ..... / 2020
Loss of taste (Ageusia)	☐ No ☐ Yes	..... / ..... / 2020
Muscle aches (myalgia)	☐ No ☐ Yes	..... / ..... / 2020
Diarrhoea	☐ No ☐ Yes	..... / ..... / 2020
Vomiting / Nausea	☐ No ☐ Yes	..... / ..... / 2020
Headache	☐ No ☐ Yes	..... / ..... / 2020
Fatigue / Malaise	☐ No ☐ Yes	..... / ..... / 2020
Skin rash	☐ No ☐ Yes	..... / ..... / 2020
Conjunctivitis	☐ No ☐ Yes	..... / ..... / 2020

6.3.1.5 Questionnaire on Warning Signs

The self-assessment of warning signs for disease progression will be performed using a set of structured questions, as shown in Table 4. Based on reported warning signs the investigator will plan an unscheduled visit if deemed necessary. Minimally any aggravation of the dyspnea and / or fever or occurence of new symptoms will trigger an unscheduled visit (see Schedule of Events, Appendix 4). The site staff will receive a notification when the questionnaire will be completed and data available for review.

Table 4. Warning Signs for Severe Progression

Question	Answer	Interpretation
How are you feeling?	Scale 0 (bad) to 10 (very good)	Positive if < 3
Have you been hospitalised for COVID?	☐ No ☐ Yes	Positive if yes
If yes, did you receive oxygen?	☐ No ☐ Yes	Positive if yes
Are you experiencing any of the following?		
High temperature (fever)	☐ No ☐ Yes	Positive if yes
If yes, what was your temperature	..... °C or ☐ Don't know	Positive if > 37.2°C
If yes, have you taken any treatment?	☐ No ☐ Yes	
If yes, what treatment did you take?	☐ Paracetamol ☐ Aspirin ☐ Other	
Chills	☐ No ☐ Yes	Positive if yes
Cough	☐ No ☐ Yes	Positive if yes
If yes, how often?	Sometimes or A lot	Positive if a lot
Difficulty breathing or breathlessness	☐ No ☐ Yes	Positive if yes
If yes, how bad is it?	Scale 0 (none) to 10 (very bad)	Positive if > 2
Chest pain	☐ No ☐ Yes	Positive if yes
If yes, how bad is it?	Scale 0 (none) to 10 (very bad)	Positive if > 2
Diarrhoea	☐ No ☐ Yes	Positive if yes
Difficulty eating or drinking properly	☐ No ☐ Yes	Positive if yes
Would you like a physician to call you back?	☐ No ☐ Yes	

6.3.2 Safety Assessments

6.3.2.1 Adverse Events

Safety will be assessed through routine monitoring of adverse events (AEs). AEs will be collected by study personnel at the time-points indicated in the Schedule of Events (Appendix 4). AEs may also be directly observed by study personnel or spontaneously reported by patients and should be reported by the investigator using concise medical terminology.

In addition, to avoid bias in eliciting AEs, each patient will be questioned about the occurrence of adverse events (define when i.e. time/frequency of questioning), with general, non-leading questions such as "Since as" Since xxx (e.g. last visit) have you had any health problem?" or "How are you feeling?".

All serious and non-serious AEs will be recorded in the eCRF regardless of whether or not a causal relationship with each IP is suspected.

Information on AEs must be evaluated by a physician.

The seriousness of AEs must be assessed by the Investigator, and each AE is to be classified as serious or non-serious (see definition in Section 6.3.2.1.2). This classification will determine the reporting procedure for the event as per local regulatory requirements.

In addition to seriousness, the severity of AEs must be graded (see Section 6.3.2.1.3), and a causality (see Section 6.3.2.1.3) assessment of each AEs with each IP will be described.

6.3.2.1.1 Definition of Adverse Event

An adverse event (AE) is defined as:

"An adverse event is any untoward medical occurrence in a patient or clinical study subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment". An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

What is not an AE

- Medical conditions present at screening that do not worsen in severity or frequency during the study are not considered as AEs.
- Symptoms, exacerbation or worsening of COVID-19 will not be considered as AEs or recorded on the AE page of the eCRF if consistent with the anticipated natural overall course of the disease or for the patient in question.
- Lack of efficacy of the IP will not be considered as an AE.

The definition of AE includes worsening in severity or increased frequency of conditions pre-existing before the first IP administration and abnormalities on clinical investigations, e.g. ECG or x-ray, or laboratory tests, which are assessed as "clinically significant".

The definition of AE implies the administration of a medicinal product and all AEs are therefore treatment emergent, however non-treatment-emergent AEs are also to be collected.

Special Cases: Screening Period

Events occurring prior to first IP administration in the study are not considered as AEs per se but as "events" that could be due to the disease or to the patient's inclusion in the study, e.g. withdrawal of a concomitant drug to enter the study.

Any non-serious "event" occurring after signature of the Informed Consent Form (ICF) assessed by the Investigator as protocol-related, should be reported on an AE form whereas all serious events occurring after ICF signature (irrespective of investigator's causality assessment) should be reported on an SAE form and an AE form.

Special Cases: Screening Failure

For screening failures, protocol-related events and updates must be recorded in the eCRF using the AE or SAE forms as appropriate until the date the patient was determined to be a screening failure. Beyond that date, only serious or medically relevant protocol-related events will be followed-up. It is therefore important to ensure that the date of screening failure is recorded.

6.3.2.1.2 Definition of Serious Adverse Event (SAE)

An AE is defined as serious if it:

- Results in death,
    - i.e. causes or contributes to the death.
- Is life-threatening,

- In this context refers to an AE in which the patient was at risk of death at the time of the AE; it does not refer to an AE that hypothetically might have caused death if more severe.

- Requires in-patient hospitalisation or prolongation of existing hospitalisation,
  - i.e. the AE requires at least an overnight admission or prolongs a hospitalisation beyond the expected length of stay. Hospital admissions for surgery planned before study entry, for social reasons, for any elective surgery (i.e. plastic surgery) or for normal disease management (including treatment adjustment) are NOT to be considered as SAE according to this criterion (i.e. if the protocol or the standard management of the disease under study requires planned hospitalisation).
- Results in persistent or significant disability or incapacity,
  - i.e. the AE resulted in a substantial disruption of the subject's ability to conduct normal activities.
- Is a congenital anomaly or birth defect,
  - i.e. an AE outcome in a child or foetus of a subject exposed to the IP before conception or during pregnancy.
- Is an important medical event, i.e., is medically significant.
  - Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious events, such as important medical events that might not be immediately life threatening or does not directly result in death or hospitalisation, but which might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse event. In addition, any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse event (as important medical event).

The Investigator will assess the seriousness of all AEs as serious or non-serious and record the assessment in the eCRF.

SAE onset/start date:

Start date of SAE or date when the AE becomes serious

SAE end/stop date:

SAE end date is the date of AE recovery.

6.3.2.1.3 Grading of AE Severity

The severity of AEs will be graded using the standardised terminology mild, moderate or severe. The terms are defined as follows:

- Mild: the patient is aware of the event or symptom, but the event or symptom is easily tolerated, and no reduction in daily activities is required;

- Moderate: the patient experiences sufficient discomfort to interfere with or reduces his or her usual level of activity;
- Severe: significant impairment of functioning: the patient is unable to carry out usual activities and/or the patient's life is at risk from the event.

Changes in the severity of an AE over time will be recorded in the patient's medical file, however only the maximum severity will be recorded in the eCRF. If an AE worsens after the start of administration of the IP, this should be recorded as a separate event. If the AE resolves but then recurs, each occurrence will be recorded as a separate AE, with the appropriate start and stop times.

6.3.2.1.4 Causality Assessment of AE

For each AE and SAE, the Investigator is required to assess the possible causal relationship between each IP and the event to determine whether there is a reasonable possibility that any IP caused or contributed to the event. This means that there is evidence to suggest a causal relationship.

Causality will be assessed using the following terms:

- Definitely related.
  - IP administration and onset of the AE are related in time and a direct association can be demonstrated.
- Probably related.
  - IP administration and onset of the AE are reasonably related in time and the IP provides a more likely explanation of the AE than other causes.
- Possibly related.
  - IP administration and onset of the AE are reasonably related in time and causes other than the IP could equally well provide an explanation for the AE.
- Probably not related.
  - A potential relationship between the IP and the AE could exist, i.e., the possibility cannot be excluded, however causes other than the IP provide a more likely explanation for the AE.
- Not Related.
  - The AE is clearly explained by another cause not related to the IP.

Causality will be assessed by the Sponsor as a binary classification. Thus, "not related" for the Sponsor corresponds to "not related" and "probably not related" while "related" corresponds to "possibly related", "probably related" and "definitely related".

6.3.2.1.5 AE Reporting Requirements

AEs and SAEs will be reported to the regulatory authorities and/or ethics committees by the Sponsor in each country in accordance with local regulatory requirements.

Investigators must report all SAEs to the Sponsor immediately, i.e. within 24 hours of their becoming aware of the SAE, via the Sponsor's dedicated e-mail address for SAE reporting, using the SAE form. Fax or telephone may be used if e-mail is not possible.

SAEs must also be recorded in the AE section of the eCRF in addition to SAE form. The information recorded in the SAE reporting form and in the AE section of the eCRF must be consistent.

The initial report is to be followed by submission of additional information, using the follow-up SAE form, as it becomes available. Follow-up information will be reported as soon as possible, and if possible within 5 working days from awareness of the information by the Investigator.

Initial reports submitted will meet the following minimal criteria (valid reports for regulatory safety reporting):

a. An identifiable patient

b. A suspect medicinal product

c. An identifiable reporting source

d. An event or outcome that can be identified as serious and unexpected

e. There is a reasonable suspected causal relationship

A copy of the submitted SAE form must be retained on file by the Investigator. The Investigator must submit the SAE to the ethics committee or/and regulatory authorities as per local reporting requirements and retain proof of these submissions in the Investigator Site File. The Sponsor must ensure that safety reporting obligations are fulfilled. Proof of submissions are to be filed in the Study Master File.

A suspected unexpected serious adverse reaction (SUSAR) is a suspected AE assessed as related to an IP that is both unexpected and serious.

The Sponsor is responsible for determining the expectedness of the AE, using the reference safety information defined for the study. The Sponsor or the Investigator will notify the ethics committee and regulatory authorities of all SUSARs and other types of SAEs (if applicable) in accordance with local safety reporting requirements.

6.3.2.1.6 Adverse Event Monitoring Period

The AE monitoring period begins upon signature of the informed consent form and ends at the end-of-study visit on Day 21 or the early withdrawal visit.

All AEs that occur during the AE monitoring period must be reported to the Sponsor, whether or not the AE is considered treatment related. In addition, any AE that occurs after the AE monitoring period that the Investigator considers to be possibly related to the IP should also be reported as an AE.

6.3.2.1.7 AE Follow-up

All AEs must be followed until they are resolved, until the Investigator assesses them as ‘chronic’ or ‘stable’, or until the end of the patient’s participation in the study, i.e. until a final report is completed for that patient or until the last contact with the patient.

All SAEs must continue to be followed even after the end of the patient’s participation in the study. SAEs must be followed until they resolve or until the Investigator assesses them as ‘chronic’ or ‘stable’.

All adverse events that occur during the adverse event reporting period specified in the protocol must be reported to the Sponsor, whether or not the event is considered medication related. In addition, any adverse event that occurs subsequent to the adverse event reporting period that the investigator assesses as possibly related to the investigational medication should also be reported as an adverse event

6.3.2.2 Laboratory Safety (Optional)

Laboratory tests may be performed for assessment of safety. In the event of an abnormal finding, the laboratory test will be repeated and the abnormality, if still present, will be assessed for clinical significance based on the following criteria:

- The abnormality suggests a disease and/or organ toxicity and the abnormality was not present at screening or is assessed as having progressed since screening
- The abnormality results in discontinuation of the IP
- The abnormality requires medical intervention or concomitant therapy
- The abnormality is associated with clinical signs and symptoms.

If a laboratory test result is abnormal and clinically significant, it should be reported as an AE.

The following parameters will be recorded in eCRF.

Hematology	**Blood Chemistry**
Red blood cell (RBC) count	Glucose
Hemoglobin	Albumin
Hematocrit	Total Protein
White blood cell (WBC) count	Sodium
Neutrophils (absolute and differential)	Potassium
Lymphocytes (absolute and differential)	Blood urea nitrogen (BUN)
Monocytes (absolute and differential)	Creatinine
Eosinophils (absolute and differential)	Alkaline phosphatase (ALP)
Basophils (absolute and differential)	Alanine amino transferase (ALT, SGPT)
Platelet count	Aspartate amino transferase (AST, SGOT)
	Lactate
	C-reactive protein
Coagulation	**Lipids**
Antithrombin III	Cholesterol
Protein C	Triglycerides
Protein S	
D-Dimer	

6.3.2.3 Exposure during Pregnancy

If a patient becomes pregnant while receiving the IP, the Investigator must report the event on a *Pregnancy Surveillance Form* and inform the Sponsor in accordance with the same process and timelines for SAEs (see Section 6.3.2.1.5). This must be done irrespective of whether an AE has occurred. The information submitted should include start date of last menstrual period and anticipated date of delivery.

The Investigator will follow the patient until completion of the pregnancy or until pregnancy termination. The Investigator will provide pregnancy follow-up and outcome information on the *Pregnancy Surveillance Form*.

Pregnancy is not an SAE. Any unfavourable outcome meeting at least one seriousness criterion i.e. in the event of unfavourable pregnancy outcome (e.g. abortion, stillbirth) or congenital abnormality should be reported using the SAE reporting form.

6.3.2.4 Overdose

Overdose with the IP should be managed in accordance with the information in the Summary of Product Characteristics for the IP.

All overdoses with the IP will be recorded in the eCRF. If the overdose is associated with an AE, it will also be reported as an AE. Overdose involving a medication error, misuse or abuse of the IP should be recorded in the eCRF and patient's medical files.

6.3.3 Other Assessments

6.3.3.1 Physical Examination

The physical examination will focus on general examination, including consciousness and/or confusion status, as well as chest auscultation.

6.3.3.2 Vital Signs

Vital signs, including blood pressure, respiratory rate, heart rate and temperature, will be assessed with the patient in the sitting position.

6.3.3.3 Electrocardiogram

Resting 12-lead ECGs will be performed with the patient in the supine position, before blood draws if possible. In the event of any abnormal finding, ECG will be repeated and the abnormality, if still present, will be assessed for clinical significance. The following data will be recorded in eCRF: Heart rate (bpm), PR interval (msec), QRS Interval (msec), RR interval value (sec), QT interval (msec), QTc interval (Bazett and Fridericia) (msec).

6.3.3.4 Chest X-ray (Optional)

Posterior-anterior chest X-ray will be performed and will focus on features suggestive of COVID-19. General assessment and presence of infiltrates will be recorded in eCRF.

6.3.3.5 Computed Tomography Scan (Optional)

Computed tomography (CT-scan) will be performed and will focus on features suggestive of COVID-19. General assessment and presence of infiltrates will be collected in eCRF.

7 Statistical Methods

7.1 General Statistical Considerations and Overall Design

The study will be designed as a master protocol or platform study, meaning that the study is designed so that it can continue, with the addition or dropping of treatment arms, e.g., dropping an arm based on demonstrated efficacy or on the futility of further investigation. Thus, the study is intended to continue beyond the evaluation of the initial IPs. The study will initially consist of a single control arm, paracetamol (PAR), and up to three active arms, labeled Arm A, B, etc…. During the conduct of the studyr, if an active arm is found to be superior to PAR, then PAR may be dropped and the superior active arm may become the new control arm against which all continuing active arms, and new arms, will compared. Each active arm will be compared to the control arm and, initially, the control arm will be PAR.

As a platform study, the number of agents that will ultimately be compared to control is unknown, so the study is designed to control to type I error/false positive rate on a "per active arm" basis, yielding the same strength of evidence as if a series of separate studies were conducted in which each active arm was compared to the control arm. The type I error rate, per active comparator arm, is controlled at 0.025 (see Section 7.2).

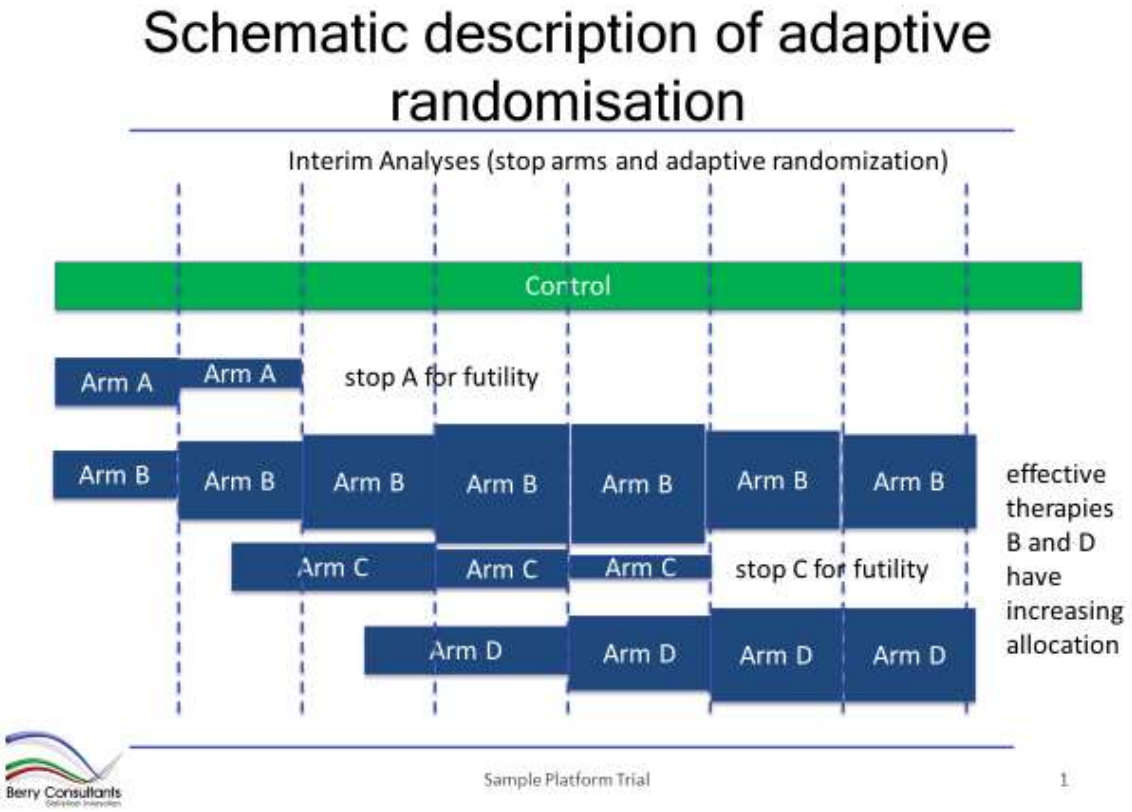
Clinical sites will be distributed across geographic regions and individual sites may or may not have the capability to randomise across all currently available treatment arms. Thus, at one site randomisation may occur between PAR and Arm A while, at other sites, randomisation may be between Arm A and Arm B, or between PAR and Arm B. Because, at least theoretially, patients who enroll at sites with one set of treatment options may differ from patients who enroll at sites with a different set of treatment options (e.g., no PAR control), the statistical model will include an adjustment for country/study site.

Further, the study design can accommodate sites that randomise between groups of IPs that include additional agents not available at other sites, as long as agents shared with other sites are included as well. After a suitable run-in period with balanced randomisation, i.e., 1:1:1, response-adaptive randomisation (RAR) will be used to preferentially randomise patients to the arm or arms at those sites that are better preforming.

Statistical inference will be based on an integrated Bayesian model with non-informative prior information, to support comparisons between each active arm and the control arm. Data from sites that randomise to PAR/Control will provide direct evidence of efficacy, while sites that randomise only between active arms will support indirect comparisons. In addition to estimating the effect of treatment arm on the proportion of patients with progression to severe disease at 21 days, the analysis model will include adjustments for site effects and for secular trends over time. Finally, as mentioned above if one of the active arms is demonstrated to be superior, it may become the new standard-of-care and the PAR arm may be dropped, without compromising the integrity of the study, and allowing the study to continue and yield additional information.

The platform study will begin with a control arm and two active treatment arms and, after a burn-in period of 300 patients, an interim analysis will be conducted and repeated after every additional 300 patients. A third active treatment arm may be included in some countries At each interim analysis, an active arm will be dropped if the IP is shown to have a very low probability of being superior to control or may be declared successful if the probability is greater than 0.992 of being superior to control, or the study may be continued with the same arms but with an adjustment in the randomisation ratios. RAR will be used to adjust the

proportions of patients randomised to the various currently available active arms, in proportion to the Bayesian probability that each is the best performing IP. This will increase the fraction of patients that, on average, receive the most effective therapies if there are differences between them, improving both the ethical balance of the study and increasing the quantity of data obtained on the best performing IP(s). The fraction of patients randomised to the control therapy will be held constant at 40% at sites that include the control therapy, as this increases the power of the study and allows for adjustment for secular trends by ensuring an adequate number of concurrently randomised control patients.



As a platform study, additional drug candidates may be added to the study as they become available. When a new candidate is added, it will be randomised in a fixed ratio until a minimum of 100 patients on the new IP have been enrolled, at which point RAR will be applied to the new arm as well. This ensures that adequate information is available on the new candidate before it is included in the RAR allocations. As mentioned above, if one of the active arms is demonstrated to be superior to the control, it may become the new standard-of-care and the PAR arm may be dropped, without compromising the integrity of the study, and allowing the study to continue and to yield additional information.

A number of potential threats to validity are specifically addressed by the proposed trial design: (1) the potential for secular changes in standard of care (SOC0 to lead to bias with RAR; (2) the potential for adoption of new agents as SOC to made continuation of the trial impossible or

scientifically inappropriate; and (3) loss of control of type I error due to frequent and numerous interim analyses. Regarding the impact of gradual secular changes, the final analysis model will include an adjustment for time of enrollment to account for secular changes over time in the effectiveness of the SOC, either because the approach to SOC changes or the enrolled patient population changes over time. The primary model will consider the effect of time on the baseline rate of respiratory deterioration; however, we will investigate time by treatment effect interactions as well in exploratory analyses. The defined constant allocation to the control therapy over time ensures that the acquired data will be sufficient to estimate and adjust for changes in outcomes over time. In a rapidly changing clinical landscape, the adoption of a new SOC threatens the continued value of any trial that cannot accommodate a change in the control therapy during trial conduct. While such an event certainly makes the analysis and interpretation of the data more complex, the Bayesian model will be structured to allow all pairwise direct and indirect comparisons, allowing the control therapy to be replaced if necessary. The new control therapy would be subject to the fixed minimum allocation ratio as described above. Type I error control of the proposed design will be demonstrated via extensive simulations, under a wide range of possibilities (e.g., all arms the same, one superior, one inferior, one each inferior, equivalent, and superior, etc.). If necessary, the criterion for superiority will be adjusted to maintain type I error control and the probability threshold given above should be considered preliminary.

The details of the statistical design of the platform study, including all rules for stopping for overall futility, stopping an individual arm for futility or success, and RAR will be prespecified in the statistical analysis plan. Detailed operating characteristics (e.g., type I error rate, power) will be determined by simulation (see Section 7.2 for initial work). The study will be run using custom-programmed software, allowing frequent interim analyses to be conducted to maximise the statistical efficiency of the study.

7.2 Sample Size Determination

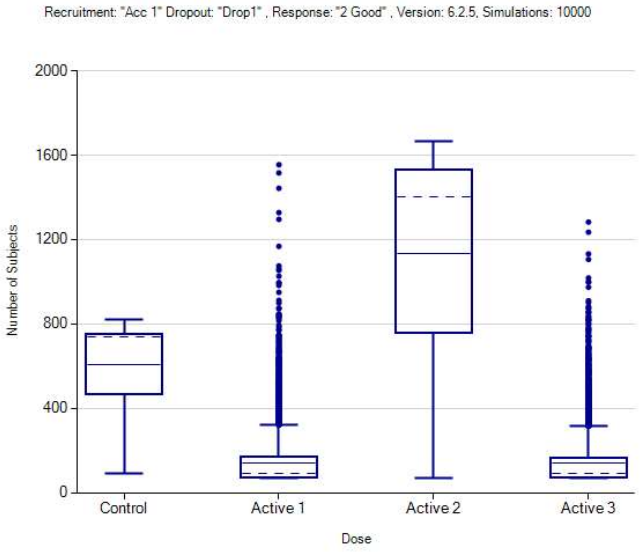
To determine the required sample size for the proposed study, expressed as the required number of patients per IP evaluated, an analogous Bayesian adaptive study was simulated using a fixed and adaptive clinical trial simulator (FACTS) software from Berry Consultants, LLC. We simulated a study evaluating four arms, i.e. the PAR control and three active drug treatment arms, anticipating addition of a new antiviral, with a sample size of 625 patients per arm (2,500 patients in total). In the design, RAR (as described in Section 7.1) was used to increase the fraction of patients randomised to the better performing IP(s), both to increase the precision of the treatment estimates for those arms and to increase the likely benefit to the individual patients of participation in the study.

The simulated clinical study began with an initial “burn-in” period, during which patients were allocated in a fixed ratio of 4:2:2:2 among the four treatment arms, until 300 patients had been randomised. From that point on, a fixed 40% of all patients were randomised to the control arm (PAR), while the remaining patients were adaptively randomised among the active treatment arms proportionally to the probability that each arm was the best performing arm. Interim analyses were conducted after every 300 patients were enrolled and, at each interim analysis, the study design included early stopping rules for futility or success, or the randomisation ratios could be adjusted for the next 300 patients. The criterion for stopping early for futility was that no IP had a probability > 0.1 of decreasing the rate of severe progression by at least 2.5% absolute difference. Similarly, the criterion for stopping early and declaring an IP superior to

control if there was > 0.95 probability that the most effective IP reduced the proportion of patients with severe progression by 5% or greater absolute difference (super-superiority). If the study did not meet any criteria for stopping early, then it was continued until the maximum sample size of 2,500 patients (a per-IP sample size of 625), then one or more IPs were declared effective if there was a probability of at least 0.992 that the IP is superior to control.

Using this design and specific criteria for demonstrating efficacy, simulation demonstrated control of the type I error rate at 0.024 and the study design achieved a power of 0.85 to demonstrate a decrease in the rate of progression to severe disease in one of the active arms from the control rate off 10% to 5%. Under the null hypothesis of no treatment effect with any of the three active IPs, the study will stop early for futility 67.0% of the time, limiting the exposure of patients to ineffective treatments. Under an alternative hypothesis in which a single IP is extremely effective, reducing the proportion of patients who deteriorate from 10% to 2.5%, the study will identify that effective therapy early, before the full sample size is enrolled, 79.8% of the time. In addition, the simulations show that if one of the active IP arms is beneficial then patients will be selectively assigned the effective therapy (see Figure 4) and, if any of the active arms is harmful, the study will effectively randomise patients away from the harmful arm(s), to minimise the risk to patients.

Figure 4. Distribution of Patient Allocation Across Simulations



In this example, based on 10,000 simulations of the adaptive study with RAR, IP 2 is assumed to be more effective than control, reducing the rate of severe progression from 10% to 5%, while IPs 1 and 3 are equal to control. Patients are selectively allocated the better therapy, improving their expected outcomes.

The simulation of the analogous design demonstrated that a sample size of 625 patients will yield a power of approximately 85% to detect a decrease in the rate of severe progression at 21 days from 10% to 5%. The simulation assumed a drop-out/lost to follow-up rate of 5%. Thus the proposed perpetual, platform study will have suitable power and control of the type I error risk for the evaluation of pharmacological interventions for the prevention of severe progression of ambulatory patients with COVID-19 in Africa.

7.3 Patient Disposition

The disposition of all patients in the safety population will be summarised by treatment arm as follows:

- Number of patients randomised
- Number of patients who completed the study

- Number of patients who discontinued the study

All patients who discontinued the study will be listed by treatment arm with the reason for discontinuation.

7.4 Populations for Analysis

The following populations will be used in the statistical analyses:

- Intent-to-treat (ITT) All patients who received at least one intake of IP
- Per protocol (PP) All patients in the ITT population who were free from major protocol violations that could lead to bias
- Safety All patients who received at least one intake of IP

Other analysis populations may be described in the Statistical Analysis Plan.

7.5 Efficacy Analyses

7.5.1 Interim Analyses and Primary Efficacy Analysis

Interim analyses and the primary analysis of an IP when it is declared either effective, ineffective or is dropped for futility will be based on the ITT population.

The stopping rules that will be applied at each interim analysis are structured to accomplish two goals:

1. To ensure that randomization to an experimental arm is stopped if the evidence is sufficient to conclude that the experimental arm is superior to control; and
2. To ensure that randomization to an experimental arm is stopped if the evidence is sufficient to conclude that the experimental arm is inferior to control (harm) or it will likely be impossible to demonstrate it is superior (futility).

In each case, the criteria for applying the rule is based on the Bayesian probability that the experimental treatment is better than control, or better by a specified margin (e.g., 5%). If that probability is very high then superiority may be concluded; if it is very low the harm/futility may be concluded. The actual criteria or thresholds are determined through simulation to control the traditional frequentist type I error rate at 2.5% (this requires a more stringent threshold, analogous to the use of an alpha spending function approach) and to minimize the fraction of arms that are terminated for harm/futility prematurely, when they actually would have gone on to be demonstrated as superior if they had not been stopped.

The primary analysis will be a Bayesian comparison of the proportions experiencing progression to severe disease with the IP versus control, with adjustments for site and temporal effects. Prior to the first interim analysis, a limited number of additional covariates may be specified for inclusion in the primary analysis, as predictors of outcome in ambulatory patients with COVID-19 become better understood. The criteria for success, chosen to control type I error risk in the setting of frequent interim analyses, are provided above.

Additional prespecified robustness analyses will include:

- A repeat of the primary analysis in the per protocol population, to evaluate the magnitude of any change in the estimate of the treatment effect;

- A "tipping point" analysis to determine the sensitivity of the primary result, if positive, to various patterns of outcomes in patients who are lost to follow- up or with undetermined status at Day 21.

In the tipping point analysis, the assumption will be made, initially, that all patients in the control group who were lost to follow-up were treatment successes and all patients treated with the IP who were lost to follow-up were treatment failures. Under this "worst case" assumption, we will determine whether the IP still meets the criterion for being declared effective. If not, then one control patient with missing data will be assumed to be a treatment failure and one IP patient with missing data will be assumed to be a treatment success, and the analysis will be repeated. This pattern will continue until we determine the least extreme pattern in missing data that would be required to convert a positive study result for the IP in question to a negative study result. This allows for assessment of the degree to which the overall study conclusion for the IP could be altered by the unknown outcomes in patients with missing data.

7.5.2 Secondary Efficacy Analyses

Traditional frequentist statistical methods will be used to summarise and analyse secondary endpoints, once an IP is declared effective, ineffective, or is removed from the study due to futility in further evaluation. Both continuous and dichotomous outcomes will be analysed using generalised estimating equations (GEE) to account for clustering within country. A logit link function will be used for dichotomous outcomes and a constant link function will be used for continuous outcomes. GEE models will include site effects and time as prespecified covariates. As above, a limited set of additional covariates may be prespecified, prior to the first interim analysis, based on emerging information regarding predictors of outcomes in patients with COVID-19. As the analysis of the secondary outcomes is descriptive, no correction will be made for multiple comparisons and a nominal one-tailed alpha of 0.025 will be used for comparisons between the active IP arms and control; a two-tailed alpha of 0.05 will be used for comparisons between pairs of active IP arms.

7.6 Safety Analysis

7.6.1 Analysis of Adverse Events

AEs will be tabulated by preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), by System Organ Class (SOC) and by severity. The subset of AEs that are assessed by the Investigator as having a relationship to the IP will be considered to be treatment-related AEs. The number and percentage of AEs and treatment-related AEs, overall and by SOC, will be tabulated by treatment arm. AEs will also be summarised by severity, relatedness and seriousness.

AEs will be analysed both by ITT and by treatment received, in the Safety Population. Comparisons of rates of AEs will be presented descriptively.

7.6.2 Analysis of Vital Signs

Findings for vital signs will be reviewed for clinically significant abnormalities, and patients with clinically significant abnormalities will be listed.

Descriptive statistics for each scheduled time-point and for change from baseline to selected time-points will be provided for vital signs. For height, weight and BMI, descriptive statistics

will be calculated by sequence and overall, while for blood pressure, heart rate and temperature descriptive statistics will be calculated by treatment and occurrence.

7.6.3 Analysis of optional assessments

Laboratory safety parameters, will also be described individually.

Abnormalities on ECG, chest X-Ray, and CT-scan will be described for each timepoint.

8 Data and Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be set up prior to study initiation, composed of 5 members independent of the Investigator and Sponsors and having expertise in COVID-19 or respiratory viruses, antiviral therapies and viral shedding, emerging epidemics and adaptive platform study design. An independent non voting statistician will be presenting interim analysis to the DSMB members. The DSMB will monitor the study in order to ensure that risks are minimised and benefits are maximised for patients. They will review the study data at pre-determined intervals and issue recommendations concerning ongoing study conduct. The data to be reviewed and interval for reviews will be agreed prior to or soon after study initiation and documented in the DSMB Charter.

Because of the innovative design of the Bayesian platform study, a representative from Berry Consultants, LLC, the group performing the statistical design work and the interim analyses necessary to run the study, will serve as a non-voting member of the DSMB, to ensure that all members of the DSMB thoroughly understand the study design and the results of the interim analyses.

9 Data Management

9.1 Data Collection

Investigational sites will be provided with access to electronic case report forms (eCRFs) in which to record protocol-specified data for patients in the study. Sites will also be provided with SAE Reporting Forms and Pregnancy Surveillance Forms. Data will be entered in the various forms by authorised personnel at the investigational centre and should be verifiable against source documents. Some data items may be entered directly into the eCRF and, in which cases, the entry in the eCRF will be considered as the source data.

The Investigator will be responsible for reviewing all data and entries in the reporting forms and will verify that the information is true and correct. Queries may be generated by the Study Monitor or Data Management personnel to request clarification of data items or provision of missing data. Queries will be sent to the investigational site electronically. The Investigator is responsible for the review and approval of all responses to queries.

In all protocol-specified data, patients will be identified only by coded numbers in order to maintain confidentiality. The exceptions are SARS-CoV-2 testing results, which may be subject to local and/or state reporting requirements, potentially on a named basis.

9.2 Data Handling on Sites

The Investigator must maintain adequate and accurate records at the investigational centre to ensure that the conduct of the study is fully documented and that study data can subsequently be checked. These documents include the Investigator Site File, source documents for study data, and patient logs.

Investigator Site File

The Investigator Site File will contain the protocol and any protocol amendments, a paper copy of the eCRF, SAE Reporting Forms or Pregnancy Surveillance Forms and query forms, ethics committee and regulatory approval with correspondence, sample of informed consent form, IP accountability records, staff curriculum vitae and authorisation forms and any other appropriate documents, file notes and correspondence as appropriate.

The Investigator Site File will be stored safely and securely so as to ensure that the documents are readily available upon request from the regulatory authorities.

Source Documents

The Investigator must maintain source documents for possible review and/or audit by the Sponsor and/or regulatory authorities. Source documents may include patient hospital/clinic reports, PCR test result, oximeter readings, original laboratory reports, ECG, X-ray, CT-scan reports and special assessment reports, signed ICFs, consultant letters.

Patient Logs

The Investigator will maintain a screening log containing the name, date of birth and/or age and sex of all patients screened for the study, together with their screening numbers. A log will also be kept of all patients randomised in the study.

9.3 Data Processing

Processing of study data will be performed in accordance with standard operating procedures and the Data Management Plan for the study, using a validated database.

9.4 Data from Screening Failures

For screening failures, at least the following data items will be recorded in the eCRF:

- Patient identification number;
- Demographic data, i.e. sex, year of birth and/or age;
- Date of informed consent;
- Reason for screening failure;
- Date of last visit or date of screening failure.

9.5 Missing Data

The analyses will be based on observed cases. For the analyses of missing data, see Section 7.5.1.

9.6 Study Monitoring

Qualified representatives of each Sponsor will monitor the study. At least every 4 weeks or after every 40 patients are randomised, the monitors will perform on-site monitoring visits at

the investigational centre, or remote visits during the pandemic, to ensure that the study is conducted in accordance with the study protocol, ICH GCP E6, as well as local GCP guidelines and regulatory requirements.

Monitoring will include verification of the authenticity and accuracy of data by reviewing eCRFs, SAE reporting forms, Pregnancy Surveillance forms and query forms, against source documents, by direct inspection. The frequency of the monitoring visits and data checks will be decided and adapted by the Sponsor and defined in the Monitoring Plan.

The Investigator and the head of the medical institution, if applicable, agrees to allow the monitors direct access to all study-related documents.

9.7 Data Archiving

The study documents will be archived according to local regulations and in accordance with the maximum period of time permitted by the investigational centre. Where the archiving procedures do not meet the minimum timelines required by the Sponsor, i.e. 25 years, alternative arrangements must be made to ensure that the study documents are archived for the required period. The Investigator or head of the medical institution will notify the Sponsor of any change in the arrangements for archiving, e.g. relocation or transfer of ownership. The study documents are not to be destroyed without the Sponsor's approval.

9.8 Audit and Inspection

To ensure compliance with ICH GCP E6 and local GCP requirements if applicable, a member of the Sponsor's quality assurance team, or a designated contract research organisation, may arrange to perform an audit to assess the conduct of the study at the investigational centre and the handling of the study documents originating there. The Investigator/institution will be informed of the audit findings.

In addition, inspections by regulatory authority and ethics committee representatives are possible. The Investigator should notify the Sponsor immediately of any such inspection.

The Investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time before, during or after completion of the study.

10 Protocol Amendments

Any change to the protocol must be made in writing by way of amendment, approved and signed in by the Sponsor and the Investigator. Amendments are to be submitted to the ethics committee and regulatory authorities, if required.

Approval from the ethics committee and regulatory authority, if applicable, must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to patients, or when the change involves only logistical or administrative aspects of the study, e.g. change in study monitor or change in telephone number.

11 Premature Study Termination

Both the Sponsor and the Investigator reserve the right to terminate the study at any time prior to inclusion of the intended number of patients, however they intend to exercise this right only for valid scientific or administrative reasons. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the patients' safety and well-being.

Reasons for early termination by the Sponsor may include but not be limited to:

- Insufficient rate of patient inclusions;
- Protocol violations;
- Inaccurate or incomplete data;
- Unsafe or unethical practices;
- Questionable safety of the IP;
- Suspected lack of efficacy of the IP;
- Following the recommendation of the DSMB, regulatory authorities or ethics committee;
- Administrative decision.

Reasons for early termination by the Investigator may include but not be limited to:

- Insufficient time or resources to conduct the study;
- Lack of eligible patients.

If the study is terminated early either by the Sponsor or by the Investigator, the Investigator is required to:

- Complete all eCRFs to the greatest extent possible;
- Return all IPs and related study materials to the Sponsor;
- Answer all questions from the Sponsor or its representatives related to data on patients recruited at the investigational centre prior to study termination;
- Ensure that patients included in the study who have not yet completed the study are followed up with the necessary medical care;
- Provide the national regulatory authorities and the Sponsor with the reasons for the decision in writing.

12 Ethical and Legal Aspects

12.1 Investigator and Other Study Personnel

All study personnel not specifically referred to in this protocol are identified in a separate list of study personnel. The list will be updated as needed. An abbreviated version with personnel relevant for the centre will be available in the Investigator Site File of the investigational centre.

Whenever the term 'Investigator' is used in the protocol, it may refer to either the Principal Investigator at the investigational centre or an appropriately qualified, trained and delegated individual in the investigational centre.

The Principal Investigator must sign the protocol signature page and must receive all required external approvals, i.e. regulatory authorities, ethics committee, Sponsor, before patient recruitment may begin at the investigational centre. Likewise, all amendments to the protocol must be signed by the Principal Investigator and must have received all required external approvals before coming into effect at the investigational centre.

12.2 Infectious risk

All site staff must take into consideration National Guidance including relevant Government Directives aimed at mitigating the spread of COVID-19 disease. Sponsors will provide Personnel Protection Equipment to clinical staff and patients. In all study procedures that involve physical contact with the participants, additional measures should be taken to factor in participants' opinions and concerns and safeguard against penalties for refusal of participation/ continuation.

12.3 Funding of the Study

The study will be funded by the Sponsors. The study is being conducted by a consortium of partners who may support the study by providing services or study materials, including IPs, free of charge.

12.4 Costs for Patients

The patients' travels costs to and from the investigational centre should be covered depending on the particular practices in the centre. Missed days of work due to participation in the study may be compensated, depending on local procedures and if permitted by the regulatory authorities and/or EC. This will be clearly stipulated in the country-specific ICF. Food during the quarantine period in hospitals or governmental facilities and any overnight stays at the investigational centre will be provided free of charge to the patient.

Any medication that is required during the study will be provided free of charge. In the event of AEs, reasonable and necessary medical treatment will be provided free of charge by the Investigator at the investigational centre. If the condition requires treatment at another hospital and is a direct result of participation in the study, the cost will be paid by the Sponsor.

12.5 Ethical and Legal Conduct of the Study

Investigational centres have been selected to ensure that patients will have appropriate rescue management in the event of disease progression.

The procedures set out in this protocol, pertaining to the conduct, evaluation and documentation of the study, are designed to ensure that the Sponsor and Investigator abide by GCP guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in accordance with applicable local laws and regulations.

Documented approval from the regulatory authorities and ethics committee will be obtained before the start of the study, in accordance with GCP, local laws and regulations. When necessary, an extension, amendment or renewal of the approval from the regulatory authorities must be obtained and forwarded to the Sponsor. The responsible unit (e.g., the regulatory authorities, head of the investigational centre/medical institution) must, upon request, provide the Sponsor with a list of the members of the ethics committees involved in the vote and a statement to confirm that the ethics committees are organised and operate according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in the protocol is required for all aspects of study conduct. The Investigator may not depart from the procedures described in the protocol. Any deviations from the protocol must be explained and documented by the Investigator.

12.6 Patient Information and Informed Consent

All relevant information on the study will be summarised in a patient information document and informed consent form, provided by the Sponsor or the investigational centre.

Patients will be included in the study only after written informed consent is obtained from the patient (for adults) or the parent/guardian (for children or incapacitated adult). The Investigator or designee is responsible for obtaining informed consent from patients, after adequate presentation of the aims, methods, anticipated benefits, and potential hazards of the study. The informed consent form will be translated into the local language or a language understood by the patients. If needed, the patient will be given time to discuss the information with members of the community or family before deciding to consent.

The informed consent form will include consent from the patient for sharing of data with other researchers after the data have been rendered anonymous.

A separate informed consent form will be used for the ancillary studies.

12.7 Publication Policy and Use of Study Data

The study will be registered with a recognised clinical study registry, e.g. www.clinicaltrials.gov, Pan African Clinical Trials Registry.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the Sponsor who may utilise them in various ways, such as for submission to regulatory authorities or shared with research institutions through IDDO in the first instance and other mechanisms as needed. Access to data will be regulated by an Independent Data Access Committee following the general governance principles of IDDO and in line with the Policy Statement by the WHO in the context of Public Health Emergency.

The final Clinical Study Report will be submitted to the ethics committee and regulatory authorities, if required.

The Sponsor encourages the communication and/or publication of the results, in accordance with the terms of the Clinical Trial Agreement.

Any reliable interim findings will be disseminated rapidly by the consortium of partner conducting the study and will be published in the names of the partners of the consortium.

12.8 Insurance

The Sponsor will cover any claim made by a patient for damage resulting directly from the study and will also indemnify the Investigator against any liability resulting from such. Coverage of damage to the patient and indemnification of the Investigator will not apply if the damages to the patient result from negligence or intentional misconduct by the Investigator.

12.9 Confidentiality and Protection of Privacy

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and regulations, will not be made publicly available.

Patient names will not be supplied to the Sponsor. Names will not be entered in the eCRF or any document or digital file supplied to the Sponsor. The patient identification number and randomisation number will be used as identification and, if the patient's name appears on any other document or file it will be redacted before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the patients will be informed in writing that representatives of the Sponsor or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the patient's identity will remain confidential.

The Investigator will maintain master patient log to enable patients to be identified.

13 List of References

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14 Appendices

Appendix 1. Investigational Products

Depending on the treatment arms, IPs relabelling may be done at the country level or IPs repackaging and relabelling will be centralised and performed in a GMP facility such as BILCARE for LOPINAVIR/RITONAVIR.

Appendix 1.1 Hydroxychloroquine Sulphate

Hydroxychloroquine Sulphate

General information on hydroxychloroquine is presented in Table 5.

Table 5. General Information on Hydroxychloroquine Sulphate

International Non-proprietary Name	Hydroxychloroquine sulphate
Dosage Form	Film-coated tablet containing 200 mg of hydroxychloroquine sulphate
Route of administration	Oral
Dosing instructions	Day 1: loading dose of 800 mg daily, divided into two daily intakes of 400 mg taken 12 hours apart Day 2-7: maintenance dose of 400 mg daily, divided into two daily intakes of 200 mg taken 12 hours apart
Duration of treatment	7 days
Composition	Round, white, film-coated tablets marked 'HCQ' on one side and '200'on the other side. Containing: hydroxychloroquine sulphate 200 mg Excipients: lactose monohydrate, maize starch, magnesium stearate, polyvidone Film-coating: Opadry OY-L-28900 (containing hypromellose, macrogol 4000, titanium dioxide (E171), lactose)

Rationale for Choice of Hydroxychloroquine Sulphate

Hydroxychloroquine sulphate is an antimalarial agent. It is on the WHO Essential Medicines List for use in rheumatic disorders and is widely prescribed as an anti-inflammatory for rheumatoid arthritis, systemic lupus erythematosus and other autoimmune syndromes.[1]

At the time of preparation of this protocol, hydroxychloroquine is still one of the drugs of choice being investigated in some major on-going clinical trials for COVID-19, as treatment of severe hospitalised cases, as prophylaxis in at-risk populations such as frontline healthcare workers, or for elderly or non-elderly patients with mild disease in trials in Australia, France and the UK (e.g. ASCOT, COVERAGE, RECOVERY).[2–9]

Hydroxychloroquine is widely recommended for selected use in some countries such as the DRC, France and the USA, however, there is no consensus on the best dose regimen, one that will provide sufficient efficacy with an acceptable level of risk. The benefit-to-risk ratio varies depending on the severity of the disease at the time of treatment initiation and should be guided

by the best informed scientific understanding of the pharmacodynamic and kinetic properties of hydroxychloroquine.

In this study, the following dosage regimen will be used:

- Day 1: 800 mg total dose divided into two intakes of 400 mg, taken 12 hours apart;
- Day 2-7: 400 mg total dose divided into two intakes of 200 mg taken 12 hours apart.

Simulated blood concentration time profiles of hydroxychloroquine using pharmacokinetic models suggest that a loading dose of 800 mg on the first day is required to obtain rapid onset of the clinical effect, followed by 200 mg twice daily for subsequent days.[10] These doses are the same as the currently recommended doses in France for the use of hydroxychloroquine in severe pneumonia.

Risks Related to Hydroxychloroquine Sulphate

The risks related to hydroxychloroquine are largely dominated by ophthalmological toxicity, primarily a rare type of maculopathy known as "bull's eye" maculopathy, seen in 0.38% to 1% of patients treated, and strongly dependent on the daily dose (> 5 or > 6.5 mg/kg/day depending on the series) and duration of exposure (> 5 years).[11] Muscular and neurological toxic effects have also been reported with hydroxychloroquine but remain rare and related to prolonged treatments, i.e. for several years.[12–16]

Hydroxychloroquine has been the subject of a large body of specific literature on the risk of cardiomyopathy, which must be dissociated into two points. The first concerns the risk of hypertrophic or restrictive cardiomyopathy, which is related to prolonged or even very prolonged treatment, although some cases have been linked to voluntary mass intake.[17,18] The second toxic effect concerns lengthening of the corrected QT segment. Synthetic antimalarial drugs are listed among the treatments at risk of lengthening of the QT segment. The reported cases of QT prolongation and torsade de pointes with hydroxychloroquine concern prolonged treatment, and often pathological (hypokalaemia) or therapeutic (β-blockers) combinations.[19–23] Several studies conducted on patients treated with hydroxychloroquine for autoimmune diseases have not shown significant prolongation of the QTc segment.[24,25]

Patients receiving an antidiabetic treatment and randomised to HCQ will be informed about the potential risk of hypoglycemia and its clinical manifestations. The treating physician may decide to adjust the antidiabetic dosage or perform regular glycemia testing.

An assessment of the safety of chloroquine and, by extrapolation the probable safety of hydroxychloroquine at high doses, as used for uncomplicated malaria in the IMPROV study showed that, among patients treated with chloroquine at 10 mg/kg on the first day, either as a single dose or two divided doses, acute vomiting within 60 minutes occurred in 1.7% of patients (22/1322), vomiting in the first 24 hours in 7% (94/1355), nausea in the first 24 hours in 14.9% (200/1346) and diarrhoea in the first 24 hours in 1.9% (25/1352).[26]

List of contra indicated medication and information on drug interaction and corresponding precaution for use (Safety guidance for Investigator-sponsored studies)

Remdesivir should not be administered in severe patients previously treated with hydroxychloroquine as there is risk of lower exposure and lower efficacy (

https://www.fda.gov/safety/medical-product-safety-information/remdesivir-gilead-sciences-fda-warns-newly-discovered-potential-drug-interaction-may-reduce)

Drugs known to prolong QT interval / with potential to induce cardiac arrhythmia

Hydroxychloroquine should be used with caution in patients receiving drugs known to prolong the QT interval, e.g., Class IA and III antiarrhythmics, tricyclic antidepressants, antipsychotics, some anti-infectives due to increased risk of ventricular arrhythmia. Halofantrine should not be administered with hydroxychloroquine.

Antidiabetic drugs

As hydroxychloroquine may enhance the effects of a hypoglycaemic treatment, a decrease in doses of insulin or antidiabetic drugs may be required.

Antimalarials

Administration of hydroxychloroquine with antimalarials known to lower the convulsion threshold (e.g. mefloquine) may increase the risk of convulsions.

Antiepileptic drugs

The activity of antiepileptic drugs might be impaired if co-administered with hydroxychloroquine.

Others

There is a theoretical risk of inhibition of intra-cellular α-galactosidase activity when hydroxychloroquine is co-administered with agalsidase.

Antacids

Concomitant administration with magnesium-containing antacids or kaolin may result in reduced absorption of chloroquine. Per extrapolation, hydroxychloroquine should therefore be administered at least four hours apart from antacids or kaolin.

Ciclosporin

An increased plasma ciclosporin level was reported when ciclosporin and hydroxychloroquine were co-administered

Digoxin

Hydroxychloroquine sulphate has been reported to increase plasma digoxin in levels. Serum digoxin levels should be closely monitored in patients receiving concomitant treatment.

CYP inhibitors or inducers

Concomitant use of cimetidine, a moderate CYP2C8 and CYP3A4 inhibitor, resulted in a 2-fold increase of chloroquine exposure. Per extrapolation, due to the similarities in structure and metabolic elimination pathways between hydroxychloroquine and chloroquine, a similar interaction could be observed for hydroxychloroquine. Caution is advised (e.g. monitoring for adverse reactions) when CYP2C8 and CYP3A4 strong or moderate inhibitors (such as gemfibrozil, clopidogrel, ritonavir, itraconazole, clarithromycin, grapefruit juice) are concomitantly administered.

Lack of efficacy of hydroxychloroquine was reported when rifampicin, a CYP2C8 and CYP3A4 strong inducer, was concomitantly administered. Caution is advised (e.g. monitoring for efficacy) when CYP2C8 and CYP3A4 strong inducers (such as rifampicin, St John's Wort, carbamazepine, phenobarbital) are concomitantly administered.

P-gp substrates

The inhibitory potential of hydroxychloroquine on P-gp substrates has not been evaluated. In vitro observations show that all other aminoquinolines tested inhibit P-gp. Therefore, there is a potential for increased concentrations of P-gp substrates when hydroxychloroquine is concomitantly administered.
An increased plasma ciclosporin level was reported when ciclosporin and hydroxychloroquine were co-administered. Increased digoxin serum levels were reported when digoxin and hydroxychloroquine were co-administered. Caution is advised (e.g. monitoring for adverse reactions or for plasma concentrations as appropriate) when P-gp substrates with narrow therapeutic index (such as digoxin, ciclosporin, dabigatran) are concomitantly administered.

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Appendix 1.2 Lopinavir/Ritonavir

Lopinavir/Ritonavir

General information on lopinavir/ritonavir is presented in Table 6.

Table 6. General Information on Lopinavir/Ritonavir

International Non-proprietary Name	Lopinavir / Ritonavir
Dosage Form	Film-coated tablet containing a fixed dose combination of lopinavir 200 mg and ritonavir 50 mg
Route of administration	Oral route
Dosing instructions	Day 1: loading dose of lopinavir 1600 mg / ritonavir 400 mg daily, divided into two daily intakes of lopinavir 800 mg / ritonavir 200 mg taken 12 hours apart Day 2-14: maintenance dose of lopinavir 800 mg / ritonavir 200 mg daily, divided into two daily intakes of lopinavir 400 mg / ritonavir 100 mg taken 12 hours apart
Duration of treatment	14 days
Composition	Oval, yellow, biconvex film-coated tablets, measuring approx. 19.0 mm in length and 10.2 mm in width, debossed with "H" on one side and "L3" on other side. Containing: lopinavir 200 mg, ritonavir 50 mg Excipients: Copovidone, sorbitan laurate, colloidal anhydrous silica, sodium stearyl fumarate Film-coating: hypromellose, titanium dioxide, hydroxypropyl cellulose, talc, colloidal anhydrous silica, macrogol, yellow ferric oxide, polysorbate 80

Rationale for Choice of Lopinavir/Ritonavir

Lopinavir and ritonavir are antiviral agents.[1] The fixed-dose combination lopinavir/ritonavir has been used for more than 20 years in the treatment of HIV-1 infection in adults and children 14 days of age and older as part of multiple-drug antiretroviral therapy.

In-vitro and *in-vivo* data, as well as clinical data in humans in the context of coronavirus infections, both SARS-CoV and MERS-CoV, have shown that the lopinavir/ritonavir fixed combination has activity against these viruses. However, there are no published data on its pharmacodynamic activity on SARS-CoV-2.

The results of a recent randomised clinical study conducted in patients hospitalised for COVID-19 in China have recently been published.[2] The daily dose in the study was the same as that used for the treatment of HIV infection, i.e. in adults, 2 tablets of lopinavir/ritonavir 200/50 mg twice daily for a total daily dose of 400/100 mg. The duration of treatment evaluated in the study was 14 days.

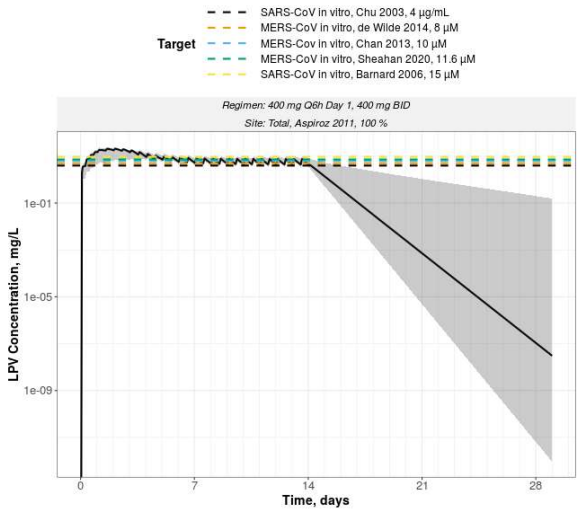
The study compared 99 patients receiving the same dosage against 100 symptomatic patients receiving standard therapy. The patients, all adult patients with confirmed CoV-2-SARS infection, were hypoxemic, i.e. SpO2 < 94%. The primary endpoint was clinical, i.e. time from

randomisation to improvement of at least 2 points on a 7-point ordinal scale, or hospital discharge if earlier. On this endpoint, the study showed no difference between the 2 groups of patients with a hazard ratio for clinical improvement of 1.24, 95% confidence interval [0.90, 1.72]. There were more gastrointestinal adverse events in the lopinavir/ritonavir group but more SAEs in the standard treatment arm. Treatment with lopinavir/ritonavir was discontinued due to AEs in 13 patients. The authors concluded that lopinavir/ritonavir therapy does not provide a benefit over standard therapy in patients hospitalised for a severe form of COVID-19.

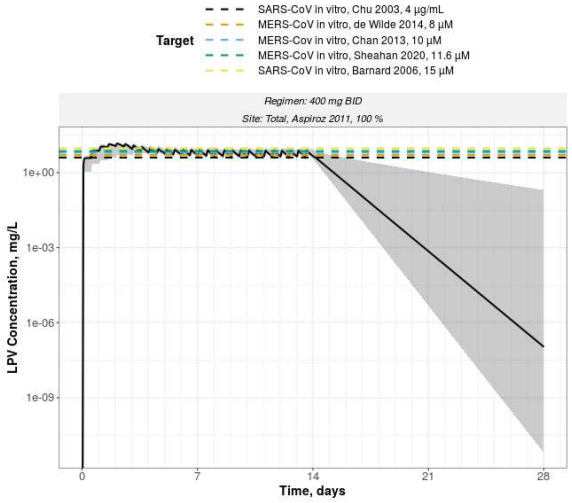
More recently, pharmacokinetic modelling assessing different lopinavir/ritonavir dose regimen was performed to identify one with the highest probability of rapidly reaching effective antiviral concentrations. For lopinavir, in the absence of human serum, the EC50 against HIV-1 ranges from 0.006 – 0.017 µg/mL, whereas in the presence of 50% human serum, the EC50 is approximately 10-fold higher (0.04 – 0.18 mcg/mL), representing the significant impact of plasma protein binding on potency. While published reports for SARS-CoV-2 are not available, in vitro potency for related coronaviruses are assumed to be similar. The published IC50s or EC50s in the absence of human serum (ie, unbound drug) for lopinavir for SARS or and MERS viruses has been reported to range from 4 to 15 µg/mL, Higher drug exposures and possibly a new dose regimen may be required to successfully treat coronaviruses with lopinavr / ritonavir in comparison with HIV.

The figures below illustrate the expected plasma concentration after either a dose of 400mg every 6 hours followed by daily regimen of 400mg bid (Panel A) or a regimen of 400mg bid daily (Panel B).

A regimen combining a loading dose of 1600 mg / 400 mg Day 1 followed by a total daily dose of 800 mg / 200 mg allows to reach the maximum expected concentrations after 24 hours, which are otherwise not reached before day 3 with the standard regimen. It is critical to reach therapeutic concentrations as early as possible and therefore the rationale for the selected dose regimen with a loading dose.

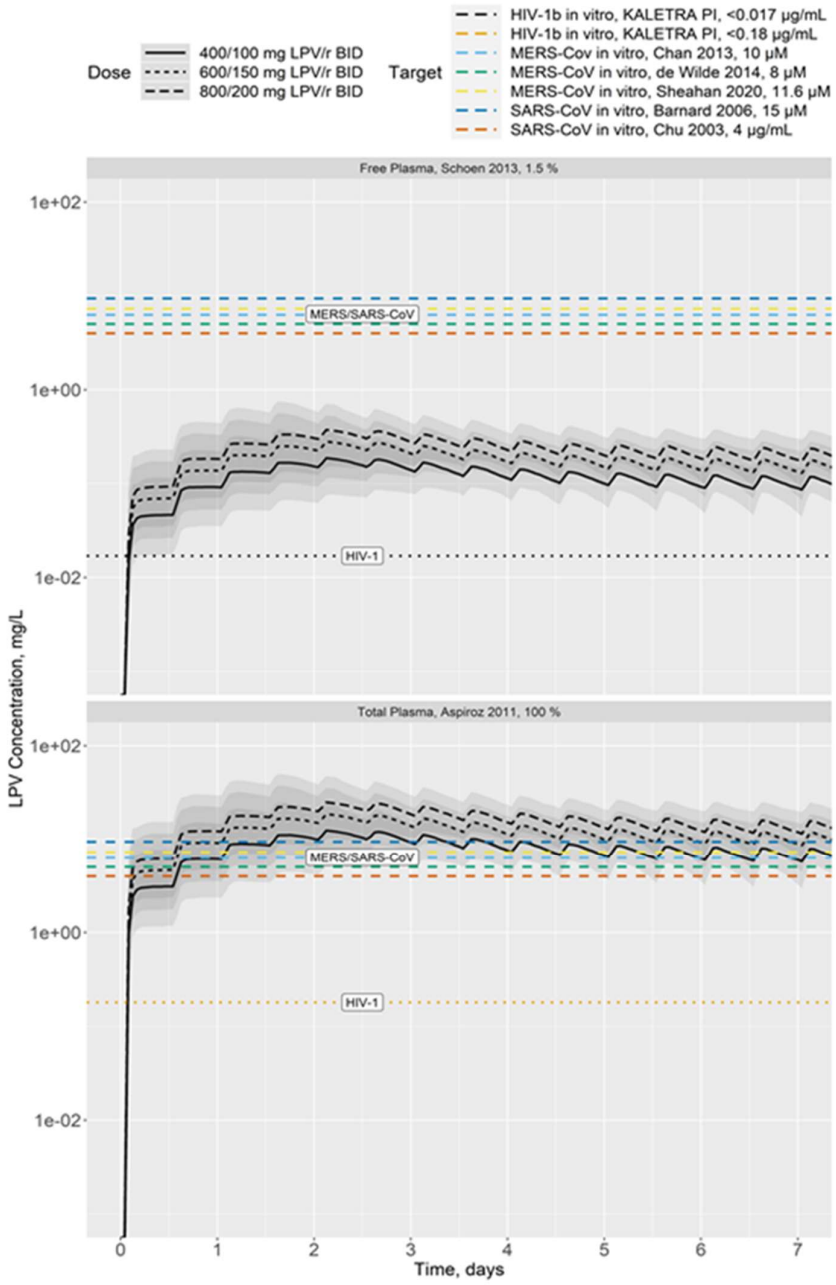


Panel A



Panel B

The last figure below shows the differences in time to reach the predicted exposure with the different regimen including the loading dose.



The proposed dose regimen is therefore 800 mg /200 mg bid on day 1 followed by 400 mg /100 mg/day bid from Day 2 to 14 included.

Risks Related to Lopinavir/Ritonavir[1]

The available safety data for lopinavir/ritonavir are those obtained in the treatment of HIV infection. The most frequent adverse effects are digestive disorders, primarily diarrhoea, nausea and vomiting, particularly at the start of treatment, and lipid abnormalities, including hypercholesterolemia and hypertriglyceridemia. Liver, pancreas and heart rhythm disorders are possible side effects.

Data (on file) after 3 days of 800 mg / 200 mg BID lopinavir/ritonavir administered in healthy normal volunteers showed more adverse events to be reported, especially gastrointestinal in nature whilst they tended to be of similar nature. Other AEs observed with a higher frequency were fatigue, hot flushes and headache. The dose of 800 mg / 200 mg has otherwise found to be well tolerated in single daily dose. Potentially clinically significant bilirubin increases were identified in 4 of the 8 subjects. No SAE was reported . Slightly higher increases than those observed after the standard regimen in QT interval were measured at Day 3. No subject experienced increase of more than 60 ms or a QT value higher than 500 ms.

It was therefore assessed that the expected benefit /risk balance of adding the loading dose would remain positive and justify this regimen to be tested for the treatment of SARS-CoV2 in symptomatic patients.

Prohibited Treatment with Lopinavir/Ritonavir[1]

Drug class	**Medicinal products within class**	**Rationale**
Increased levels of concomitant medicinal products		
Alpha$_1$-adrenoreceptor antagonist	Alfuzosin	Increased plasma concentrations of alfuzosin which may lead to severe hypotension. The concomitant administration with alfuzosin is contraindicated
Antianginal	Ranolazine	Increased plasma concentrations of ranolazine which may increase the potential for serious and/or life-threatening reactions
Antiarrhythmics	Amiodarone, dronedarone	Increased plasma concentrations of amiodarone and dronedarone. Thereby, increasing the risk of arrhythmias or other serious adverse reactions (
Antibiotic	Fusidic Acid	Increased plasma concentrations of fusidic acid. The concomitant administration with fusidic acid is contraindicated in dermatological infections
Anticancer	Neratinib	Increased plasma concentrations of neratinib which may increase the potential for serious and/or life-threatening reactions

	Venetoclax	Increased plasma concentrations of venetoclax. Increased risk of tumour lysis syndrome at the dose initiation and during the ramp-up phase
Anti-gout	Colchicine	Increased plasma concentrations of colchicine. Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment
Antihistamines	Astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine. Thereby, increasing the risk of serious arrhythmias from these agents
Antipsychotics/ Neuroleptics	Lurasidone	Increased plasma concentrations of lurasidone which may increase the potential for serious and/or life-threatening reactions
	Pimozide	Increased plasma concentrations of pimozide. Thereby, increasing the risk of serious haematologic abnormalities, or other serious adverse effects from this agent
	Quetiapine	Increased plasma concentrations of quetiapine which may lead to coma. The concomitant administration with quetiapine is contraindicated
Ergot alkaloids	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Increased plasma concentrations of ergot derivatives leading to acute ergot toxicity, including vasospasm and ischaemia
GI motility agent	Cisapride	Increased plasma concentrations of cisapride. Thereby, increasing the risk of serious arrhythmias from this agent
Hepatitis C virus direct acting antivirals	Elbasvir/grazoprevir	Increased risk of alanine transaminase (ALT) elevations
	Ombitasvir, paritaprevir, ritonavir with or without dasabuvir	Increased plasma concentrations of paritaprevir; thereby, increasing the risk of ALT elevations
Lipid-modifying agents HMG Co-A Reductase Inhibitors	Lovastatin, simvastatin	Increased plasma concentrations of lovastatin and simvastatin; thereby, increasing the risk of myopathy including rhabdomyolysis
Microsomal triglyceride transfer protein inhibitor	Lomitapide	Increased plasma concentrations of lomitapide

Phosphodiesterase (PDE5) inhibitors	Avanafil	Increased plasma concentrations of avanafil
	Sildenafil	Contraindicated when used for the treatment of pulmonary arterial hypertension only. Increased plasma concentrations of sildenafil. Thereby, increasing the potential for sildenafil-associated adverse events (which include hypotension and syncope).
	Vardenafil	Increased plasma concentrations of vardenafil
Sedatives, hypnotics	Oral midazolam, triazolam	Increased plasma concentrations of oral midazolam and triazolam. Thereby, increasing the risk of extreme sedation and respiratory depression from these agents. For caution on parenterally administered
Decreased levels of lopinavir/ritonavir		
Herbal products	St. John's wort	Herbal preparations containing St John's wort (*Hypericum perforatum)* due to the risk of decreased plasma concentrations and reduced clinical effects of lopinavir and ritonavir

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Appendix 1.3 Paracetamol

Paracetamol

General information on paracetamol is presented in Table 7.

Table 7. General Information on Paracetamol

International Non-proprietary Name	Paracetamol
Dosage Form	Tablets containing 500 mg of paracetamol
Route of administration	Oral route
Dosing instructions	One to two tablets every 4-6 hours as required, to a maximum of 6 tablets (3 grams) daily in divided doses
Duration of treatment	Up to 14 days
Composition	Capsules or white, uncoated tablets. Containing: 500 mg paracetamol PhEur Excipients: maize starch, pregelatinized maize starch, stearic acid

Rationale for Choice of Paracetamol

Paracetamol will be used as the reference standard of care in the primary comparison. It will be investigated when used alone and when added to all patients requiring symptomatic treatment for fever and pain in all treatment arms. The maximum dose will be 3 grams per day in adults.

Risks Related to Paracetamol[1]

Adverse effects related to paracetamol are rare, however hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia, neutropenia, pancytopenia, leukopenia and agranulocytosis but these were not necessarily causality related to paracetamol. Very rare cases of serious skin reactions have been reported.

Prohibited Treatment with Paracetamol[1]

Anticoagulants the effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding. Occasional doses have no significant effect.

Metoclopramide may increase speed of absorption of paracetamol.

Domperidone may increase speed of absorption of paracetamol.

Cholestyramine may reduce absorption if given within 1 hour of paracetamol.

Concomitant regular paracetamol use should be avoided or restricted in patients treated with imatinib.

References

1. Summary of Product Characteristics, paracetamol.

Appendix 2. Immunological Study

To be added if applicable.

Appendix 3. Epidemiological Study

To be added if applicable.

Appendix 4. Schedule of Events

Table 8. Schedule of Events in Master Study

	Screening	Monitoring				
Time (and window, if allowed)	**Day 0**	**Day 1[C]**	**Days 2-6, 8-13 and 15-20[A]**	**Days 7 and 14**	**Day 21**	**Unscheduled**
Patient information and informed consent	X					
Demographic data	X					
Medical history	X					
Urine Pregnancy test	X					
Review inclusion and non-inclusion criteria[1]	X	X				
Collection of COVID-19 symptoms	X			X	X[B]	X
Physical examination[2]		X		X	X[B]	X
Height, weight and body-mass index	X					
Vital signs[3]	X	X		X	X[B]	X
Blood oxygen saturation level (SpO2)	X	X		X	X[B]	X
mMRC Dyspnoea Scale		X		X	X[B]	X
WHO Clinical progression Scale		X		X	X[B]	X
Hospitalisation for aggravation COVID-19				X	X[B]	
ECG	X			X[4]	X[4 B]	X
Blood sampling for laboratory tests[4]	X			X	X[B]	X
Chest x-ray[4]	X			X	X[B]	X
CT-scan[4]	X			X	X[B]	X
Questionnaire on warning signs			X			
Randomisation		X				
Start of IP administration		X				

	Screening	Monitoring				
Time (and window, if allowed)	**Day 0**	**Day 1[C]**	**Days 2-6, 8-13 and 15-20[A]**	**Days 7 and 14**	**Day 21**	**Unscheduled**
Check treatment compliance				X	X [B]	X
Adverse event monitoring	X	X		X	X [B]	X
Review concomitant treatments	X	X		X	X [B]	X
Patient status[5]					X	

[A] Visits via telephone interview and/or telephone application
[B] Day 21 is end-of-study visit or in the event of early withdrawal from the study (to be conducted as soon as possible after withdrawal)
[C] Day 1 assessments and treatment could be performed at Day 0
[1] Including result for COVID-19 screening test, which must be performed within 24 hours prior to screening
[2] Physical examination to include chest examination (auscultation)
[3] Vital signs to include respiratory rate, blood pressure, heart rate and temperature
[4] Optional, performed at investigational centres equipped to do tests and that do them as routine measures for patients with COVID-19.
[5] Only in patients withdrawn before Day 21. In patients who withdraw early, this is the only assessment performed on Day 21. May be performed on-site or by telephone.

Appendix 5. Country Specific

To be added if applicable.