

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 –Uganda Ifakara Health Institute –Tanzania Inserm /ARNS – Burkina Faso, Guinea Institute of Tropical Medicine – Ethiopia ISGlobal – Mozambique Ministère de la Santé et des Affaires Sociales - Mali
Study Protocol Version/Date	Version 13 dated 21 October 2021, including Amendment 03

Important Information:

This is a Multi-centre Study with a Master Protocol describing the research aims and methods that will be utilised. The study will be conducted in several countries by different sponsors.

DNDi will coordinate activities of the Master study.

All Sponsors will submit this ANTICOV 01 COV Master protocol in their countries. Treatment arms as well as country specificities will be described in the Appendices Appendix 1 and Appendix 5 (or country specific format), respectively.

Additional countries may be selected to participate in ANTICOV to support recruitment. Countries currently on stand-by may be activated if changes in the epidemiological situation in-country justifies this decision. Such decision will be made by the ANTICOV Consortium Joint Steering Committee.

Information highlighted in yellow needs to be updated by each Sponsor.

The Clinical trial application of this protocol was processed via AVAREF (The African Vaccine Regulatory Forum) procedures and the protocol was reviewed during joint review meetings with the Ethics Committees and Regulatory authorities of the countries involved in this project.

Each Ethics Committees and Regulatory authorities will approve the clinical trial application in their respective country.

The WHO-ERC also reviewed the protocol and approved this version on 24 November 2020. The approval does not apply to countries who initiated the trial before this date (DRC, Kenya, Ghana).

The WHO ERC reviewed this protocol amendment and approved version 7.1 on 6 January 2021, included in this Version 9.0.

The WHO ERC reviewed this protocol amendment 2 and approved version 10.0 on 30 April 2021, included in this Version 11.0.

The WHO ERC reviewed this protocol amendment 3 and approved version 13.0 on 28 October 2021

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	<p>The secondary objectives are:</p> <ul style="list-style-type: none"> • 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 rate of hospitalisations for other reason than 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 $SpO_2 \leq 93$ in 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	<p><i>Inclusion Criteria</i></p> <ol style="list-style-type: none"> 1. Male or female patients, 2. Patients at risk defined as either: Adults ≥ 18 years of age at the time of screening AND having History of one or more of the following risk factors at screening as evidenced by previous medical records: Diabetes and/or heart diseases and/or chronic renal disease and/or Chronic Obstructive Pulmonary disease and/or cerebrovascular diseases and/or judged to be over or under weight with BMI > 25 or ≤ 16 OR Male or female patients ≥ 60 years of age without any co-morbidity. Or Pregnant women Children > 12 years of age may be included if recommended by the DSMB after the interim analyses 3. COVID-19 confirmed by molecular biology or validated antigenic test available in the country for SARS-Cov2 according to national guidelines, based on result within 24 hours prior to screening and maximum 2 days after sampling. 4. Viral syndrome with or without uncomplicated pneumonia, defined as blood oxygen saturation level (SpO₂) $\geq 94\%$. 5. Criteria removed due to removal of hydroxychloroquine and lopinavir / ritonavir arms. 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. <p><i>Non-inclusion Criteria</i></p> <ol style="list-style-type: none"> 1. Abnormal physical examination findings: <ol style="list-style-type: none"> 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.
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	<p>d. recurrent diarrhoea or vomiting episodes (> 3 in the last 24 hours) or hypokalaemia (< 3.5 mmol/L).</p> <ol style="list-style-type: none"> 2. Criteria removed due to removal of hydroxychloroquine and lopinavir / ritonavir arms. 3. Feeling unwell for more than 7 days prior to screening. 4. Criteria removed due to removal of hydroxychloroquine and lopinavir / ritonavir arms. 5. Criteria removed due to removal of hydroxychloroquine and lopinavir / ritonavir arms. 6. Criteria removed due to removal of hydroxychloroquine and lopinavir / ritonavir arms. 7. Criteria removed due to removal of hydroxychloroquine and lopinavir / ritonavir arms. 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. Criteria removed due to removal of hydroxychloroquine and lopinavir / ritonavir arms. 10. Criteria removed due to removal of hydroxychloroquine and lopinavir / ritonavir arms. 11. Criteria removed due to removal of hydroxychloroquine and lopinavir / ritonavir arms. 12. Criteria removed due to removal of hydroxychloroquine and lopinavir / ritonavir arms. 13. Criteria removed due to removal of hydroxychloroquine and lopinavir / ritonavir arms. 14. On-going treatment at screening with <ul style="list-style-type: none"> • Chronic systemic glucocorticosteroid > 40 mg daily • immunosuppressive treatment; 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 or cannot use an inhalation chamber. 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.
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	<p>19. Known pulmonary arterial hypertension (PAH) or fibrosis.</p> <p>20. Use of concomitant medications that are contraindicated with ciclesonide, known hypersensitivity to ciclesonide or any other ingredient in the formulation.</p> <p>21. Known hypersensitivity to nitazoxanide or any other ingredient in the formulation.</p> <p>22. Use of concomitant medication that are contraindicated with ASAQ and/or known hypersensitivity to ASAQ or any other ingredient in its formulation</p> <p>23. Use of concomitant medication that are contraindicated with IVM and/or known hypersensitivity to IVM or any other ingredient in its formulation</p> <p>24. Previous haematological event during treatment with amodiaquine,</p> <p>25. Patients living in a <i>Loa loa</i> endemic region unless they have a negative test for <i>Loa loa</i> at screening (IVM)</p> <p>26. Prior treatment with IVM within 6 months prior to screening</p> <p>27. Patients vaccinated against SARS CoV-2</p> <p>28. Known macular degeneration, or other known retinal diseases, or 4-aminoquinolone-induced visual impairment (ASAQ)</p> <p>29. Known cirrhosis and/or jaundice due to IVM and amodiaquine</p> <p>30. Known renal impairment as clinically assessed or by blood analysis if available (ASAQ)</p> <p>31. Currently receiving, or recently received (within 30 days prior to randomization) treatment with any antimalarial drug (ASAQ)</p> <p>32. Pregnancy based on urine pregnancy test at screening or breast feeding for the ivermectin/ASAQ arm.</p> <p>33. Use of concomitant medications that are contraindicated with fluoxetine, known hypersensitivity to fluoxetine or any other ingredient in the formulation.</p> <p>34. Use of concomitant medications that are contraindicated with budesonide, known hypersensitivity to budesonide or any other ingredient in the formulation.</p> <p>35. Patients with known suicidal ideation, severe psychiatric disorders or major uncontrolled depression or controlled with any of the prohibited drugs (see appendix 1.4) (fluoxetine)</p> <p>36. History of known severe ventricular cardiac arrhythmia (ventricular tachycardia, patients with ventricular fibrillation recovered) or Long QT Syndrome (fluoxetine)</p>
Study Design	Multicentre, randomised, open-label, adaptative master protocol / platform study

Data and Safety Monitoring Board	For this study, the DSMB members were selected by the ANTICOV Consortium JSC based on a set of criteria as defined in the protocol. 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, adaptive platform trial design, bayesian statistical methods and analysis, and ethics. 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 $\text{SpO}_2 \leq 93\%$ within 21 days after randomisation to treatment, including death for any reason
Secondary Endpoints	<p>The secondary endpoints are:</p> <ul style="list-style-type: none"> • 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 $\text{SpO}_2 \geq 94\%$ at Day 21 and no hospitalisation for COVID-19 • Occurrence of death • Time to worsening of $\text{SpO}_2 \leq 93\%$ within 21 days • Failure rate for each study arm • Occurrence of $\text{SpO}_2 \leq 93\%$ or death or hospitalisation due to COVID-19 • Sub-group analysis of failure rate for each study arm
Sample Size Calculation	<p>The maximum sample size of 700 per arm was determined by clinical trial simulation. The simulation was carried out for a study evaluating four 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 assumption was to apply a lower rate of progression (10%) than the one observed in other regions of the world (reported to be around 20%), especially due to the younger population. By lowering the threshold, this would better reflect the expected proportion of patients that would worsen. This increased the sample size in comparison with a 20% hypothesis.</p> <p>If it is a recommendation from DSMB to include adolescents as well as younger children, we may indeed need to re-assess and increase the sample size (the protocol will be amended accordingly).</p>

	<p>The simulated trial design began with an initial “burn-in” period, during which patients were allocated in a fixed ratio of 3:2:2:2 among the four treatment arms, until 300 patients had been randomised. After the initial interim analysis, allocation will depend on the available arms at each site. The control arm will receive a fixed allocation probability of $1/K$, where K is the total number of arms enrolling participants in the platform including control (e.g. $K = 4$ for control and three active interventions), subject the maximal sample size of $N=700$ patients on paracetamol. The remaining $(K-1)/K$ allocation probability will be divided among the active intervention arms. Let these allocation probabilities be denoted by q_a, where $a = 0$ corresponds to the control arm and $a > 0$ corresponds to active intervention arms. The RAR probabilities for the intervention arms ($q_a, a > 0$) will be proportional to the Bayesian posterior probability that a given intervention is superior to control, $Pr(\text{superiority})_a$. The set of randomization probabilities sums to 1. If paracetamol has reached its maximal sample size, then the allocation probability for paracetamol will be reallocated proportionally to the remaining arms in the study. This allocation will be renormalized as needed if certain arms are not enrolling at certain sites, including the control. See the adaptive design report for details.</p> <p>After the initial interim analysis, subsequent interim analyses will be conducted after every 450 patients are enrolled and, at each interim analysis, study design included early stopping rules for futility or success.</p> <p>We determine the probability of super-superiority of 0.3151 on the log odds scale, a difference corresponding to the difference between 10% and 7.5%. Showing superiority to this degree typically requires data closer to the difference between 10% and 5%. An intervention arm is halted at the interim analysis for early success if $Pr(\text{super-superiority})_a > 0.98$. An intervention satisfying this criterion has demonstrated clinically meaningful benefit with accumulating trial data. An intervention arm is halted at the interim analysis for early futility if $Pr(\text{super-superiority})_a < 0.10$ for failure to provide evidence of clinically meaningful benefit with accumulating trial data.</p> <p>If an arm reaches its maximum sample size, the final analysis for that arm will occur at the first interim analysis after full followup on that arm is complete. Efficacy will be declared if the posterior probability of superiority exceeds 98.5% (this value accounts for the multiple interim analyses in order to obtain overall 2.5% type I error).</p> <p>Using this design and specific criteria for demonstrating efficacy, simulations demonstrated control of the type I error rate at 2.5% and the trial design achieved a power of 85% to demonstrate a decrease in</p>
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	<p>the rate of progression to severe disease in one of the active arms from the control rate of 10% to 5%. 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.</p> <p>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 and maintained 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.</p>
Statistical Analyses	<p>The following populations will be used in the statistical analyses.</p> <ul style="list-style-type: none"> • 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 <p><i>Efficacy Analyses</i></p> <p>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.</p> <p>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</p>

	<p>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.</p> <p><i>Safety Analysis</i></p> <p>AEs will be analysed both by ITT and by treatment received, in the Safety Population. Comparisons of rates of AEs will be presented descriptively.</p> <p>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</p>
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List of Abbreviations

AE	adverse event
ASAQ	Artesunate amodiaquine
ASM	Acid Sphingomyelinase
BP	blood pressure
BMI	Body mass index
CNS	Cerebral Nervous System
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
ICU	Intensive Care Unit
IDDO	Infectious Diseases Data Observatory
IP	investigational product
ITT	intent-to-treat (population)
IVM	Ivermectin
MAOI	Monoamine inhibitor oxidase
MERS-CoV	Middle East respiratory syndrome-related coronavirus
MedDRA	Medical Dictionary for Regulatory Activities
MRC	Medical Research Council
NGO	Non governmental organisation
PAR	Paracetamol
PCR	polymerase chain reaction
PP	per protocol
PPE	Personnel Protection Equipment
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
SSRI	Selective Serotonin Reuptake Inhibitor
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. $\text{SpO}_2 \geq 94\%$, crackles on auscultation, irregular breathing difficulties but respiratory rate $< 25/\text{min}$;
- moderate to severe pneumonia with $\text{SpO}_2 \leq 93\%$, with or without mental confusion, with or without respiratory rate $\geq 25/\text{min}$, with or without BP $< 90/60\text{mm Hg}$.

The primary endpoint ($\text{SpO}_2 < 93\%$ on repeated measurement within 21 days after randomisation of treatment) is based on the experience of the African investigators actively involved in the COVID response, pulmonary complication remains the most common critical one, the most measurable one and the one responsible for the majority of hospitalisations. Death for any reason was added as a coprimary endpoint.

In order not to miss other reasons for hospitalisation, all cases of hospitalisation will be reported and compared between treatment arms, as secondary objectives. We may learn on the disease progression in the African context, and in a younger population.

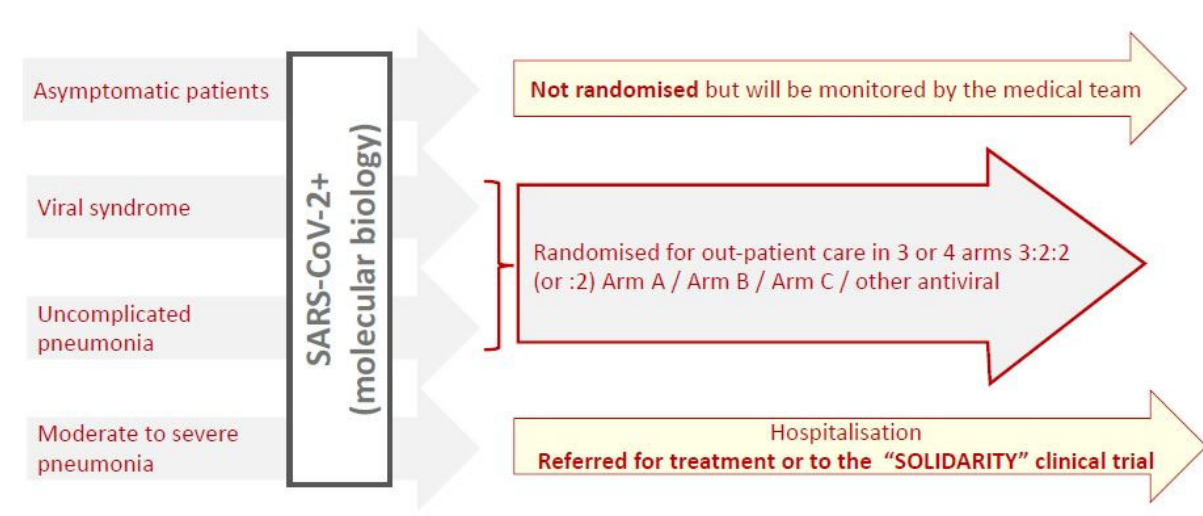
All patients will be tested for the presence of SARS-CoV-2 using the available molecular assay or validated antigenic test.

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*.

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

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 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 or validated antigenic test 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 whilst 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 Randomised 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 of 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 perspective 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.

Based on WHO guidelines released on 18 December 2020 and following DSMB recommendations, the hydroxychloroquine and lopinavir/ritonavir arms were dropped from the protocol.

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
<i>Primary</i>	
<ul style="list-style-type: none"> To compare the efficacy of alternative treatment strategies versus control on the risk of progression to severe respiratory disease 	<ul style="list-style-type: none"> 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.
<i>Secondary</i>	
<ul style="list-style-type: none"> To compare the safety of each study arm to control, up to Day 21 of follow-up 	<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> To compare the rate of hospitalisations[§] due to COVID-19 in each study arm versus control 	<ul style="list-style-type: none"> Number of hospitalisations due to severe progression

Objectives	Endpoints
<ul style="list-style-type: none"> To compare the time to hospitalisation due to COVID-19 in each study arm versus control To compare the rate of hospitalisations for other reason than Covid-19 in each study arm versus control To compare the disease-free rate in each study arm versus control 	<ul style="list-style-type: none"> Time to hospitalisation Number of hospitalisations due to other reason than progression of Covid-19 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
<ul style="list-style-type: none"> To compare the death rate in each study arm versus control To compare time to worsening of SpO₂ ≤ 93 in each study arm versus control To compare the capacity to prevent severe progression between study arms To identify risk factors for severe progression 	<ul style="list-style-type: none"> Occurrence of death Time to worsening of SpO₂ ≤ 93 within 21 days Failure rate for each study arm (see Primary Endpoint) Occurrence of SpO₂ ≤ 93 or death or hospitalisation due to COVID-19
<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Sub-group analysis of failure rate for each study arm

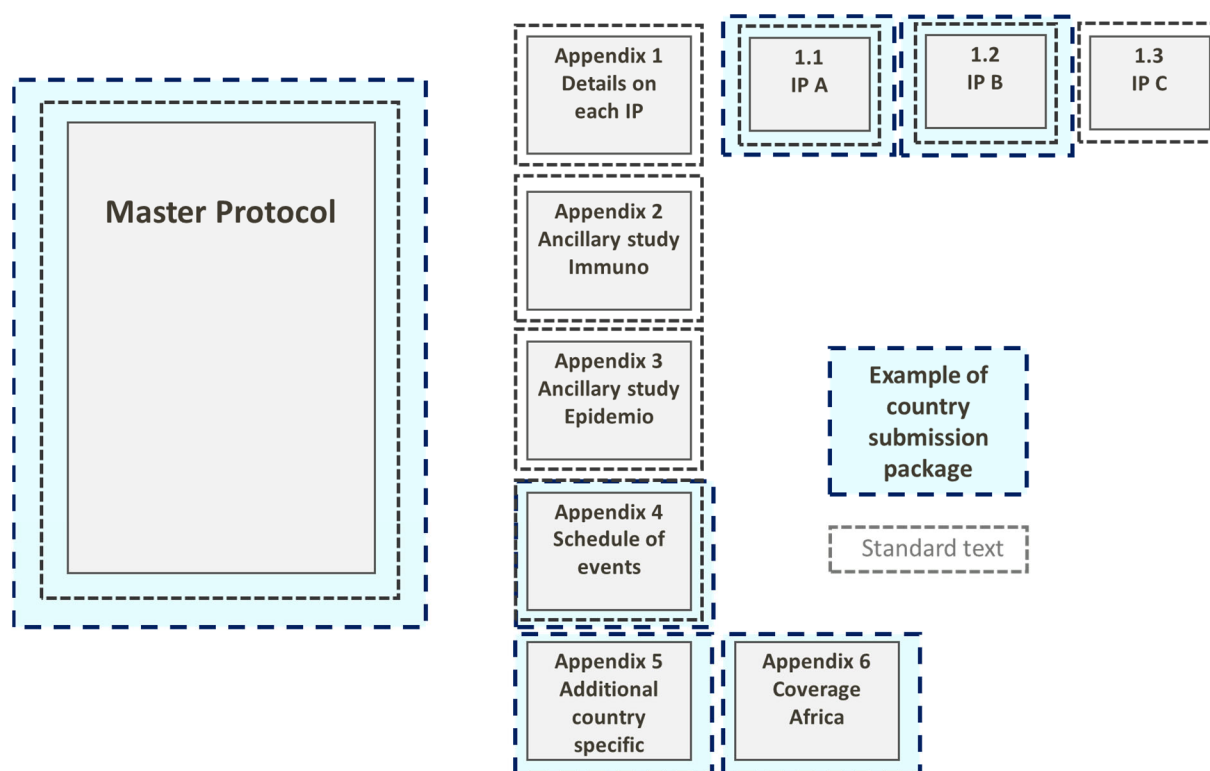
§Hospitalisation is defined as worsening of Covid 19 Symptoms and not related to isolation/quarantine of Covid 19 patients at hospitals. Country and Site-specific random effects will be included in the modelling to account for differences among nations.

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.

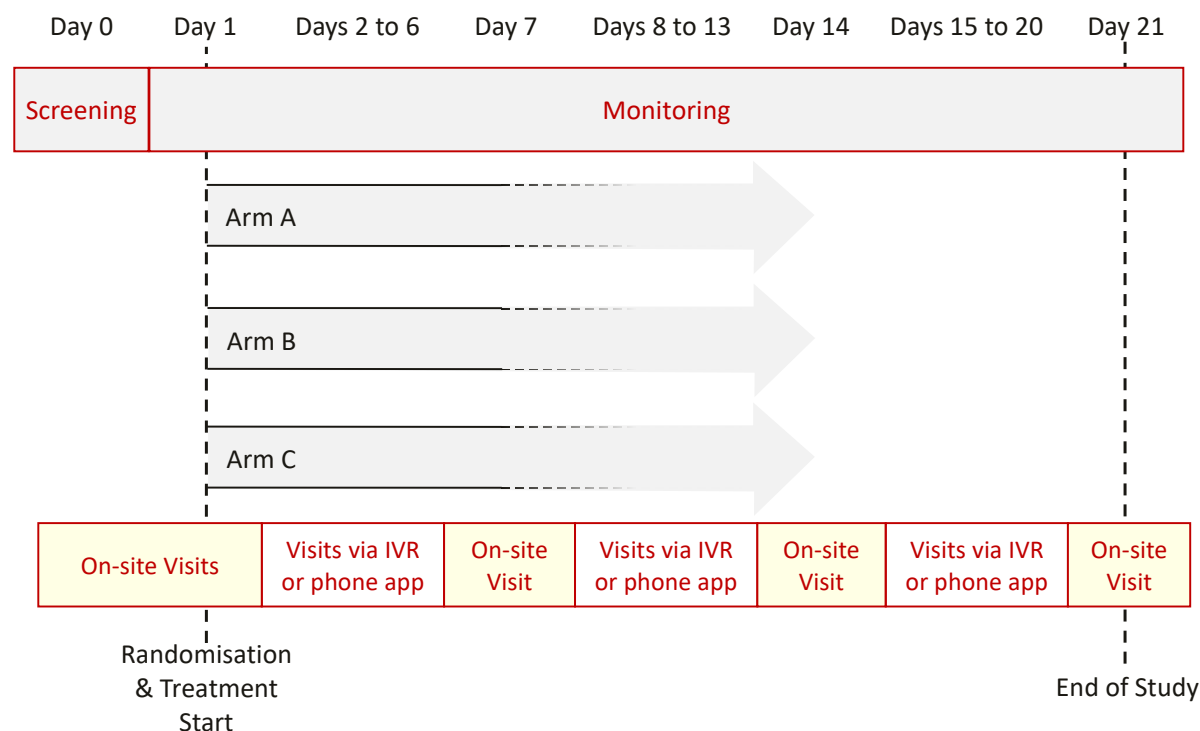
The study will begin with unbalanced randomisation of participants 1:1:1 to a control arm, paracetamol alone, and to two test arms (see Study Flowchart in Figure 3). If paracetamol cannot be administered as a control arm in some countries, patients will only be randomised (with equal probability) to 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 questionnaires using an electronic 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).

Pregnant or breast feeding women will be randomized only in the treatment arms without contraindication for pregnancy and breast feeding (see inclusion / exclusion criteria, section 4.1, and Appendix 1).

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 7 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 (Immunology, Epidemiology and Coverage Africa) 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. Patients at risk defined as either:

Adults ≥ 18 years of age at the time of screening AND having History of one or more of the following risk factors at screening as evidenced by previous medical records:
Diabetes and/or heart diseases and/or chronic renal disease and/or Chronic

Obstructive Pulmonary disease and/or cerebrovascular diseases and/or judged to be overweight or underweight with BMI > 25 or ≤ 16

OR

Male or female patients ≥ 60 years of age without any co-morbidity.

Or

Pregnant women

Children > 12 years of age may be included if recommended by the DSMB after interim analyses.

3. COVID-19 confirmed by molecular biology or validated antigenic test available in the country for SARS-Cov2 according to national guidelines, based on result within 24 hours prior to screening and maximum 2 days after sampling.
4. Viral syndrome with or without uncomplicated pneumonia, defined as blood oxygen saturation level (SpO₂) ³ 94%.
5. Criteria removed due to removal of hydroxychloroquine and lopinavir / ritonavir arms.
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. Criteria removed due to removal of hydroxychloroquine and Lopinavir/Ritonavir.
3. Feeling unwell for more than 7 days prior to screening.
4. Criteria removed due to removal of hydroxychloroquine and Lopinavir/Ritonavir.
5. Criteria removed due to removal of hydroxychloroquine and lopinavir / ritonavir arms..
6. Criteria removed due to removal of hydroxychloroquine and lopinavir / ritonavir arms.
7. Criteria removed due to removal of hydroxychloroquine and lopinavir / ritonavir arms.
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. Criteria removed due to removal of hydroxychloroquine and lopinavir / ritonavir arms.
10. Criteria removed due to removal of hydroxychloroquine and lopinavir / ritonavir arms..
11. Criteria removed due to removal of hydroxychloroquine and lopinavir / ritonavir arms..
12. Criteria removed due to removal of hydroxychloroquine and lopinavir / ritonavir arms.
13. Criteria removed due to removal of hydroxychloroquine and lopinavir / ritonavir arms..

14. On-going treatment at screening with:
 - systemic glucocorticosteroid > 40 mg daily;
 - immunosuppressive treatment;
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 or cannot use an inhalation chamber.
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
19. Known pulmonary arterial hypertension (PAH) or fibrosis
20. Use of concomitant medications that are contraindicated with ciclesonide, known hypersensitivity to ciclesonide or any other ingredient in the formulation,
21. Known hypersensitivity to nitazoxanide or any other ingredient in the formulation
22. Use of concomitant medication that are contraindicated with ASAQ and/or known hypersensitivity to ASAQ or any other ingredient in its formulation
23. Use of concomitant medication that are contraindicated with IVM and/or known hypersensitivity to IVM or any other ingredient in its formulation
24. Previous haematological event during treatment with amodiaquine,
25. Patients living in a *Loa loa* endemic region unless they have a negative test for *Loa loa* at screening (IVM)
26. Prior treatment with IVM within 6 months prior to screening
27. Patients vaccinated against SARS CoV-2
28. Known macular degeneration, or other known retinal diseases, or 4-aminoquinolone-induced visual impairment (ASAQ)
29. Known cirrhosis and/or jaundice due to IVM and amodiaquine
30. Known renal impairment as clinically assessed or by blood analysis if available (ASAQ)
31. Currently receiving, or recently received (within 30 days prior to randomization) treatment with any antimalarial drug (ASAQ)
32. Pregnancy based on urine pregnancy test at screening or breast feeding for the ivermectin/ASAQ arm.
33. Use of concomitant medications that are contraindicated with fluoxetine, known hypersensitivity to fluoxetine or any other ingredient in the formulation.
34. Use of concomitant medications that are contraindicated with budesonide, known hypersensitivity to budesonide or any other ingredient in the formulation.
35. Patients with known suicidal ideation, severe psychiatric disorders or major uncontrolled depression or controlled with any of the prohibited drugs (see appendix 1.4) (fluoxetine)
36. History of known severe ventricular cardiac arrhythmia (ventricular tachycardia, patients with ventricular fibrillation recovered) or Long QT Syndrome (fluoxetine).

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).

The first two treatment arms to be tested in this study are Hydroxychloroquine Sulphate and/or Lopinavir/Ritonavir which were selected based on (i) the *in vitro* evidence of their potential activity against SARS-CoV-2 (ii) their well-known safety in another indication (iii) their ability to be manufactured at scale and at an affordable cost, and (iv) to provide scientific evidence on their activity in **mild** and **non-hospitalised** patients. This study would have provided rapid evidence in favour or against their use in non-hospitalised Covid-19 patients, especially in Africa where no study has been conducted yet with these two treatments in this patient population.

Based on WHO guidelines released on 18 December 2020 and recommendations from the DSMB, the hydroxychloroquine and lopinavir / ritonavir arms were definitively dropped from the protocol in January 2021.

The rationale for the selection of new therapeutic options will be based on the same criteria as described above with an emphasis on the preclinical evidence of efficacy (for example the antiviral activity of compounds in the recent Syrian hamster model) or clinical evidence from PoC antiviral studies, as well as modelling data supporting the best dose regimen. For compounds having a different mode of action (non antiviral) the scientific rationale for selection will be adapted. The new products with credible PoC data will also be evaluated.

New treatment arm and all information and requirements related to this arm, will be added in a Protocol Amendment and submitted for approval to Ethical Committees and Regulatory Authorities in each applicable country.

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 Scaling-up the Diagnostic testing in the countries

The current COVID-19 pandemic is creating lot of challenges for the LMICs who need to prioritise testing for severe cases. Today, the testing capacity is widely disparate between HICs and LMICs and even within LMICs with testing per population that can range from 2/100,000 to > 1000/100,000. In order to support them in the early identification of cases, this effort we will collaborate with the FIND NGO to procure additional amount of Ag - based RDTs (listed in the WHO emergency use listed products) and extend testing to all patients with symptoms (mild, moderate and severe) where acceptable locally¹⁴ (The test selected for use in a specific country will need to be recognized by local authorities as a valid diagnostic).

The data regarding the number of tests done and positive and negative case frequency will be aggregated by site and shared with FIND, which will give them a better insight of the situation in the ANTICOV countries. No individual data will be transferred to FIND. All individual positive cases will be managed as per the local covid 19 policies, and such data will not be transferred to FIND.

6.3 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.

6.3.1 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) for non pregnant woman with childbearing potential
- Pregnancy status (and assessment of gestational weeks)
- 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/mm³;
 - 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 6.4.1.1)
- ECG (optional unless if ECG will be performed at follow-up visits see Section 6.4.3.3)
- Blood sample collection for laboratory tests (optional unless if blood sample will be collected at follow-up visits) - see Section 6.4.2.2)
- 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 6.4.3.4)
- CT-scan (optional unless if CT-scan will be performed at follow-up visits - see Section 6.4.3.5)
- Collection of vital signs (see Section 6.4.3.2)
- Collection of symptoms compatible with COVID-19 (see Section 6.4.1.4)
- Collection of adverse events
- Collection of concomitant treatments

6.3.2 Day 1 (can be performed 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 6.4.3.1)
- Collection of vital signs (see Section 6.4.2.1.7)
- Blood oxygen saturation level (SpO₂) (see Section 6.4.1.1)
- mMRC Dyspnoea Scale (see Section 6.4.1.26.4.1.2)
- WHO Clinical progression scale (see Section 6.4.1.3)
- Collection of concomitant treatments
- Collection of adverse events
- Randomisation
- Start of IP administration

6.3.3 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 6.4.1.5)

6.3.4 Days 7 and 14

The following procedures and data collection will be performed:

- Physical examination (see Section 6.4.3.1)
- Hospitalisation due to aggravation of COVID-19, including hospitalisation's reason as described below
 - Request of mechanical ventilation and/or Intensive Care Unit (ICU)
 - Non-ICU hospitalisation, requiring supplemental oxygen
 - Non-ICU hospitalisation, not requiring supplemental oxygen
- Hospitalisations not due to aggravation of COVID-19
- Collection of vital signs (see Section 6.4.3.2)
- Collection of symptoms compatible with COVID-19 (see Section 6.4.1.4)
- Blood oxygen saturation level (SpO₂) (see Section 6.4.1.1)
- mMRC Dyspnoea Scale (see Section 6.4.1.2 6.4.1.2)
- WHO Clinical progression scale (see Section 6.4.1.3)
- Blood sample collection for laboratory tests (optional - see Section 6.4.2.2)
- Chest x-ray (optional - see Section 6.4.3.4)
- CT-scan (optional - see Section 6.4.3.5)
- ECG (optional - see Section 6.4.3.3)
- Check treatment compliance
- Collection of adverse events
- Collection of concomitant treatments

6.3.5 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 withdraw from the study prematurely:

- Physical examination
- Hospitalisation due to aggravation of COVID-19, including hospitalisation's reason as described below
 - Request of mechanical ventilation and/or Intensive Care Unit (ICU)
 - Non-ICU hospitalisation, requiring supplemental oxygen
 - Non-ICU hospitalisation, not requiring supplemental oxygen
- Hospitalisations not due to aggravation of COVID-19
- Collection of vital signs (see Section 6.4.3.2)
- Blood oxygen saturation level (SpO₂) (see Section 6.4.1.1)
- Collection of symptoms compatible with COVID-19 (see Section 6.4.1.4)
- mMRC Dyspnoea Scale (see Section 6.4.1.26.4.1.2)
- WHO Clinical progression scale (see Section 6.4.1.30)
- Blood sample collection for laboratory tests (optional - see Section 6.4.2.2)
- Chest x-ray (optional - see Section 6.4.3.4)
- CT-scan (optional - see Section 6.4.3.5)
- ECG (optional - see Section 6.4.3.3)
- Check treatment compliance
- Collection of adverse events
- Collection of concomitant treatments/procedures

For patients who 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.

6.3.6 Day 35 call

Site to call the patients to report any SAEs and/or pregnancy.

6.4 Description of Study Assessments

6.4.1 Efficacy Assessments

6.4.1.1 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 or equal 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.

A study specific work instruction has been developed, based on WHO's guidance, and will be provided to all sites to explain how oximeter should be used to avoid accuracy issues.

6.4.1.2 Modified MRC Dyspnoea Scale

The modified Medical Research Council (mMRC) Dyspnoea Scale will be used to assess respiratory status.^{adapted from 15} 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

6.4.1.3 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, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	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, pO_2 : partial pressure of oxygen, SpO_2 : oxygen saturation, *if hospitalized for isolation only, record status as for ambulatory patient

Note: For score=1, we will only consider the asymptomatic status as PCR is not expected to be performed for viral load measure during the study.

6.4.1.4 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
<i>Fever</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes / / 2020
<i>Cough</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes / / 2020
<i>Shortness of breath</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes / / 2020
<i>Sore throat</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes / / 2020
<i>Runny nose (rhinorrhoea)</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes / / 2020
<i>Loss of smell (Anosmia)</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes / / 2020
<i>Loss of taste (Ageusia)</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes / / 2020
<i>Muscle aches (myalgia)</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes / / 2020
<i>Diarrhoea</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes / / 2020
<i>Vomiting / Nausea</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes / / 2020
<i>Headache</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes / / 2020
<i>Fatigue / Malaise</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes / / 2020
<i>Skin rash</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes / / 2020
<i>Conjunctivitis</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes / / 2020

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

6.4.2 Safety Assessments

6.4.2.1 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 6.4.2.1.2). 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 6.4.2.1.3), and a causality (see Section 6.4.2.1.3) assessment of each AEs with each IP will be described.

6.4.2.1.1 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.

6.4.2.1.2 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 (i.e. social distancing), 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). Hospitalisation in Intensive Care Unit (ICU) and/or start of mechanical ventilation MUST be considered as serious and reported as a SAE.
- 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.

6.4.2.1.3 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.

6.4.2.1.4 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".

6.4.2.1.5 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. SAE data will be entered into the central clinical DB and reconciliation will be done against each sponsor PV systems. Line listings and reports will be provided to the DSMB by the Data Management representative.

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.

6.4.2.1.6 Adverse Event Reporting Period

The AE reporting 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 reporting 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 reporting period and until Data Base lock, that the Investigator considers to be possibly related to the IP should also be reported as an AE. Any SAE considered as possibly related to the IP that occurs after the reporting period should also be reported as an SAE. At day 35 a call will be made to the patients to ensure that any pregnancy and/or SAEs are reported.

6.4.2.1.7 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.

6.4.2.2 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

Red blood cell (RBC) count
Hemoglobin
Hematocrit
White blood cell (WBC) count
Neutrophils (absolute and differential)
Lymphocytes (absolute and differential)
Monocytes (absolute and differential)
Eosinophils (absolute and differential)
Basophils (absolute and differential)
Platelet count

Coagulation

Antithrombin III
Protein C
Protein S

Blood Chemistry

Glucose
Albumin
Total Protein
Sodium
Potassium
Blood urea nitrogen (BUN)
Creatinine
Alkaline phosphatase (ALP)
Alanine amino transferase (ALT, SGPT)
Aspartate amino transferase (AST, SGOT)
Lactate
C-reactive protein

Lipids

Cholesterol
Triglycerides

D-Dimer

6.4.2.3 Exposure during Pregnancy

For women who are pregnant at the time of randomisation or for women who become pregnant while receiving the IP up to day 35, 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 6.4.2.1.5). 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.

6.4.2.4 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.

6.4.3 Other Assessments

6.4.3.1 Physical Examination

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

6.4.3.2 Vital Signs

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

6.4.3.3 Electrocardiogram (Optional)

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).

6.4.3.4 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.

6.4.3.5 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 study, 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 be compared. Each active arm will be compared to the control arm and, initially, the control arm will be PAR. Note that an adaptive design report, describes some of the algorithms in greater detail.

As a platform study, the number of agents that will ultimately be compared to control is unknown, so the study is designed to control 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. Type I error rate is addressed by using a conservative threshold for primary success that accounts for the multiple interim analyses. This threshold was determined by trial simulation based on methods suggested in Park, Thorlung and Mills publication (Critical concepts in adaptive clinical trials. *Clin Epidemiol.* 2018, 10:343-351), which heavily emphasized pre-specifications and firewalls controlling information about aggregated trial results. 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 theoretically, 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.

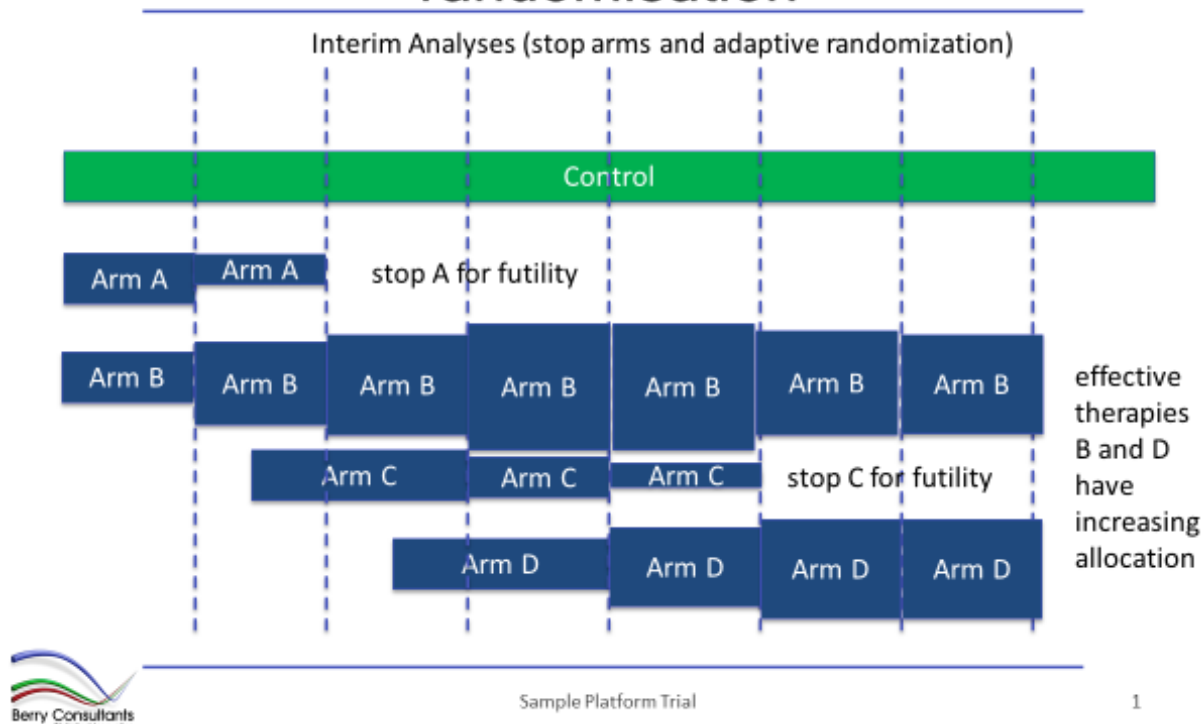
Further, the study design can accommodate sites that randomise between groups of IPs that include additional agents not available at other sites, as long as agents shared with other sites are included as well. After a 300 patients run-in with 1:1:1 randomization, response-adaptive

randomisation (RAR) will be used to preferentially randomise patients to the arm or arms at those sites that are better performing.

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 450 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 0.985 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).

Schematic description of adaptive randomisation



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 equal to the control arm 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 (SOC) to lead to bias with RAR; (2) the potential for adoption of new agents as SOC to make 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 are prespecified in the adaptive design report. Detailed operating characteristics (e.g., type I error rate, power) were determined by simulation.

7.2 Trial Decision Rules, RAR and Sample Size Determination

The sample size of 700 patients per arm was determined by simulation to obtain 85% power under scenarios where the progression rate was 10% on the control arm and 5% on the active arms.

The assumption was to apply a lower rate of progression (10%) than the one observed in other regions of the world (reported to be around 20%), especially due to the younger population. By lowering the threshold, this would better reflect the expected proportion of patients that would worsen. This increased the sample size in comparison with a 20% hypothesis.

As data are collected, the DSMB will review the hospitalisation rate in the control arm and may request modification of inclusion/exclusion criteria should the ratio in the control arm be very different from the initial assumption.

If it is a recommendation from DSMB to include adolescents as well as younger children, we may indeed need to re-assess and increase the sample size.

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 3:2:2: among the three treatment arms, until 300 patients had been randomised. From that point on, within each site enrolling control, a fixed $1/K$ proportion are assigned to control, where K is the number of arms including control that are enrolling at that site. The remaining patients are adaptively randomised among the active treatment arms proportionally to the probability that each arm is superior to control. Interim analyses were conducted after the initial 300 patients are enrolled and every 450 patients thereafter. At each interim analysis, the study design includes early stopping rules for futility or success and allows the randomisation ratios to be adjusted for the next 450 patients.

At each interim analysis we determine the probability of super-superiority using a margin of $\text{logit}(0.075) - \text{logit}(0.10)$, which is the log-odds difference required for a **decrease in respiratory deterioration rate from 10% to 7.5%**. Showing superiority to this degree typically requires data closer to the difference between 10% and 5%. Then, the posterior probability that arm a is super-superior to control is

$$Pr(\text{super-superiority})_a = Pr(\theta_a < \text{logit}(0.075) - \text{logit}(0.10) = -0.3151)$$

An intervention arm is halted at the interim analysis for **early success** if $Pr(\text{super-superiority})_a > 0.98$. An intervention satisfying this criterion has demonstrated clinically meaningful benefit with accumulating trial data.

An intervention arm is halted at the interim analysis for **early futility** if $Pr(\text{super-superiority})_a < 0.10$ for failure to provide evidence of clinically meaningful benefit with accumulating trial data.

An arm reaching its maximum sample size of 700 will have its primary analysis at the first scheduled interim after reaching full followup. The arm will be declared efficacious if the posterior probability of superiority is greater than 0.985.

Using this design and specific criteria for demonstrating efficacy, simulation demonstrated control of the type I error rate at 2.5% and the study design achieved a power of 85% to demonstrate a decrease in the rate of progression to severe disease in one of the active arms from the control rate of 10% to 5%.

The allocation probabilities are also changed at each interim. Some arms are only available at a subset of sites. This complicated allocation in this trial. At the start of the trial, participants will be allocated with a fixed ratio of 1:1:1 to Paracetamol control and three intervention arms. At any individual site missing arms will be zeroed out for the burning allocation. Response adaptive randomization (RAR) will be activated at the time of the first interim analysis and will be used at every subsequent interim analysis to determine allocation probabilities for active interventions. An arm is considered active in the platform trial framework if it is eligible to

receive participants (i.e., has not stopped early for success or futility, reached its maximum capacity, or conducted its final analysis). The purpose of RAR is to preferentially randomize participants to the arm or arms that are better performing.

When RAR is activated, the control arm will receive a fixed allocation probability of $1/K$, where K is the total number of arms enrolling participants on the platform including control (e.g. $K = 4$ for control and three active interventions), subject the maximal sample size of $N=700$ patients on paracetamol. The remaining $(K-1)/K$ allocation probability will be divided among the active intervention arms. Let these allocation probabilities be denoted by q_a , where $a = 0$ corresponds to the control arm and $a > 0$ corresponds to active intervention arms. The RAR probabilities for the intervention arms ($q_a, a > 0$) will be proportional to the Bayesian posterior probability that a given intervention is superior to control, $Pr(\text{superiority})_a$. The set of randomization probabilities sums to 1. If paracetamol has reached its maximal sample size, then the allocation probability for paracetamol will be reallocated proportionally to the remaining arms in the study.

Individual clinical sites may not have the capability to randomize to all active interventions or to Paracetamol control, so an augmented set of allocation probabilities may be required. In this case, let K_{site} be the number of active arms enrolling at the site. If there is no control participation at the site set $q_0 = 0$, and set $q_0 = 1/K_{site}$ otherwise. The allocation probabilities for the active intervention arms available at the site (q_a for $a > 0$) are renormalized to comprise the remaining allocation probability, $1 - q_0$.

For example, suppose a site is capable of randomizing to control, Hydroxychloroquine, and Lopinavir/Ritonavir, but not to Telmisartan. Then $K_{site} = 3$, $q_0 = 1/3$, and the remaining $2/3$ allocation probability is distributed between the active arms proportional to their $Pr(\text{superiority})_a$ values.

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).

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

For this study, the Data Safety Monitoring Board (DSMB) members were selected by the ANTICOV Consortium JSC based on a set of criteria as defined in the protocol. The 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, bayesian statistical methods and analysis, and ethics. An independent non voting statistician will be presenting interim analysis to the DSMB members. The trial statistician (blinded) and independent unblinded statistician performing the interim analyses are separate individuals. Both are from

the same company, but when unblinded data transfers begin, they will be firewalled from each other for this trial, according to the company SOP. The non-voting independent unblinded statistician that leads the team performing the interim analyses will participate in the closed session of the DSMB meeting to present interim analysis results, and answer DSMB questions. The presentation of interim analysis results can only occur in closed sessions because it involves unblinded information regarding treatment efficacy, and the DSMB needs to have the ability to receive direct answers to questions about the interim analysis report. The DSMB will also have the option to hold an executive session which does not include the independent unblinded statistician.

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.

There will be an interim analysis and a DSMB meeting after a group of 300 subjects are randomized. Following interim analyses (DSMB meetings) will be performed after each group of 450 patients are randomized. Focus will be given on the reported SAEs and nonserious AEs that caused treatment discontinuation and efficacy. During the trial, the Chair of the DSMB may request an emergency meeting based on Safety reports, i.e., SAE reports and nature of the events, and information that must urgently be considered can prompt extraordinary meetings. DSMB meetings will be organized by DNDi, in consultation with the Chair.

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.

Given the importance of developing safe and effective interventions for treatment of COVID-19 for use in adolescent patients, the DSMB and JSC will include assessment of the risk/benefit ratio as it applies to potential inclusion of adolescents (and potentially younger children) and/or pregnant women or breastfeeding women for any arms from which they have been excluded, as part of the planned interim analyses on safety and efficacy of all candidate interventions. If a decision is made to include adolescents (and potentially younger children) and/or pregnant women or breastfeeding women for any arms from which they have been excluded, the protocol will be amended, and the related IP risk/benefit will be adjusted accordingly.

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 Blinding

Despite the study is open label, the access to any efficacy and safety data by allocated treatment will not be available to the Sponsor and clinical study teams until after the database lock. Processes to keep maintain the Sponsor and Clinical study Trial teams blinded to the subject study treatment allocation, will be implemented to ensure more objective results as well as unbiased analyses of results at the interim / final analyses. Investigators, site staff, Sponsor monitoring team and Data Management/Statistical teams will not be blinded to the subject study treatment allocation study treatment as this is an open-label design.

9.5 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.

9.6 Missing Data

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

9.7 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.

9.8 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.

Data archiving conditions are specified in the country specific appendices and ICFs.

9.9 Audit and Inspection

To ensure compliance with ICH GCP E6 (R2) 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 offer Personnel Protection Equipment (PPE) to all clinical staff working in the same facility even if not part of the study staff. PPE will be provided to all patients and site staff will ensure they will be protected according to the local guidelines. 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 the ANTICOV 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.

ANTICOV study requires building trust in communities and services and understanding community perspectives. This includes communication with relevant groups to share information about the ANTICOV trial, discussing key perceptions, risks and challenges with communities, and determining the best solutions for them. We are also conducting trainings in GCP that will be useful outside the trial settings. Results of the trial will be shared with the participants and the community.

12.6 Patient Recruitment

Recruitment strategy was discussed with local community members prior to study start. Community engagement will be an ongoing process throughout the conduct of the study.

Following recent observations on the very low rate of diagnosed patients, it became apparent that communities do not have early access to diagnostic and are often referred to hospitals (sites where the study is being conducted) at an advanced stage. It was therefore proposed to provide additional Ag-based RDTs to detect more patients but also to detect them earlier in the disease. This active screening will either be done via the community healthcare workers, as part of the country's strategy and where FIND will provide tests, or directly by the study teams.

Country specific aspects are described in Country Specific Appendix 5, if applicable.

Active screening may be conducted as part of existing in-country programs that are independent from the study.

When conducted by study teams, active screening is not necessarily an activity only linked to the study, the purpose of the active screening is to increase the diagnosis capacity at the community level. Positive patients may be referred to ANTICOV sites for potential inclusion in the study or referred to the local covid 19 response programs.

When the ANTICOV study team is directly involved in active screening the following will apply:

- individuals will be identified and approached by the team working with the community and in keeping with the recommendations of the ANTICOV Consortium Independent Community Advisory Group using antigen RDTs donated by FIND
- individuals will be referred to study sites for potential participation in ANTICOV or referred to the local covid 19 response programs
- the informed consent process will be managed by the study team as per local regulatory requirements

12.7 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. These documents were developed with the support of local community members and were approved by the regulatory bodies of each country participating to this multicentric study. The consent procedure will include sufficient time to discuss any difficulties with the patient and identify if he/she might be affected by participating and being identified with COVID-19, as stigmatization is one of the aspects, community members have reported.

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.

Communication on the treatment arms and how they are or are not part of current treatment recommendation will be routinely given to patients during the informed consent process. Any reservation from patients to consent due to the potential ongoing controversies will be addressed and patient's right not to consent will be respected.

Given the adaptative design of the study, if an arm is dropped for futility, patients already randomised to this arm, will be informed of the decision made during their next visit or at the time EC/NRA will be informed. Patients will be informed that they have the choice to stop their current treatment and to be treated under the current standard of care in their country.

In case the arm is stopped for safety reasons, efforts will be made to inform patients within 24 to 48 hours after investigators have been informed.

Once the decision is made to add a new arm, patients enrolled in the study will receive an ICF addendum informing them about the change.

For the new treatment arm, the ICF will be updated accordingly and approved by ECs before patients could be randomised to this arm.

Separate informed consent forms will be used for the Immunology and Epidemiology ancillary studies.

An adapted ICF will be submitted for Coverage Africa.

If the DSMB recommends inclusion of children above 12 years of age (and potentially younger children), a specific ICF will be developed for assent by adolescents, based on local regulations. A parental/guardian ICF will also be signed by parent/guardian.

12.8 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 ANTICOV consortium of partners conducting the study and will be published in the names of the partners of the ANTICOV consortium.

12.9 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.

12.10 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 ANTICOV Governance

All sponsors management teams as well as implementing partners of the study, and partners involved in operational part of the study conduct (training, diagnosis, scientific review of candidates), are part of a Consortium Joint Steering Committee (JSC). A Governance agreement, signed by all parties, describes the nomination, scope, meetings, voting conditions of the JSC.

The JSC consists of three subcommittees, each including Sponsor's representatives and each with their own term of references:

- The **internal safety sub-committee** includes representatives of the sponsors' pharmacovigilance and/or safety teams and interact with the DSMB. It shares SAEs observed in each country and reviews together the safety summaries provided by the CRO in charge of the global database. It reports back to the JSC.
- The **operations sub-committee** includes representatives of the sponsors' project management teams and oversees all direct project-related questions: site and staff GCP training, data entry supervision, monitoring, progress reports etc ... It reports back to the JSC.
- An additional **communication sub-committee** constituted of sponsors' communication staff was also set-up to safeguard common messages, including after interim analyses, should a decision of stopping a treatment arm would be made. It reports back to the JSC.

Each Committee meets regularly (at least monthly).

DNDi's Project Management Team's is responsible to coordinate and chair each Committee, set-up agendas and ensure minutes are taken, circulated amongst committee members and actions followed up. DNDi also hosts a workspace for the ANTICOV Consortium members on SharePoint. and is responsible for the data management and statistics activities.

Figure 4. ANTICOV Consortium Governance Structure

ANTICOV Consortium Governance Structure



14 List of References

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15 Appendices

Appendix 1. Investigational Products

The first two treatment arms to be tested in this study are Hydroxychloroquine Sulphate and Lopinavir/Ritonavir which were selected based on (i) the *in vitro* evidence of their potential activity against SARS-CoV-2 (ii) their well-known safety in another indication (iii) their ability to be manufactured at scale and at an affordable cost, and (iv) to provide scientific evidence on their activity in mild patients.

No study has been conducted yet in Africa to inform on the efficacy and safety of Hydroxychloroquine and Lopinavir/Ritonavir in mild or moderate non-hospitalised Covid-19 patients.

Based on WHO guidelines released on 18 December 2020 and on DSMB recommendations , the hydroxychloroquine and lopinavir / ritonavir arms were dropped from the protocol.

The rationale for the selection of new therapeutic options will be based on the same criteria as described above with an emphasis on the preclinical evidence of efficacy (for example the antiviral activity of compounds in the recent Syrian hamster model) or clinical evidence from PoC antiviral studies, as well as modelling data supporting the best dose regimen. For compounds having a different mode of action (non antiviral) the scientific rationale for selection will be adapted. The new products with credible PoC data will also be evaluated.

New treatment arm and all information and requirements related to this arm, will be added in a Protocol Amendment, and submitted for approval to Ethical Committees and Regulatory Authorities.

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 Paracetamol

Paracetamol

General information on paracetamol is presented in Table 5.

Table 5. 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 Paracetamol¹

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 Paracetamol¹

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 1.2 nitazoxanide and inhaled ciclesonide

This section describes the combination treatment for SARS-CoV-2 infections using a combination of nitazoxanide and inhaled ciclesonide. Information is provided on the individual drug components, as well as in combination.

Table 6. General Information on Ciclesonide

International Non-proprietary Name	Ciclesonide
Dosage Form	Inhalation aerosol, 160 mcg / actuation
Route of administration	Oral inhalation with inhalation chamber
Dosing instructions	320 mcg BID per day
Duration of treatment	14 days
Composition	Containing: Active ingredient: ciclesonide Inactive ingredients: propellant HFA-134a and ethanol

Rationale for choice of ciclesonide

Since the start of the COVID-19 pandemic, the risk of clinical deterioration and hospitalization appears to be lower among asthma and chronic obstructive pulmonary disease (COPD) patients infected with SARS-CoV-2, as compared to the general population (1). This suggested a possible early protective effect of inhaled corticosteroids (ICS) against SARS-CoV-2 infection. Furthermore, studies carried out recently are in favor of an in-vitro antiviral effect of some ICS, in addition to their anti-inflammatory effect (2).

Value of and anti-inflammatory effect in early stages of the infection

It is usual to propose only antiviral drugs for early stage COVID-19 patients. However, the clinical aggravation which occurs generally at day 8-10 is linked with inflammatory response and associated with worst outcome (3). In addition, for mild patients, viral cultures are negative after a median of 8 days after the onset of symptoms (4) which can explain the rather low efficacy of anti-viral treatment alone administered after a week of symptoms. Finally, several studies highlighted that the viral load at day 7 and day 14 did not differ between severe and mild patients (5), which constitute another argument that the host inflammatory response could also play an important role in disease outcome.

ICS have a known anti-inflammatory effect on the bronchial mucosa. This anti-inflammatory effect may also have an indirect protective effect against viral infection by allowing interferon production as a response to the viral infection. Furthermore, ICSs have been evaluated in combination with a long-acting beta-agonist (budesonide and formoterol) in hospitalized

patients at risk for ARDS. The combination decreases local inflammation markers and improves gas exchange (6).

Observational data from the UK general medicine platform OpenSAFELY on nearly one million patients with asthma or COPD could not show a protective effect of ICS against COVID-19 as was expected (7). However, the severity of the comorbidities in this cohort was a significant confounding factor and this result does not enable final conclusions on the effectiveness of ICS on COVID-19.

Finally, general administration of corticosteroids have proven efficacy to reduce mortality among hospitalized patients with mechanical ventilation or simple oxygen therapy in the Recovery study (8). However, it did not show protective effect in the less severe patients.

Potential for a direct antiviral effect

In addition to their anti-inflammatory action that targets the main mechanism behind clinical worsening in COVID-19, ICS may have an antiviral effect. The antiviral effect is thought to be mediated through two mechanisms:

- A decrease in the capacity of SARS-CoV-2 to infect the cell. Cell-entry depends on angiotensin-converting enzyme 2 (ACE2), the cellular receptor for SARS-CoV2, and on the host-cell transmembrane serine 2 protease (TMPRSS2). Both ACE2 and TMPRSS2 gene expression has been shown to be decreased in sputum cells from asthma patients on ICS (9).
- An interaction with a non-structural virus protein, NSP15, which is an important enzyme in viral replication, resulting in a decrease in viral replication (2). This effect was found for ciclesonide and mometasone furoate. Interestingly, a mutation conferring resistance to ciclesonide does not lead to cross resistance with mometasone furoate. In addition, this effect appears to be independent of the corticosteroid effect because neither fluticasone nor dexamethasone had an antiviral effect in the same model up to concentrations of 100 μ M. Budesonide has only been tested in vitro up to 100nM in human cells infected with the 229 E coronavirus, and has no antiviral effect at this concentration (10).

Ciclesonide was evaluated in an in vitro study selecting potentially effective molecules from molecules already marketed and approved by the FDA (11). Among all drugs which showed antiviral efficacy with a median inhibitory concentration (IC₅₀) between 0.1 μ M and 10 μ M against SARS -CoV-2 on Vero cells, ciclesonide showed interesting in vitro efficacy with an IC₅₀ at 4.33 μ M. In addition, another team tested ciclesonide antiviral activity in epithelial human cells, which are a better model than Vero cells to mimic SARS-CoV-2 infection in-vivo, and found an EC₉₀ at 6 μ M, which looks promising (2). Such a concentration is difficult to achieve by the systemic route but can be reached and exceeded locally by the topical route.

Selection of ciclesonide amongst other ICS

The molecules of interest today are mainly ciclesonide and budesonide. ICS in COVID-19 are currently tested 9 ongoing treatment trials:

- 5 trials in hospitalized patients (NCT04355637 / Budesonide; NCT04331054 / Budesonide-Formoterol; NCT04331470 / Budesonide-Formoterol-Levamisole; NCT04330586-Ciclesonide; NCT04381364-Ciclesonide)
- 4 trials in ambulatory patients (NCT04435795-Ciclesonide inhaled and nasal; NCT04377711-ciclesonide; NCT04416399-Budesonide; NCT04356495-ciclesonide). The COVERAGE study (NCT04356495), run in France, has just had the regulatory clearance for starting inclusion for at risk mild patients.

In our trial, we chose ciclesonide based on its favorable safety profile.

Ciclesonide pharmacokinetics

Ciclesonide has a low affinity for glucocorticoid receptors. After oral inhalation, it undergoes enzymatic metabolism in the lungs. Its main metabolite, desisobutyryl-ciclesonide (des-CIC), exerting a strong anti-inflammatory effect, is considered to be the active metabolite. Conversion from the drug to the active metabolite is fast (79% of metabolite detectable in the lung 2h after administration) and the level of peripheral lung deposit is high (56%) (12,13). The risk of systemic passage is minor, thus minimizing the risk of drug interactions with potential inhibitors of its metabolism and the risk of systemic effects.

Dosing considerations for a COVID-19 trial

The selected daily dose of 640 µg per day aims at optimizing the anti-inflammatory and antiviral effects. In patients with asthma, this daily dosage allows better control of severe asthma from the first day of treatment on, compared to the 160 µg dose.

The use of an inhalation chamber in addition with the metered dose inhaler will allow both an easier use and better inhalation in the peripheral lung as well as a deposit in the nasopharyngeal track in addition to the oral and pulmonary deposit.

Risks Related to ciclesonide

Ciclesonide appears to be well tolerated.

Approximately 5% of patients experienced adverse reactions in clinical trials with Alvesco® given in the dose range 40 to 1280 micrograms per day. In the majority of cases, these were mild and did not require discontinuation of treatment with Alvesco®.

Rare adverse events (less or equal to 1%) were described, such as hoarseness, headache, bad taste in mouth, nausea, vomiting, dry mouth or dry throat, buccal mycosis, mouth or throat burning sensation.

Systemic effects observed after long-term administration are not expected after a 14 days short-course treatment.

There are no adequate and well controlled studies in pregnant women. As with other ICS preparations, Ciclesonide is not to be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the mother or foetus. Based on WHO information, when pregnant women develop severe disease, they also seem to more often require care in intensive care units than non-pregnant women of reproductive age (Coronavirus disease (COVID-19): Pregnancy and childbirth (who.int)). Therefore, it is considered that benefit/risk ratio is in favor of including pregnant woman in this study.

Ciclesonide and the risk of tuberculosis

Steroids are recommended in the treatment of tuberculosis meningitis and pericarditis that require anti-inflammatory drugs in addition to antituberculosis drugs. A Cochrane meta-analysis found that there were no criteria to formally reject or recommend use of general corticosteroids in pulmonary tuberculosis (14). When steroids can be used with risk in patients on controlled TB treatment, a higher risk of developing tuberculosis itself has been described in patients receiving high doses of ICS (1000 micrograms of inhaled fluticasone [is] estimated to be equivalent to approximately 10 mg of prednisone per day), findings in patients receiving high dose of ICS are compatible with the increased risk of TB seen with equivalent dose of oral corticosteroids (15) . This association was found for asthma and COPD patients receiving ICS repeatedly for long durations (at least 30 days (14) or 3 prescription within the last 12 months (16)). But more recent NICE recommendation (17) on COVID and COPD support continuing the use of inhaled steroids in COVID-COPD patients. In summary, the potential risk to TB patients receiving inhaled corticosteroids appears to be both dose and duration dependent. With the proposed short course and low-dosing regimen of ciclesonide this risk is minimal whilst the potential benefit of treating a co-infection with SARS-CoV-2 in that population would be high. We therefore propose not to exclude patients with active tuberculosis treatment.

Precautions for co-administration

Based on the SmPC, in vitro data indicate that CYP3A4 is the major enzyme involved in the metabolism of the active metabolite of ciclesonide M1 in man. In a drug-drug interaction study at steady state with ciclesonide and ketoconazole as a potent CYP3A4 inhibitor, the exposure to the active metabolite M1 increased approximately 3.5 fold, whereas the exposure to ciclesonide was not affected. Therefore the concomitant administration of potent inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole and ritonavir or nelfinavir) should be avoided during chronic treatment of ciclesonide. However, this is not considered as a risk for a short-course administration of inhaled steroid with low systemic distribution (C_{max} 1,55 microg/l after a 1280 mg inhaled dose).

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Table 7: General Information on nitazoxanide

International Non-proprietary Name	Nitazoxanide
Dosage Form	Film-coated tablets containing 500 mg of nitazoxanide
Route of administration	Oral route
Dosing instructions	2000 mg nitazoxanide daily, divided into two daily intakes of two tablets of nitazoxanide 500 mg taken 12 hours apart with a meal
Duration of treatment	14 days
Composition	Containing: Active substance: 500 mg of nitazoxanide Other components: Core: microcrystalline cellulose, lactose, croscarmellose sodium, hydrogenated castor oil, purified talc Coating: Opredy II yellow, purified water

Rationale for choice of nitazoxanide

Nitazoxanide is a broad-spectrum antiparasitic drug that is used in medicine for the treatment of primarily helminthic, protozoal infections. Nitazoxanide has also been identified as a potential pan anti-viral agent investigated in clinical trial where it was shown to reduce duration of symptoms and virus burden of uncomplicated influenza [1].

Nitazoxanide is rapidly hydrolyzed in plasma to its deacetylated metabolite tizoxanide. Both nitazoxanide and tizoxanide inhibits viral replication in SARS-CoV-2 infected with EC₅₀ values of 1.0-4.0 µM reported for nitazoxanide and 3.1 µM for tizoxanide [2-4]. The mean plasma C_{max} at the standard dosing 500 mg BID is 13.8-fold higher than the EC₅₀, and 6.3-fold higher than the calculable EC₉₀. It is predicted to have a C_{min} above the EC₅₀ in both lung (free drug) and plasma (total drug) [5].

The mechanism of action of nitazoxanide/tizoxanide are not fully understood but is believed to be acting on the host impairing viral uptake, assembly and excretion. Studies on on H1N1 (swine flu) and strains of influenza A virus suggests that thiazolides, such as nitazoxanide, blocks the maturation of the viral hemagglutinin and thus impairs the hemagglutinin intracellular trafficking and insertion into the host plasma membrane, a key step for correct assembly and exit of the virus from the cell [6].

Several studies on the effects of nitazoxanide in COVID-19 patients doses ranging from 500 – 1000 mg BID are ongoing. The results of a recent randomised placebo controlled clinical study conducted in mild COVID-19 patients in Brazil using a 500 mg TID (1500 mg/day) dosing for 5 days have recently been published by Rocco *et al.* [7]. This study demonstrated, as shown in Table below, a significant decrease in viral load as well as a significant difference in viral clearance at the 1-week follow up. Nitazoxanide failed to meet the primary outcome on symptom improvement when evaluated after 5 days of therapy, but when evaluated at the 1-

week follow-up, 78% in the nitazoxanide arm and 57% in the placebo arm reported complete resolution of symptoms ($p=0.048$).

Table 8: Secondary outcomes after 5 days of Nitazoxanide Therapy

Table 3. Secondary outcomes after 5 days of therapy

	Nitazoxanide (n=194)	Placebo (n=198)	p value
Nasopharyngeal swab			
RT-PCR viral load (Log_{10} copies/mL), median (IQR)	3.63 (0-5.03)	4.13 (2.88-5.31)	0.006
RT-PCR status, n (%)			
Positive	136 (70.0)	162 (82.8)	0.009
Negative	58 (29.9)	36 (18.2)	
WBC ($\times 10^3/\text{mL}$), median (IQR)	6.1 (5.1-7.3)	6.4 (5.3-7.8)	0.080
Neutrophils ($\times 10^3/\text{mL}$), median (IQR)	3.4 (2.6-4.4)	3.6 (2.7-4.7)	0.327
Lymphocytes ($\times 10^3/\text{mL}$), median (IQR)	2.1 (1.7-2.5)	2.2 (1.7-2.6)	0.078
Platelets ($\times 10^3/\text{mL}$), median (IQR)	240 (209-288)	239 (198-285)	0.275
CRP (mg/L), median (IQR)	5.0 (1.0-16.2)	4.5 (2.0-13.0)	0.445
	Nitazoxanide (n=88)	Placebo (n=100)	p value
Cytokine concentration (pg/dL), median (IQR)			
IL-6	0 (0-0.03)	0 (0-0.03)	0.992
IL-8	2.73 (0-12.24)	2.70 (0-11.42)	0.855
IL-1 β	0 (0-0)	0 (0-0)	0.399
TNF- α	0 (0-0)	0 (0-0)	0.627
IFN- γ	0 (0-12.54)	0 (0-3.25)	0.286

Dosing considerations for a covid-19 trial

The recommended nitazoxanide dosing in the treatment of diarrhoea caused by *Giardia lamblia* or *Cryptosporidium parvum* is 500 mg BID. However nitazoxanide given at higher doses have been explored in studies for treatment of pulmonary tuberculosis at 1000 mg BID [8], in repeated dosing PK studies up to 7 days at 1000 mg BID [9] and in dose escalation studies single doses up to 4000 mg administered [10].

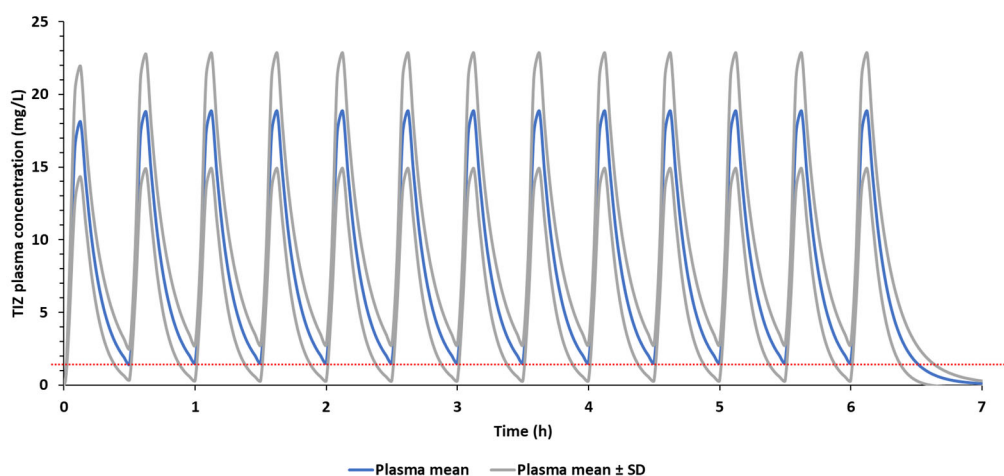
In a repeated dose Phase I study in healthy volunteers, 1000 mg BID led to higher rate (twice) of gastrointestinal events and accumulation of tizoxanide and its glucuronide (a doubling after 7 days). In this study, 3/10 subjects receiving 1000 mg BID reported moderate diarrhea and/or abdominal pain while the other adverse events were of mild intensity. No serious adverse event was reported [9].

In the dose escalation study, thirty-two healthy male volunteers were randomly assigned to 1 of 4 treatment groups. In each successive group, 2 subjects received a placebo and 6 received a single oral dose of 1000 mg, 2000 mg, 3000 mg, or 4000 mg of nitazoxanide, first under fasted conditions and a week later with a standardized breakfast. Tolerability was good up to the maximum dose of 4 g, with mild, mostly gastrointestinal side effects observed. No significant changes were noted in the ECGs, vital signs and laboratory tests [10].

For SARS-CoV-2, simulations indicate that only about 1% of the COVID-19 patient population would achieve EC_{90} at C_{trough} with the standard recommended daily 500 mg BID doses of nitazoxanide. On the other hand, a dose of 1000 mg BID is predicted to result in that 48% of the patient population achieves an *in vitro* EC_{90} at C_{trough} (Figure 5 below). Simulations take into consideration the potential for accumulation of tizoxanide following 7 days of administration at 1,000 mg bid dosing.

A 1,000 mg BID dose is presently being used in a Nigerian Phase II COVID-19 trial, and there will be an opportunity to monitor ongoing safety information, to lower the dose if needed. To date, no safety concerns are reported by the co-investigator.

Figure 5: Tizoxanide EC_{90} SARS-CoV-2 infection in Vero cells = 1.5mg/L



Wang et al, Cell Research 2020

Risks Related to nitazoxanide

The most common adverse reactions reported with nitazoxanide are abdominal pain, , headache, chromaturia, nausea (>2%). (Alinia SmPC, US FDA)

The pharmacokinetics of nitazoxanide in patients with compromised renal or hepatic function have not been studied. Therefore, nitazoxanide must be administered with caution to patients with hepatic and biliary disease, to patients with renal disease and to patients with combined renal and hepatic disease.

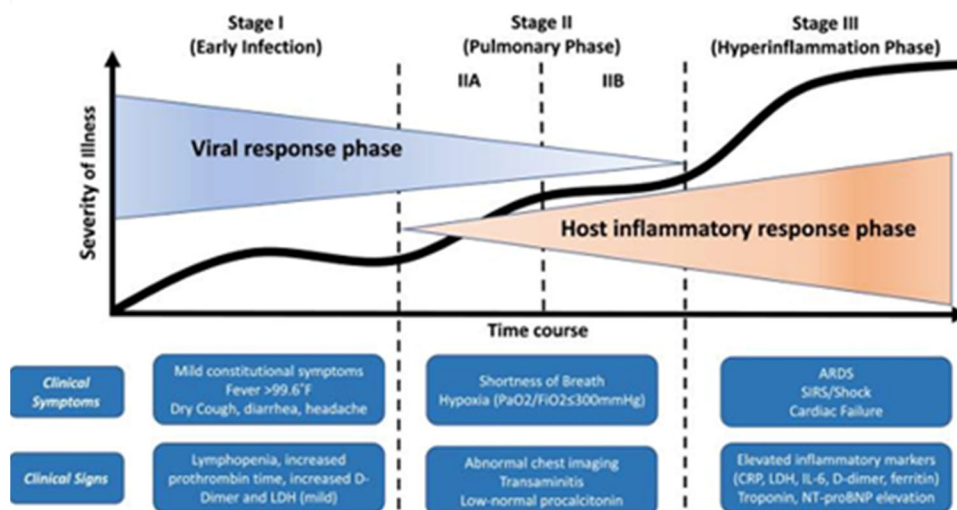
Tizoxanide is highly bound to plasma protein (>99.9%). Therefore, caution should be used when administering nitazoxanide concurrently with other highly plasma protein-bound drugs with narrow therapeutic indices, as competition for binding sites may occur (*e.g.*, warfarin). *In vitro* metabolism studies have demonstrated that tizoxanide has no significant inhibitory effect on cytochrome P450 enzymes. Although no drug-drug interaction studies have been conducted *in vivo*, it is expected that no significant interaction would occur when nitazoxanide is co-administered with drugs that either are metabolized by or inhibit cytochrome P450 enzymes.

The dose of 2000 mg daily was studied in a placebo-controlled trial in persistent diarrhoea in Zambian acquired immune deficiency syndrome patients treated for 14 days. No difference was observed in the number of adverse events, Only yellowing of the sclera and urine, reported by 32 (33%) and 19 (20%) respectively, could definitely be attributed to nitazoxanide without abnormalities in the hepatic test or bilirubin [11].

Reproduction studies have been performed and have revealed no evidence of impaired fertility or harm to the fetus due to Nitazoxanide. There are, however, no adequate and well-controlled studies in pregnant women.

Rationale for Ciclesonide + Nitazoxanide Combination

SARS-CoV-2 infection is now better described and understood and can typically be divided in 2 sequential stages: the first one, with virus replication followed by the development of clinical symptoms that slowly decreases in 10 to 12 days whereas the developping inflammatory response starts being uncontrolled around day 8-10 leading to the severe pulmonary and systemic complications. This is described in the graph below.



In real-life setting, patients may be diagnosed at different stages of the infection and it is therefore important to combine treatments with complementary mechanisms of action to cover for both stages; a drug with a primary antiviral activity but some level of immune host effect, and a treatment administered locally to primarily control the local inflammation whilst also potentially having an inhibitory effect on SARS-CoV-2 replication. Even in the absence of a direct antiviral effect of ciclesonide, combining it with nitazoxanide will decrease any potential risk of viral replication.

Risks Related to Ciclesonide and Nitazoxanide Combination

There is no reported use of the drug combination of Nitazoxanide and inhaled ciclesonide and no formal safety studies have been conducted on the combination. Pharmacodynamic studies in murine models of SARS-CoV2 have been performed and have not indicated a pattern of increased toxicity. Given the SmPCs of the two individual compounds there is no expected drug-drug interactions or additional safety concerns due to the combination.

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[WHO EM Application]

[Nitazoxanide Data Sheet]

Appendix 1.3 Amodiaquine (as hydrochloride)/Artesunate (ASAQ) and Ivermectin (IVM)

This section describes the combination treatment for SARS-CoV-2 infections using a combination of ASAQ and IVM. Information is provided on the individual drug components, as well as in combination.

General information on ASAQ is presented in Table below.

Table 9:. General Information on ASAQ

International Non-proprietary Name	Amodiaquine (as hydrochloride)/Artesunate
Dosage Form	Tablets containing 100 mg of artesunate and amodiaquine hydrochloride equivalent to 270 mg of amodiaquine
Route of administration	Oral route
Dosing instructions	200 mg artesunate and 540 mg amodiaquine daily, two tablets of 100 mg of artesunate and 270 mg of amodiaquine
Duration of treatment	3 days
Composition	ASAQ (100mg/270mg) is a fixed dose combination of amodiaquine and artesunate Round bilayered tablets: the artesunate layer is white and the amodiaquine hydrochloride is yellow, and the white side is engraved with “100”. Excipients: Calcium carbonate, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone and pregelatinised starch

Rationale for Choice of ASAQ.

Amodiaquine (as hydrochloride) /Artesunate (ASAQ) is indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* strains which are susceptible to amodiaquine as well as to artesunate.

ASAQ is an artemisinin-based combination therapy which consists of two blood schizonticides, with independent modes of action and different intraparasitic biochemical targets ¹.

Artesunate: Artesunate is a hemisuccinate derivative of dihydroartemisinin, which is obtained by the reduction of artemisinin, a sesquiterpene lactone endoperoxide extracted from a plant used in traditional Chinese medicine, known as sweet or annual wormwood (*Artemisia annua*). The chemical mechanism of action of artesunate has been widely studied and appears well established. The artesunate endoperoxide bridge is split by haeme within the infected erythrocyte, generating singlet oxygen. Parasite proteins, particularly in membranous structures, are thus alkylated, leading to parasite death.

Amodiaquine: Amodiaquine is a synthetic 4-aminoquinoline antimalarial. Its activity is characterized by a schizonticidal action on *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae* by destroying intraerythrocytic forms.

Amodiaquine (AQ) and desethylamodiaquine (DEAQ, primary active metabolite of AQ), are active against SARS-CoV-2 (Vero76 cell assay) in vitro with plasma/blood EC₅₀ of 1.8 µM, <0.3 µM ². Moreover, PBPK modelling of lung penetration indicates AQ, DEAQ to be well-distributed to lungs, with a C_{max} lung/plasma ratio of 13 for AQ and 40 for DEAQ, supporting the selection of these compounds for this trial².

In contrast with AQ, the available data on the activity of artesunate against SARS-CoV-2 are limited^{3,4}. The inclusion of artesunate is therefore largely driven by the availability of AQ as existing fixed-dose combinations with artesunate (ASAQ) with established safety, tolerability and efficacy in malaria.

There are currently six clinical trials and one observational cohort registered in clinicaltrials.gov using artesunate for Covid-19. Two of them use ASAQ (combination of artesunate and amodiaquine)⁵. Hypothesis are made based on the antiviral properties of the drugs. All studies aim at a population with mild to moderate symptoms.

Dosing considerations for a COVID-19 trial

Amodiaquine's active metabolite, Desethylamodiaquine, has a terminal half-life of 9-18 days. Artesunate has a plasma half-life of 3-29 minutes. The active metabolite DHA has a plasma half-life of 40 to 95 minutes.

Assessment of human maximum plasma concentrations and modelling of predicted maximum lung concentrations of ASAQ was done based on the doses for which the drug is currently licensed. Therefore, the safety and tolerability are well understood at these doses and they are deemed appropriate for this study.

The selected daily dose will be similar as the one used for malaria: Artesunate-amodiaquine (ASAQ) 100/270 mg artesunate/amodiaquine fixed dose combination, 2 tablets daily (200/540mg) for 3 days.

Risks Related to ASAQ

Based on SmPC for malaria patients¹, about 30% of treated patients experienced adverse reactions. Most of the reported adverse reactions were similar to symptoms usually seen during a malaria attack.

The most frequent adverse reactions observed were:

- anorexia, abdominal pain, nausea, asthenia, somnolence, insomnia and cough.

The most serious adverse reactions observed were:

- asthenia, anaemia and vertigo.

Amodiaquine is likely to induce cardiovascular adverse effects, particularly transient prolongation of QT interval duration at 30 mg/kg administered orally. This dose level corresponds to approximately 2-fold the maximum recommended therapeutic dose.

Concomitant drugs known to prolong the QT interval should be used with caution (see detailed list in the end of this appendix).

The detailed list of adverse events can be found in the SmPC of ASAQ.

Special warnings and precautions for use:

Symptoms suggestive of the following diseases should be carefully monitored:

- Hepatitis, pre-icteric phase and especially when jaundice has developed,

- Agranulocytosis (as suggested, for instance, by a clinical condition including fever and/or tonsillitis and/or mouth ulcers).

When these symptoms develop or exacerbate during therapy with ASAQ, laboratory tests for liver function and/or blood cell counts should be performed at once. Immediate discontinuation of treatment may be required.

Cardiovascular effects have been reported with other amino-4-quinoline derivatives during high dose treatment. There is no evidence that an overdose of amodiaquine causes any of the life-threatening cardiovascular complications often seen after an overdose of chloroquine. However, by chemical class analogy, caution should be exercised, especially with patients who have recently taken other antimalarial drug with cardiovascular side effects (quinine, quinidine, halofantrine, lumefantrine, mefloquine) or those who are under treatment with cardiovascular drugs or other drugs with the potential to prolong the QT interval.

A list of prohibited medication can be found below.

Use during pregnancy and breastfeeding:

The safety of amodiaquine in pregnant women has not been conclusively established, although many years of experience with the drug have not indicated any teratogenicity.

Data on a limited number of exposed pregnant women do not indicate any adverse effect of artemisinin on pregnancy or on the health of the fetus/newborn child. Animal data indicate a limited embryotoxic effect at doses of 6 mg/kg/day or more.

During 1st trimester of pregnancy, ASAQ (100mg/270mg) should not be used unless clearly necessary e.g., if treatment is lifesaving for the mother, and if another antimalarial is not suitable or not tolerated.

During 2nd or 3rd trimesters of pregnancy, ASAQ (100mg/270mg) may be used with caution, only if other antimalarials are unsuitable.

The amounts of antimalarials in breast milk are small. Therefore, lactating women can receive artemisinin-based combination therapies (including ASAQ) for malaria treatment.

General information on Ivermectin is presented in the table below.

Table 10. General Information on Ivermectin

International Non-proprietary Name	Ivermectin	
Dosage Form	Tablets containing 9mg of Ivermectin	
Route of administration	Oral route	
Dosing instructions	Daily single dose according to body weight: 0,4 mg/kg in fasted condition	
	Weight kg	nb tablets
	45-60	2
	61-80	3
	81-101	4
	102-122	5
	123-130	6
Duration of treatment	5 days	
Composition	Ivermectin 9mg Excipients: lactose monohydrate; cellactose 80; sodium starch glycolate; magnesium stearate; talcum powder	

Rationale for Choice of IVM

Ivermectin is FDA- approved to treat onchocerciasis due to the nematode parasite *Onchocerca volvulus* (150 to 200 µg/kg as single dose), strongyloidiasis of the intestinal tract (single dose 200-mcg/kg). The drug has been used since 1987 in MDA programs to treat onchocerciasis and is used in combination with DEC and albendazole for the treatment of lymphatic filariasis.

Reports from in vitro studies suggest that ivermectin acts by inhibiting the host importin alpha/beta-1 nuclear transport proteins, which are part of a key intracellular transport process that viruses hijack to enhance infection by suppressing the host's antiviral response^{6,7,8}. In addition, ivermectin docking may interfere with the attachment of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein to the human cell membrane. Ivermectin is thought to be a host-directed agent, which may be the basis for its broad-spectrum activity in vitro against the viruses that cause dengue, Zika, HIV, and yellow fever^{4,7-9}. Despite this in vitro activity, no clinical trials have reported a clinical benefit for ivermectin in patients with these viruses. Some studies of ivermectin have reported potential anti-inflammatory properties, which have been postulated to be beneficial in people with COVID-19.

A meta-analysis⁹ conducted on clinical studies on ivermectin for Covid-19 suggests faster time to viral clearance, shorter duration of hospitalizations, improved rates of clinical recovery and survival. It also demonstrates a dose response effect, strongest effect seen in trial with 3 to 5 days of ivermectin compared to a single dose. On March 22nd, EMA released a statement that “Results from clinical studies were varied, with some studies showing no benefit and others reporting a potential benefit. Most studies EMA reviewed were small and had additional limitations, including different dosing regimens and use of concomitant medications. EMA therefore concluded that the currently available evidence is not sufficient to support the use of

ivermectin in COVID-19 outside clinical trials. Although ivermectin is generally well tolerated at doses authorised for other indications, side effects could increase with the much higher doses that would be needed to obtain concentrations of ivermectin in the lungs that are effective against the virus [*note: based on published data, a dose of 10mg/kg / day would be required to reach concentrations of EC90 in the lung – which are not well tolerated and highly above the study recommended one aiming at reaching an anti-inflammatory effect*]. Toxicity when ivermectin is used at higher than approved doses therefore cannot be excluded.

EMA therefore concluded that use of ivermectin for prevention or treatment of COVID-19 cannot currently be recommended outside controlled clinical trials. Further well-designed, randomised studies are needed to draw conclusions as to whether the product is effective and safe in the prevention and treatment of COVID-19¹⁰.

Dosing considerations for a COVID-19 trial

Ivermectin shows dose linear exposure at doses of 30, 60, 90 and 120 mg. The exposure increased when administered in fed conditions¹¹.

The selected daily dose will be 0,4 mg/kg for 5 days in order to reach a significant anti-inflammatory effect while controlling a potential food effect. The dose of 0,4 mg/kg in human is 2 fold the anti-inflammatory effect in mouse OVA model (2mg/kg) .

Clinical trials evaluating IVM for Covid-19 have been using doses from 0,2mg/kg to 0.6 mg/kg, daily either as single dose administration or repeated dose – maximum (documented) 0,6 mg/kg, 5 day. In the study, 0,6mg/kg for 5 days was well tolerated with 13 cases (43%) in the IVM group and 5 (33%) in the control group reporting adverse events. Most frequent adverse event and the only experienced by more than 1 case in the IVM group was rash in 3 (10%) cases (all mild, self-limited and lasting approximately 24 h); in the control group, single events of abdominal pain, dizziness, anxiety, anguish, and hyperglycemia (all mild) were reported to date. Clinical data in COVID-19 suggests improved outcomes with multiple dose regimens (>3 days) with no safety concern¹². In a more recent study conducted in Colombia, total of 154 patients (77%) in the ivermectin group and 161 (81.3%) in the placebo group reported AEs between randomization and day 21. Fifteen patients (7.5%) in the ivermectin group vs 5 patients (2.5%) in the placebo group discontinued treatment due to an AE. Serious AEs developed in 4 patients, 2 in each group, but none were considered by the investigators to be related to the trial medication¹³.

Large clinical safety database with existing ivermectin regimens – most data on non-COVID indications reflect single administration regimens 0.2-0.4 mg/kg (annually or every 6 months) are safe. To date data from clinical trials on covid-19 patients using doses from 0,2mg/kg to 0.6 mg/kg, either as single dose administration or repeated dose – maximum (documented) 0,6 mg/kg, 5 days does not raise new safety concern¹⁴.

Risks Related to IVM

Undesirable effects:

Based on the SmPC of Ivermectin^{15,16}, transient hypereosinophilia, liver dysfunction including acute hepatitis, increased liver enzymes, hyperbilirubinemia and haematuria have been reported regardless the therapeutic indication.

Visual disturbances side effects may also occur, such as blurred, reduction in visual acuity, photophobia.

Very rarely, toxic epidermal necrolysis and Stevens-Johnson syndrome have also been reported as post-marketing experience.

Side effects are related to the parasite density and are mild and transient in the majority of cases, but their severity may be increased in patients infected with more than one parasite, particularly in the case of infestation with *Loa loa*.

Rarely, severe and potentially fatal cases of encephalopathy have been described following administration of ivermectin, particularly in patients also heavily infected with *Loa loa*. In these patients, the following adverse reactions have also been reported: back or neck pain, ocular hyperaemia, subconjunctival haemorrhage, dyspnoea, urinary and/or faecal incontinence, difficulty in standing/walking, mental status changes, confusion, lethargy, stupor or coma.

In patients receiving ivermectin for the treatment of strongyloidiasis, the following adverse reactions have been reported: asthenia, abdominal pain, anorexia, constipation, diarrhoea, nausea, vomiting, dizziness, somnolence, vertigo, tremor, transient hypereosinophilia, leukopenia/anaemia and increase in ALAT/alkaline phosphatases. In the treatment of *Wuchereria bancrofti* filariasis, the intensity of undesirable effects does not seem to be dose-dependent but is related to the microfilarial density in blood. The following have been described: fever, headache, asthenia, feeling of weakness, myalgia, arthralgia, diffuse pain, digestive disorders such as anorexia, nausea, abdominal and epigastric pain, cough, feeling of respiratory discomfort, sore throat, orthostatic hypotension, chills, vertigo, profuse sweating, testicular pain or feeling of discomfort.

Following administration of ivermectin in patients infected with *Onchocerca volvulus*, the hypersensitivity reactions observed resulting from microfilarial death pertain to Mazzotti-type reactions: pruritus, urticarial rash, conjunctivitis, arthralgia, myalgia (including abdominal myalgia), fever, oedema, lymphadenitis, adenopathies, nausea, vomiting, diarrhoea, orthostatic hypotension, vertigo, tachycardia, asthenia, headache. Rarely, these symptoms have been severe. A few cases of asthma exacerbation have been described. In these patients, abnormal sensation in the eyes, eyelid oedema, anterior uveitis, conjunctivitis, limbitis, keratitis and chorioretinitis or choroiditis have also been described. These manifestations, which may be due to the disease itself, have also been described occasionally after treatment. They were rarely severe and generally resolved without corticosteroid treatment.

Onset of conjunctival haemorrhage has been reported in patients with onchocerciasis.

Observations of adult *Ascaris* expulsion have been described following ingestion of ivermectin.

In patients with scabies, transient exacerbation of pruritus may be observed at the start of treatment¹⁷.

Use during pregnancy and breastfeeding:

Pregnancy category C (FDA).

In pregnant women, the prescription of Ivermectin is not recommended; the administration of Ivermectin at doses close to or equal to maternal toxic doses involve fetal malformations in most species of laboratory animals. It is teratogenic in mice, rats and rabbits when given in repeated doses 0.2; 8.1 and 4.5 times the maximum recommended human dose, respectively (on a mg / m² / day basis). Teratogenicity was characterized in the 3 species evaluated by cleft palate; in rabbits, equinovarus front legs were also observed. These developmental defects were only found at doses close to the maternal toxic in pregnant women. Therefore, Ivermectin does not appear to be selectively fetotoxic to the developing fetus. There are no adequate and well-controlled studies in pregnant women. It is difficult to appreciate from these studies the risk of a shot single low dose.

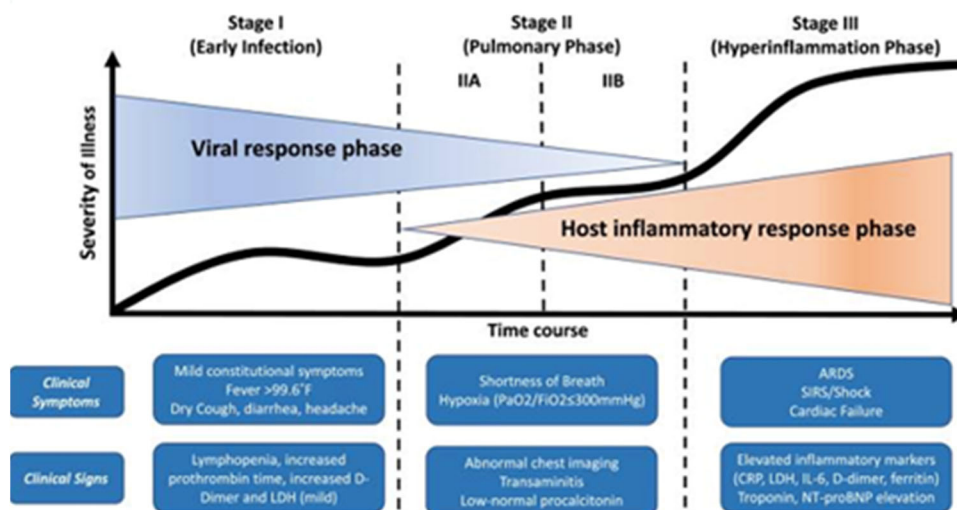
Published studies showing very low certainty of evidence, concluded that current evidence does not support whether IVM is safe in pregnant women (limitation small cumulative numbers of exposed women 899 exposed vs 3104 not exposed).

Ivermectin should not be used during pregnancy since safety in pregnancy has not been established.

Ivermectin is excreted in human milk in low concentrations. Treatment of mothers who intend to breastfeed should only be undertaken when the risk of delayed treatment to the mother outweighs the possible risk to the newborn.

Rationale for ivermectin and ASAQ Combination

SARS-CoV-2 infection is now better described and understood and can typically be divided in 2 sequential stages: the first one, with virus replication followed by the development of clinical symptoms that slowly decreases in 10 to 12 days whereas the developing inflammatory response starts being uncontrolled around day 8-10 leading to the severe pulmonary and systemic complications. This is described in the graph below.



In real-life setting, patients may be diagnosed at different stages of the infection and it is therefore important to combine treatments with complementary mechanisms of action to cover for both stages; a drug with a primary antiviral activity, and a treatment to primarily control the inflammation whilst also potentially having an inhibitory effect on SARS-CoV-2 replication and some level of immune host effect. Even in the absence of a direct antiviral effect of ivermectin, combining it with ASAQ will decrease any potential risk of viral replication.

Risks Related to ASAQ and IVM Combination

Given the SmPCs of the two individual products there is no expected drug-drug interactions or additional safety concerns due to the combination. Based on the available in vitro data on P-gp and CYP interaction and clinical data, the risk of interaction between ivermectin and artesunate/DHA as well as ivermectin and amodiaquine/DEAQ is currently considered very low: Ivermectin is a CYP3A4 and P-gp substrate, as well as a P-gp inhibitor. Artesunate, DHA, amodiaquine and DEAQ do not inhibit CYP3A4 nor P-gp. Artesunate, DHA and amodiaquine are not P-gp substrates (however data on DEAQ transport by P-gp are not available). Amodiaquine is a CYP2C8 substrate, and ivermectin does not inhibit this enzyme. DHA is metabolized via UGT11A9 and 2B7, but UGT inhibition data for ivermectin are not available.

Prohibited Medications:

ASAQ is not recommended to be administered concomitantly with drugs known to inhibit CYP2A6 (e.g., methoxsalen, pilocarpine, tranlycypromine) and/or CYP2C8 (e.g., trimethoprim, ketoconazole, ritonavir, saquinavir, lopinavir, gemfibrozil, montelukast).

The following drugs are known to induce prolongation of the QT-interval. Their concomitant use with ASAQ should be carefully evaluated:

- antiarrhythmics (e.g., amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, hydroquinidine, sotalol)

- neuroleptics (e.g., phenothiazines, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, or thioridazine) and antidepressant agents known to cause significant QT-interval prolongation (e.g., citalopram, escitalopram)
- certain antimicrobial agents, including agents of the following classes:
 - macrolides (e.g., erythromycin, clarithromycin)
 - fluoroquinolones (e.g., moxifloxacin, sparflaxacin)
 - imidazole and triazole antifungal agents
 - pentamidine
 - saquinavir
- certain non-sedating antihistamines (e.g., terfenadine, astemizole, mizolastine)
- cisapride
- droperidol
- domperidone
- bepridil
- diphemanil
- probucol
- levomethadyl
- methadone
- vinca alkaloids
- arsenic trioxide.

Interactions with drugs used for treatment of HIV (protease inhibitor-based antiretroviral regimens and efavirenz) and/or tuberculosis may occur, though little clinical data is available. Caution should be observed, and patients should be closely monitored for adverse events potentially related to such interactions, including liver toxicity and neutropenia.

Ivermectin increases the effects of warfarin by an unknown mechanism. Increased blood levels of drugs may occur with rare but serious interactions. In case of concomitant use, it should be closely monitored.

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Appendix 1.4 Fluoxetine and Inhaled Budesonide

This section describes the combination treatment for SARS-CoV-2 infections using a combination of fluoxetine and inhaled budesonide. Information is provided on the individual drug components, as well as in combination.

General information on Fluoxetin is presented in table below.

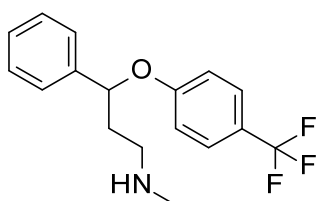
Table 11. General Information on fluoxetine

International Non-proprietary Name	Fluoxetine
Dosage Form	Capsules containing 20mg of Fluoxetine
Route of administration	Oral route
Dosing instructions	40 mg per day, once a day with two capsules of fluoxetin 20 mg
Duration of treatment	7 days
Composition	Active ingredient: Fluoxetine hydrochloride Excipients: Lactose monohydrate, microcrystalline cellulose, anhydrous colloidal silica, magnesium stearate. Shell of the capsule: titanium dioxide (E171), yellow iron oxide (E172), quinoline yellow (E104), indigo carmine (E132), gelatin.

Rationale for Choice of Fluoxetine

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) used in the treatment of major depressive disorder, obsessive-compulsive disorder (OCD), bulimia nervosa, panic disorder, and premenstrual dysphoric disorder. It is approved for use in adolescents and children 8 years of age. Fluoxetine was approved by the US FDA in December 1987. However, due to another mechanism of action, it is considered to hold both antiviral and anti-inflammatory properties that make it an attractive option for mild to moderate COVID patients, as described below. As it readily distributes in the CNS, this activity could also be seen as useful to treat the CNS-related symptoms and possibly prevent some of the post-COVID condition symptoms, namely brain fog¹.

Fluoxetine structure
Mw: 309.3



Data supporting the use in treatment of COVID-19

Preclinical:

- *In vitro*, fluoxetine and several other antidepressants (i.e., amitriptyline, fluvoxamine) inhibit the functional activity of Acid Sphingomyelinase (ASM) by detaching ASM from the cell membrane.
- ASM is a glycoprotein that functions as a lysosomal hydrolase, catalyzing degradation of sphingomyelin to phosphorylcholine and ceramide. The generation of ceramide alters the biophysical properties of the plasma membrane, these membrane changes mediate viral uptake. ASM is activated within 20 to 30 min after treatment with pp-VSV-SARS-CoV-2 spike
- Functional inhibition of ASM prevents uptake of SARS-CoV-2 virus by epithelial cells. Amitriptyline, following oral administration in humans, prevents infection by pp-VSV-SARS-CoV-2 of nasal epithelial cells *ex vivo*².
- *In vitro*, fluoxetine inhibits SARS-CoV-2 viral replication in the μM range: EC_{50} 0.69 μM (Vero E6), 0.82 μM (Calu-3). Fluoxetine remains effective against SARS-CoV-2 pseudo viruses with N501Y, K417N, and E484K spike mutations, and the B.1.1.7 (alpha) and B.1.351 (beta) variants of SARS-CoV-2³. There are currently no studies describing the efficacy of fluoxetine for the new delta and iota variants. Fluoxetine by inhibiting the functional activity of acid sphingomyelinase is reducing ceramide cell membrane levels used by the SARS-CoV-2 virus to enter the cells thus its efficacy is not predicted to be affected by mutations of the viral spike protein.
- Fluoxetine efficacy confirmed in SARS-CoV-2 infected human lung slices with a 2-3 log reduction in infectious virus titers after 3-days at 5.2 μM ⁴
- Fluoxetine significantly reduces infections viruses (-2.5 log vs saline) in a mouse model of SARS-CoV-2 infection at day 2 [unpublished data Céline Cougoule et al]
- Sigma-1 receptor (S1R) agonists, such as fluoxetine and fluvoxamine are reported to reduce inflammatory mediators associated with severe COVID-19, including IL-6, IL-10, TNF- α , and CCL-2⁵

Pharmacokinetics:

- Fluoxetine has measured human data showing a fluoxetine human lung: plasma split of 60:1⁶. Experimental data indicates similar lung: plasma split in experimental animals i.e., hamster [DNDi internal data].
- Report on desmethylfluoxetine half-life allowing a once-a-day administration and no need to taper^{7,8}
- PopPK modelling predicts that at a daily dose of 40 mg/day 90% of the population achieves the C_{trough} antiviral EC_{90} target in lung at day 4, and 92% are above by day 7⁸. Extended effect beyond end of dosing due to long elimination half-lives for fluoxetine (3 d) and desmethylfluoxetine (16 d)

Clinical:

- Based on retrospective observations there is a strong association between the use of antidepressants and reduced risk of death or intubation in patients hospitalized for COVID-19. Meta analysis show a significant association between use of antidepressant and reduced risk of intubation or death (HR, 0.56; 95% CI, 0.43–0.73, $p < 0.001$)⁹. Fluoxetine shows a strong association with the reduction of mortality or intubation (reduction potential up to 74%) in the same study.
- Fluvoxamine, a milder inhibitor of ASM activity¹⁰, showed significant effects in a randomized placebo-controlled study including 152 adult outpatients with confirmed COVID-19 and within 7 days symptom onset. The primary outcome measuring clinical deterioration within 15 days of randomization defined by meeting both criteria of (1) shortness of breath or hospitalization for shortness of breath or pneumonia and (2) oxygen saturation less than 92% on room air or need for supplemental oxygen to achieve oxygen saturation of 92% or greater. In this study clinical deterioration was observed in 0 patients treated with fluvoxamine vs 6 (8.3%) patients treated with placebo over 15 days¹¹.
- In a second placebo-controlled study in 1480 patients dosed with fluvoxamine significant effects on primary outcomes were demonstrated: 1) Emergency room visits due to the clinical worsening of COVID-19 (defined as participant remaining under observation for > 6 hours) 2) Hospitalization due to the progression of COVID-19 (defined as worsening of viral pneumonia) and/or complications within 28 days of randomization¹².

Dosing considerations for a COVID-19 trial

Fluoxetine is usually administered at a daily dose of 20 to 80 mg/day.

Based on the PK/PD modelling (F1000Research 2021, 10:477 (<https://doi.org/10.12688/f1000research.53275.1>), a daily dose of 40mg would allow to achieve the required concentrations for 55% of patients at Day 1 and over 90% at day 4. Given its long half-life, a one-week treatment will be sufficient to provide adequate plasma and lung concentrations for over 2 weeks. It is the proposed dose regimen.

Risks Related to Fluoxetine:

Fluoxetine is an antidepressant drug that functions as a selective serotonin reuptake inhibitor and is often used to treat depression, obsessive compulsive disorder and bulimia. It has fewer unwanted effects than other antidepressants. Its risk profile below is for chronic use in a psychiatrically ill population; the risks for short-term use are likely lower.

Undesirable effects (for the exhaustive list, refer to the SmPC):

General:

The most common side effects reported in patients treated with fluoxetine were headache, nausea, insomnia, fatigue, diarrhea. Undesirable effects may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

The following adverse events come from clinical trials in adults (n = 9297) and from spontaneous notification (full list of adverse events is detailed in the SmPC):

Very common ($\geq 1/10$): insomnia, headaches, asthenia

Common ($\geq 1/100$, $<1/10$): Anxiety, nervousness, impatience, decreased libido, sleeping troubles, abnormal dreams, decreased appetite, attention disorder, dizziness, dysgeusia, lethargy, drowsiness, tremors, blurred vision, palpitations, prolongation of the QT interval on ECG ($QTc \geq 450$ msec), flushing, yawning, vomiting, dyspepsia, dry mouth, skin rash, urticaria, itching, hyperhidrosis, arthralgia, gynecological bleeding, erectile dysfunction, ejaculation disorders, frequent urination, chills, weight loss.

Uncommon ($\geq 1/1000$, $<1/100$): Exaltation, euphoria, abnormal thoughts, abnormal orgasms, bruxism, suicidal thoughts and behavior, psychomotor hyperactivity, dyskinesia, ataxia, balance disorder, myoclonus, memory impairment, tinnitus, mydriasis, hypotension, dyspnea, epistaxis, dysphagia, gastrointestinal bleeding, alopecia, increased tendency to bruise, cold sweat, increased transaminases and gamma-glutamyl transferases, faintness, sexual disorders.

Rare ($\geq 1/10000$, $<1/1000$): Thrombocytopenia, Neutropenia, Leukopenia, anaphylactic reaction, Inappropriate secretion of antidiuretic hormone, Hypomania, Mania, Hallucinations, Agitation, Panic attacks, Confusion, Aggression, hyponatremia, Convulsions, Orofacial dyskinesias, Serotonin syndrome, Ventricular arrhythmia including torsade de pointes, Vasodilatation, Pharyngitis, Pulmonary involvement (process inflammatory diseases of various histological types and / or fibrosis), idiosyncratic hepatitis, angioedema, ecchymosis, photosensitivity, purpura, erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis (Lyell syndrome), myalgia, urinary retention, galactorrhea, hyperprolactinemia, priapism.

Special warnings and precautions for use (for the exhaustive list, refer to the SmPC):

Fluoxetine should be used with caution in patients with congenital long QT, a history of familial QT prolongation or other clinical conditions predisposing to arrhythmias (for example, hypokalemia, hypomagnesemia, bradycardia, acute myocardial infarction, or decompensated heart failure) or increased exposure to fluoxetine (for example in hepatic insufficiency), or concomitant use with drugs causing QT prolongation and / or torsade de pointes.

As with all antidepressants, treatment with **fluoxetine** should be discontinued in patients with manic state.

Fluoxetine should be avoided in patients with unstable epilepsy; close surveillance is necessary in patients with controlled epilepsy. There is a potential risk of seizures during treatment with antidepressants. Therefore, fluoxetine should be initiated with caution in patients with a history of epilepsy. Treatment should be discontinued in any patient with a seizure or increased frequency of these.

Fluoxetine can lead to the development of akathisia, characterized by agitation that is perceived as unpleasant or distressing and the need to be always on the move, which is often associated with an inability to sit or stand still. Rather, these symptoms occur during the first few weeks of treatment.

In diabetic patients, blood sugar levels may be disturbed during treatment with SSRIs. Ongoing hypoglycemia treatment and hyperglycemia upon discontinuation of **fluoxetine** have been reported. The dosage of insulin and / or oral antidiabetic therapy may need to be adjusted.

Rashes, anaphylactoid reactions and progressive systemic manifestations, sometimes severe (involving skin, kidneys, liver or lungs) have been reported. As soon as a rash or any other manifestation appears allergic for which no other etiology has been identified, it is necessary to discontinue **fluoxetine**.

Since cases of mydriasis have been reported (uncommon), **fluoxetine** should be prescribed with caution in patients with patients with increased pressure in the eye or at risk for acute angle-closure glaucoma.

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Use during pregnancy and breastfeeding:

Pregnancy category C (FDA).

A few epidemiological studies suggest an increased risk of cardiovascular malformations associated with the use of fluoxetine during the first trimester of pregnancy. The mechanism is not known. Overall, the data suggest that the risk of cardiovascular malformation in children after maternal exposure to fluoxetine is approximately 2/100, while the expected rate for this type of malformation is approximately 1/100 in the general population.

Epidemiological data suggest that the use of SSRIs during pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension (PPHN) in the newborn. The observed risk was about 5 cases per 1000 pregnancies. In the general population, the risk of PPHN is 1 to 2 cases per 1000 pregnancies.

Fluoxetine should not be used during pregnancy unless its use justifies the potential risk to the fetus.

Data from observational studies indicate an increased risk (less than 2-fold) of postpartum hemorrhage following exposure to SSRIs / SNRIs in the month following birth.

Following the update communication of the FDA in 2011, on the use of SSRI antidepressants by women during pregnancy and the potential risk of the rare heart and lung condition known as persistent pulmonary hypertension of the newborn (PPHN), the FDA stated that there was

not sufficient evidence to conclude that SSRI use in pregnancy causes PPHN, and therefore recommends that health care providers treat depression during pregnancy as clinically appropriate^{15, 16, 17}.

Pregnant and recently pregnant women with covid-19 attending or admitted to the hospitals for any reason are less likely to manifest symptoms such as fever, dyspnoea, and myalgia, and are more likely to be admitted to the intensive care unit or needing invasive ventilation than non-pregnant women of reproductive age^{16, 18}.

Therefore, there is benefit of early treatment in pregnant women with COVID 19.

Fluoxetine and its metabolite norfluoxetine are secreted in breast milk. Adverse events have been reported in children who are breastfed by mothers treated with fluoxetine. If treatment with fluoxetine is necessary, discontinuation of breastfeeding should be considered. However, if breast-feeding is continued, the minimum effective dose of fluoxetine should be prescribed^{13,14}.

The average amount of drug in breastmilk is higher with fluoxetine than with most other SSRIs and the long-acting, active metabolite, norfluoxetine, is detectable in the serum of most breastfed infants during the first 2 months postpartum and in a few thereafter. Adverse effects such as colic, fussiness, and drowsiness have been reported in some breastfed infants. Decreased infant weight gain was found in one study, but not in others¹⁹. No adverse effects on development have been found in a few infants followed for up to a year¹⁸. Infants from mothers taking fluoxetine (20-40 mg daily) during pregnancy and lactation and a control group of infants from medication-free mothers were compared on weight and neurological development through 1 year. Infant weights were not significantly different between the two groups and the neurological development of all infants was judged as normal by pediatricians and physiotherapists²⁰.

If fluoxetine is required by the mother, it is not a reason to discontinue breastfeeding. A safety scoring system finds fluoxetine use to be possible during breastfeeding, although others do not recommend its use. Several rating scales exist for determining risks of medications used in lactation, ranging from “contraindicated in breastfeeding” to “compatible/safest,” which is reserved for agents that have been studied in breastfeeding humans and have not demonstrated any AEs in infants. Uguz recently proposed a third scoring system specifically for psychotropic medications²¹. Although these categorical ratings are important to keep in mind and may be a good starting point for researching the effects of medications during breastfeeding, not all researchers agree with their adoption, more in-depth resources should be consulted in order to fully inform clinical decisions²². As with any clinical decision, the risks and benefits of continuing or initiating a medication during breastfeeding must be carefully weighed by the investigator jointly with the patient.

If the mother was taking fluoxetine during pregnancy or if other antidepressants have been ineffective, most experts recommend against changing medications during breastfeeding. Otherwise, agents with lower excretion into breastmilk may be preferred, especially while nursing a newborn or preterm infant. The breastfed infant should be monitored for behavioral side effects such as colic, fussiness or sedation and for adequate weight gain. Breastfed infants exposed to an SSRI during the third trimester of pregnancy have a lower risk of poor neonatal adaptation than formula-fed infants¹⁸.

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General information on inhaled Budesonide is presented in table below.

Table 12. General Information on Budesonide

International Non-proprietary Name	Budesonide
Dosage Form	Inhalation rotacaps, 400 mcg / capsule
Route of administration	Oral inhalation
Dosing instructions	400 mcg BID per day
Duration of treatment	7 days
Composition	Active ingredient: Budesonide Excipients: q.s

Rationale for Choice of Budesonide

- Budesonide is an inhaled corticosteroid developed for treatment of asthma by local treatment in the lung
- Potent GR agonist providing high efficacy in the lung with limited systemic spill-over effect
- Budesonide available using a dry powder inhaler offering increased ease of use and higher lung deposited dose compared to corresponding aerosol delivery systems
- Budesonide has a good safety profile and is approved for use in children >12 months
- 400 µg BID provides an anti-inflammatory effect when used in treatment of mild to moderate asthma without significant side effects

Data supporting the use in treatment of COVID-19 Rational

Two clinical studies indicate positive outcome from the use of inhaled budesonide reducing the risk for disease progression:

Budesonide STOIC PhII study: Data suggest a potentially effective treatment to prevent the long-term morbidity from persistent COVID-19 symptoms

- Open-label, parallel-group, phase 2, randomized controlled trial (STOIC)¹, 167 patients recruited, 400 µg bid until symptom resolution
- Clinical recovery was **1 day shorter** in the budesonide group compared with the usual care group (median 7 days [95% CI 6 to 9] in the budesonide group vs 8 days [7 to 11] in the usual care group; log-rank test p=0.007)
- Mean proportion of days with a fever in the first 14 days was **lower in the budesonide** group (2%, SD 6) than the usual care group (8%, SD 18; Wilcoxon test p=0.051)

- **Fewer participants randomly assigned to budesonide had persistent symptoms at days 14 and 28** compared with participants receiving usual care (difference in proportions 0.204, 95% CI 0.075 to 0.334; $p=0.003$)
- The mean total score changes in the Common Cold Questionnaire (CCQ) and the InFLUenza Patient Reported Outcome Questionnaire (FLUPRO) over 14 days was significantly better in the budesonide group compared with the usual care group (CCQ mean difference -0.12 , 95% CI -0.21 to -0.02 [$p=0.016$]; FLUPRO mean difference -0.10 , 95% CI -0.21 to -0.00 [$p=0.044$]).
- Blood oxygen saturations and SARS-CoV-2 load were not different between the groups.

Budesonide PRINCIPLE platform study²: Interim analysis, inhaled budesonide reduced time to recovery by a median of 3 days in people with COVID-19 with risk factors for adverse outcomes.

- Multicenter, open-label, multi-arm, adaptive platform randomized controlled trial (PRINCIPLE)
 - People aged ≥ 65 years, or ≥ 50 years with comorbidities, and unwell ≤ 14 days with suspected COVID-19.
 - Participants were randomized to usual care, usual care plus inhaled budesonide (800µg twice daily for 14 days)
- Interim analysis 4663 patients March 4, 2021:
 - Time to first self-reported recovery **was shorter in the budesonide group** compared to usual care (hazard ratio 1.208 [95% BCI 1.076 – 1.356], probability of superiority 0.999, estimated benefit [95% BCI] of 3.011 [1.134 – 5.41] days)
 - At 28 days follow up, there were 59/692 (8.5%) COVID-19 related hospitalizations/deaths in the budesonide group vs 100/968 (10.3%) in the usual care group (estimated percentage benefit, 2.1% [95% BCI -0.7% – 4.8%], probability of superiority 0.928)

Dosing considerations for a COVID-19 trial

The proposed dosage is similar to the one used in the STOIC COVID studies, with good tolerability for a total duration of 7 days.

Risks Related to Budesonide:

Undesirable effects (for the exhaustive list, refer to the SmPC):

As per the SmPC and patient's leaflet of Budesonide, the following adverse reactions were reported in clinical trials in patients treated with budesonide, an incidence of $\geq 3\%$:

Respiratory infection, pharyngitis, sinusitis, rhinitis, voice alteration, headache, flu syndrome, pain, back pain, fever, oral candidiasis, dyspepsia, gastroenteritis, nausea, arthralgia, cough.

The following adverse reactions were reported in clinical trials in patients treated with budesonide, an incidence of 1 to 3%:

Neck pain, syncope, abdominal pain, dry mouth, vomiting, weight pain, fracture, myalgia, hypertonia, migraine, ecchymosis, insomnia, taste perversion.

Use during pregnancy and breastfeeding:

Pregnancy Category B^{2,3}

Results from a large prospective epidemiological study and from worldwide post marketing experience indicate no increased teratogenic risk associated with the use of inhaled budesonide. In animal studies, glucocorticosteroids have been shown to induce malformations. This is not likely to be relevant for humans given recommended doses, but therapy with inhaled budesonide should be regularly reviewed and maintained at the lowest effective dose. Administration of budesonide during pregnancy requires that the benefits for the mother be weighed against the risks for the fetus. Budesonide should only be used during pregnancy if the expected benefits outweigh the potential risks.

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Results from a large population-based prospective cohort epidemiological study reviewing data from 3 Swedish registries covering approximately 99% of the pregnancies from 1995-1997 indicate no increased risk for congenital malformations from the use of inhaled drug during early pregnancy. These same data were used in a second study bringing the total to 2,534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of congenital malformations among infants whose mother were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).

Budesonide, like other corticosteroids, is secreted in human milk. However, at therapeutic doses of budesonide no effects on the suckling child are anticipated. Budesonide can be used during breast feeding⁴.

Rationale for Fluoxetine and Inhaled Budesonide Combination

SARS-CoV-2 infection is now better described and understood and can typically be divided in 2 sequential stages: the first one, with virus replication followed by the development of clinical symptoms that slowly decreases in 10 to 12 days whereas the developing inflammatory

response starts being uncontrolled around day 8-10 leading to the severe pulmonary and systemic complications.

In real-life setting, patients may be diagnosed at different stages of the infection and it is therefore important to combine treatments with complementary mechanisms of action to cover for both stages; a drug with a primary antiviral activity but some level of immune host effect, and a treatment administered locally to primarily control the local inflammation whilst also potentially having an inhibitory effect on SARS-CoV-2 replication. Combining Budesonide with Fluoxetine will allow impacts on both stages of the disease.

Risks Related to Fluoxetine and Inhaled Budesonide Combination

There is no reported use of the drug combination of Fluoxetine and Inhaled Budesonide and no formal safety studies have been conducted on the combination. Pharmacodynamic studies in murine models of SARS-CoV2 have been performed and have not indicated a pattern of increased toxicity. Given the SmPCs of the two individual compounds there is no expected drug-drug interactions or additional safety concerns due to the combination.

Prohibited Medications related to Fluoxetine (for the exhaustive list, refer to the SmPC):

Monoamine Oxidase Inhibitors (MAOIs):

The use of MAOIs intended to treat psychiatric disorders with fluoxetine or within 5 weeks of stopping treatment with Fluoxetine is contraindicated due to an increased risk of serotonin syndrome. The use of Fluoxetine within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated.

Starting Fluoxetine in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome.

The use of **Fluoxetine** is contraindicated with the following:

- Pimozide
- Thioridazine

Pimozide and thioridazine prolong the QT interval. Fluoxetine can increase the levels of pimozide and thioridazine through inhibition of CYP2D6 and can also prolong the QT interval.

- Metoprolol: the risk of side effects with metoprolol, including excessive bradycardia, may be increased by inhibits its metabolism by fluoxetine

Combinations requiring caution (for the exhaustive list, refer to the SmPC):

The concomitant use of **fluoxetine** and drugs that induce QT prolongation should be carefully evaluated. These include specific antipsychotics (e.g., ziprasidone, iloperidone, chlorpromazine, mesoridazine, droperidol); specific antibiotics (e.g., erythromycin, gatifloxacin, moxifloxacin, sparfloxacin); Class 1A antiarrhythmic medications (e.g., quinidine, procainamide); Class III antiarrhythmics (e.g., amiodarone, sotalol); and others

(e.g., pentamidine, levomethadyl acetate, methadone, halofantrine, mefloquine, dolasetron mesylate, probucol or tacrolimus).

CNS Acting Drugs: Caution is advised if the concomitant administration of **fluoxetine** and such drugs is required. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status.

Drugs Metabolized by CYP2D6:

Fluoxetine is primarily metabolized by CYP2D6. Concomitant treatment with CYP2D6 inhibitors can increase the concentration of fluoxetine. Fluoxetine inhibits the activity of CYP2D6 and may make individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer.

Coadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., Tricyclic antidepressants (TCAs)), antipsychotics (e.g., phenothiazines and most atypicals), and antiarrhythmics (e.g., propafenone, flecainide, and others) should be approached with caution.

Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous 5 weeks. Thus, his/her dosing requirements resemble those of poor metabolizers.

If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (e.g., flecainide, propafenone, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued.

Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, Warfarin):

Concomitant use of fluoxetine and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation should be approached with caution since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents have been associated with an increased risk of bleeding.

Altered anticoagulant effects, including increased bleeding, have been reported when SNRIs or SSRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when fluoxetine is initiated or discontinued.

Benzodiazepines — The half-life of concurrently administered diazepam may be prolonged in some patients. Coadministration of alprazolam and fluoxetine has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels.

Antipsychotics — Some clinical data suggests a possible pharmacodynamic and/or pharmacokinetic interaction between SSRIs and antipsychotics. Elevation of blood levels of haloperidol and clozapine has been observed in patients receiving concomitant fluoxetine.

Anticonvulsants — Patients on stable doses of phenytoin and carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment.

Lithium — There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity and increased serotonergic effects have been reported. Lithium levels should be monitored when these drugs are administered concomitantly.

Drugs Tightly Bound to Plasma Proteins — Because fluoxetine is tightly bound to plasma proteins, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (e.g., Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect.

Drugs Metabolized by CYP3A4 — In an *in vivo* interaction study involving coadministration of fluoxetine with single doses of terfenadine (a CYP3A4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine.

Tamoxifen – As a decrease in the effect of tamoxifen cannot be excluded, the combination with strong inhibitors of CYP2D6 (including fluoxetine) should be avoided as much as possible.

Alcohol should be avoided while treatment with Fluoxetine.

Prohibited medications related to Budesonide (for exhaustive list, refer to SmPC):

Concomitant administration of other known inhibitors of CYP3A4, such as, itraconazole, clarithromycin, ketoconazole, erythromycin, HIV protease inhibitors and cobicistat-containing products, may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Care should be exercised when budesonide is coadministered with long-term ketoconazole (weak interaction)⁵ and other known strong CYP3A4 inhibitors.

Raised plasma concentrations of and enhanced effects of corticosteroids have been observed in women also treated with oestrogens and contraceptive steroids, but no effect has been observed with budesonide and concomitant intake of low dose combination oral contraceptives.

Because adrenal function may be suppressed, an ACTH stimulation test for diagnosing pituitary insufficiency might show false results (low values).

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5. <https://www.covid19-druginteractions.org/checker>

Appendix 2. Immunological Study

To be added if applicable.

Appendix 3. Epidemiological Study

To be added if applicable.

Appendix 4. Schedule of Events**Table 13. Schedule of Events in Master Study**

Time (and window, if allowed)	Screening		Monitoring				
	Day 0	Day 1 ^C	Days 2-6, 8-13 and 15-20 ^A	Days 7 and 14	Day 21	Day 35	Unscheduled
Patient information and informed consent	X						
Demographic data	X						
Medical history	X						
Urine Pregnancy test ⁶	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		
Hospitalisation not due to aggravation of COVID-19				X	X ^B		
ECG ⁴	X			X	X ^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					

	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	Day 35	Unscheduled
Start of IP administration		X					
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		
SAE and/or pregnancy monitoring						X ^D	

^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

^D Via telephone

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.

⁶ Only for non pregnant woman with childbearing potential

Appendix 5. Country Specific

Document here treatment used for your countries, if not using All the arms (

Document here local community engagement, if applicable.

Clarify here how reimbursement of transportation and/or missed days is done for your country

Document here duration of data and/or sample storage if less than 25 years

Please add any campaign plan for recruitment if applicable

Document here how active screening will be performed in the country

For Countries participating to the Ancillary studies:

Document if Biobanking is done at site level or centralised. If done at site level, please explain (governance: for ex: controlled access to sample storage, anonymisation of patient Ids, sample only for Study purpose etc..).

Appendix 6. Coverage Africa Study

To be added if applicable.