Protocol

Protocol for: Reis G, Silva EASM, Silva DCM, et al. Effect of early treatment with ivermectin among patients with Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2115869

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

EFFECT OF EARLY TREATMENT WITH IVERMECTIN AMONG PATIENTS WITH COVID-19

TOGETHER Trial Protocols

SUPPLEMENTARY APPENDIX PROTOCOL AND STATISTICAL ANALYSIS PLAN

Contents:

Clinical Trial Protocol

COVID19_AMB_Brazil

A multicenter, adaptive, double-blind, randomized, placebo-controlled study to evaluate the effect of fluvoxamine, ivermectin, and metformin in reducing hospitalization in patients with mild COVID-19 and high risk for complications.

Authors: Gilmar Reis MD, PhD[1,2]; Eduardo Augusto dos Santos Moreira Silva MD, PhD[1,2]; Daniela Carla Medeiros Silva MD, PhD[1,2]; Edward J Mills, PhD[3]; Lehana Thabane, PhD[3], Gordon H. Guyatt MD[3].

Document Type	Clinical Trial Protocol
Study Code	COVID19_AMB_Brazil_2
Registration Number	None
Version Number	v1.0 (Original Protocol)
Development Phase	III (New Indication)
Release Date	15-FEB-2021

1. Cardresearch - Cardiology Care and Research, Belo Horizonte, Brazil
2. Pontifical Catholic University of Minas Gerais, Belo Horizonte, Brazil
3. McMaster University, Hamilton, Canada

INDEX

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ARtD	Adverse reactions to the drug
AE	Adverse event
BP	Blood pressure
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Group
DSMC	Data Security Monitoring Committee
EAC	Event Adjudication Committee
IEC	Independent Ethics Committee
CONEP	National Commission for Ethics in Research
ECG	Electrocardiogram
EOS	End of study
ET	Early Termination
GCP	Good Clinical Practice
HR	Hazard ratio
ICF	Informed Consent Form
ICH	International Council for Harmonisation
REC	Research Ethics Committee
IWRS	Interactive Internet response system
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SUS	Single Health System
SUSAR	Suspected Unexpected Serious Adverse Reaction
EADT	Adverse event resulting from treatment
AESI	Adverse Event of Special Interest

GLOSSARY OF TERMS

Evaluation	A procedure used to generate data needed for the study
Cohort	A group of newly enrolled participants treated at a specific dose and regimen (i.e., treatment group) at the same time
Control medication	Any drug (an active drug or an inactive drug, such as a placebo) that is used as a comparator for the drug tested in the trial
Drug Level	The dose of the medication administered to the participant (daily or weekly total etc.).
Inclusion	Point/moment of the participant's entry into the study for which informed consent needs to be obtained (i.e., before starting any procedure described in the protocol)
Period	A part of the study that serves a specific purpose. Typical periods are: selection/recruitment, *washout* period, treatment, and follow-up
Drug under investigation	The drug whose properties are being tested in the study; this definition is consistent with US CRF 21, Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Treatment under investigation	All the drugs whose properties are being tested in the study as well as their associated control treatments. This *includes* any placebo, any active control, and also approved drugs used outside their approved indications/doses or tested in a fixed combination. The treatment under investigation generally *does not include* concomitant background therapies specified by the protocol when these are standard treatments in this indication
Drug Number	A unique identifier on the label of each package of the study/investigational drug in studies that dispense medication using an IRT system
Protocol	A written record of all procedures to be followed in a study, which describes all administrative, documentation, analytical, and clinical processes to be used in the study.
Part	A single component of a trial that contains different objectives or populations within such a single trial. Common parts within a trial are: a single-dose part and a multi-dose part, or a part in patients with established disease and those with newly diagnosed disease.
Period	A subdivision of a crossover study
Premature withdrawal of a participant/patient	The time point when the participant exits the trial before the planned completion of all trial treatment administration and/or assessments; at this time, all trial treatment administration is discontinued, and no further assessments are planned unless the participant is followed up for progression and/or survival
Randomization Number	A unique identifier assigned to each randomized participant, corresponding to a specific treatment arm designation
Study drug/treatment	Any single drug or combination of drugs administered to the patient as part of required study procedures; includes the investigational drug, active treatment periods (*run-in*) or background therapy

Study/investigational treatment discontinuation	Point/time at which the participant permanently stops using the study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Participant number	A number assigned to each patient who is included in the study
Variable	A measured value or an assessed response that is determined in a specific evaluation and used in data analysis to assess the drug tested in the trial

PROTOCOL OVERVIEW

Protocol – COVID-19_MG_AMB_2

Title:	A multicenter, adaptive, double-blind, randomized, placebo-controlled study to evaluate the effect of fluvoxamine, ivermectin, and metformin in reducing hospitalization in patients with mild COVID-19 and a high risk of complications.
Short Title:	Repositioning of available medications for outpatient treatment of patients with COVI-19 and mild symptoms.
Product under Investigation:	Fluvoxamine, Ivermectin, Metformin
Indication:	COVID-19 Infection in Outpatients
Phase:	PHASE III – New indication
Sponsor	CARDRESEARCH – Cardiology Care and Research LTDA
Study code	COVID19_AMB_2
Coordinating Researchers:	Gilmar Reis, Eduardo Augusto dos Santos Moreira Silva, Daniela Carla Medeiros Silva, Edward J Mills, Lehana Thabane, Gordon H Guyatt
Proposing Institutions:	Cardresearch – Cardiology Care and Research LTDA
Researchers / Collaborating Institutions	Ed. J Mills PhD Lehana Thabane PhD McMaster University, Hamilton, Canada
Objectives:	<u>Primary Objective(s)</u> • To evaluate the effect of fluvoxamine, ivermectin, and metformin in reducing the need for emergency care AND observation for longer than 06h due to worsening COVID-19; • To evaluate the effect of fluvoxamine, ivermectin and metformin in reducing the need for Hospitalization due to COVID-19 related complications <u>Co-primary objective:</u> • To evaluate the effect of fluvoxamine, ivermectin and metformin in reducing mortality associated with COVID-19 up to 28 days from randomization. <u>Secondary objective(s)</u> • To evaluate, in comparison with placebo, the effect of fluvoxamine, ivermectin and metformin on the following parameters: o Reduction in viral load after randomization ($D_3$and D_7); o Number of days with respiratory symptoms after randomization; o Serious adverse events after randomization; o Time from start of treatment to need for hospital admission/emergency care due to progression of COVID-19 o Time from start of treatment to the need for hospitalization for any cause; o Effect of Metformin in diabetic patients who used metformin before versus those who did not use metformin. o Safety and tolerability of the proposed treatment regimens; o Quality of life and symptoms scale (Eq-5D-5L, WHO Flu Scale).

<table>
<tr><td></td><td>

Time from start of treatment to death in 14, 28 days, and 60 days.
Safety and tolerability

</td></tr>
<tr><td>Design:</td><td>Multicenter, double-blind, adaptive, prospective, randomized, parallel-group, placebo-controlled, 8-week follow-up after randomization.</td></tr>
<tr><td>Treatment:

Treatment (continued):</td><td>
Table 1 - Study treatment regimen
<table>
<tr><th></th><th colspan="3">Treatment Scheme</th></tr>
<tr><th>Visit
Clinic</th><th>Fluvoxamine</th><th>Ivermectin</th><th>Metformin XR</th></tr>
<tr><td>D_0 – randomization</td><td>100 mg</td><td>See Table 2 and 3</td><td>750 mg BID</td></tr>
<tr><td>D_1 to D_2</td><td>100 mg BID</td><td>See Table 2 and 3</td><td>750 mg BID</td></tr>
<tr><td>D_3 to D_9</td><td>100 mg BID</td><td>No medication</td><td>750 mg BID</td></tr>
</table>
<table>
<tr><th>Peso (kg)</th><th>Número de comprimidos de 06 mg</th><th>Dose total mg</th><th>Dose (mcg kg)</th></tr>
<tr><td>40 - 45</td><td>3</td><td>18</td><td>400 – 450</td></tr>
<tr><td>46 – 50</td><td>3</td><td>18</td><td>360 - 391</td></tr>
<tr><td>51 - 55</td><td>4</td><td>24</td><td>436 - 470</td></tr>
<tr><td>56 – 60</td><td>4</td><td>24</td><td>400 - 428</td></tr>
<tr><td>61 – 65</td><td>4</td><td>24</td><td>369 - 393</td></tr>
<tr><td>66 – 70</td><td>5</td><td>30</td><td>428 - 450</td></tr>
<tr><td>71 - 80</td><td>5</td><td>30</td><td>422 - 375</td></tr>
<tr><td>80 - 90</td><td>6</td><td>36</td><td>400 - 450</td></tr>
<tr><td>> 91</td><td>6</td><td>36</td><td>Até 400</td></tr>
</table>
Tabela 2 – Posologia considerando comprimidos de ivermectina 06 mg
</td></tr>
</table>

Peso (kg)	20 mg Wafer	05 mg Wafer	Dose total mg	Dose (mcg/ kg)
40 – 45	01 (20 mg)	não	20	444 - 500
46 – 50	01 (20 mg)	não	20	400 - 434
51 - 55	01 (20 mg)	01 (05 mg)	25	454 - 490
56 – 60	01 (20 mg)	01 (05 mg)	25	416 - 446
61 – 65	01 (20 mg)	01 (05 mg)	25	384 – 409
66 – 70	01 (20 mg) + 01 (10 mg)	não	30	428 – 454
71 – 80	01 (20 mg) + 01 (10 mg)	não	30	375 – 422
80 – 90	01 (20 mg) + 01 (10 mg)	01 (05 mg)	35	388 – 437
> 91	01 (20 mg) + 01 (10 mg)	01 (05 mg)	35	Até 384

Tabela 3 – Posologia ivermectina formulação sublingual (comp. de 05 e 20 mg)

Considering results from previous studies of the effects of medications in reducing viral load and in current studies in patients with COVID-19, where there are indications of benefits (non-randomized studies, or open randomized or randomized and not placebo-controlled) and the current situation of the virtual absence of effective treatment associated, This will be re-evaluated through an interim blinded analysis, by a committee independent of the research, which will be carried out when we reach 25, 50, and 75% of the initially projected sample of participants. At this time, we will reevaluate the sample calculation considering the actual number of outcomes obtained during the course of the trial, and an evaluation will also be performed considering the possibility of the futility of any of the arms.

This analysis will be performed in a blinded fashion, evaluating the endpoints with simulations to limit type I errors below 5% (97.5% or greater probability of superiority over the control group). Decisions can be made at this point regarding (1) terminating arms of the study if there are no acceptable projections of benefit over futility or terminating the protocol if futility criteria are met for all proposed arms. The doses of the drugs used will be as described in Table 1.
After the patient signs the Informed Consent Form and has the study procedures related to the screening visits, the research subject will be randomized to one of the four study arms: (1) Fluvoxamine; (2) Ivermectin; (3) Metformin and (4) Placebo, with doses as provided in the clinical protocol (table 1). This day will be considered as D_1 (Randomization).
This will be followed by daily administration of the investigational products according to the treatment proposal according to the research arms until D_{10}. All patients will undergo a rapid test for confirmation of COVID-19 at the time of screening. The viral load will be evaluated in the initial 600 patients (150 patients per treatment group) through nasopharyngeal/oral samples, which will be collected immediately before randomization, on D_3 and on D_7 for RT-PCR.

Inclusion Criteria	

Inclusion Criteria (Continued)	1. Patients over 18 years of age with the capacity to provide informed consent 2. Patients seen at a Primary Care Unit of the Brazilian National Health System (SUS), or patients seen at SUS or supplementary care units with an acute clinical picture compatible with COVID 19 and symptoms beginning within 7 days of the screening date; 3. Patients over 18 years of age and with at least ONE of the following criteria a. Age 50≥ years (do not need any of the other criteria) b. *Diabetes mellitus* requiring oral medication or insulin c. Hypertension requiring at least 01 oral medication for treatment d. Known cardiovascular diseases (heart failure, congenital heart disease, valve disease, coronary artery disease, myocardiopathy under treatment, clinically manifest heart diseases with clinical repercussions) e. Lung disease symptomatic and/or under treatment (emphysema, fibrosing diseases) f. Patients with symptomatic asthma requiring chronic use of agents for symptom control. g. Smoking h. Obesity, defined as BMI > 30 kg/m^2 on weight and height information provided by the patient; i. Transplant Patients j. Patient with stage IV chronic kidney disease or on dialysis. k. Immunosuppressed patients/in use of corticotherapy (equivalent to at least 10 mg prednisone per day) and/or immunosuppressive therapy) l. Patients with a history of Cancer in the past 05 years or currently undergoing oncological treatment 4. Patient with a positive rapid test for SARS-CoV2 antigen performed at the time of screening or patient with a positive diagnostic test for SARS-CoV2 within 7 days of symptom onset. 5. Willingness to use the proposed investigational treatment and follow the procedures foreseen in the research
Exclusion Criteria:	1. negative diagnostic test for SARS-CoV2 associated with acute influenza symptoms (patient with a negative test taken early and becomes positive a few days later is eligible, provided he/she is < 07 days from the onset of influenza symptoms); 2. Patients with an acute respiratory condition compatible with COVID-19 seen in the primary care network and with a decision to hospitalize; 3. Patients with an acute respiratory condition due to other causes; 4. Patients Vaccinated for SARS-CoV-2

Criteria for Exclusion (cont...)	5. Dyspnea secondary to other acute and chronic respiratory causes or infections (e.g., decompensated COPD, acute bronchitis, pneumonia, primary pulmonary arterial hypertension); 6. Acute influenza presenting at least ONE of the criteria below: a. Respiratory Rate > 28/min; b. SaO2 < 90% or < 93% on nasal oxygen therapy at 10 l/ min; c. PaO_2/FIO_2 < 300 mmHg 7. Patients taking serotonin reuptake inhibitors (Donepezil, Sertraline) 8. Use of the following medications in the last 14 days: a. Monoamine-Oxidase-Inhibitors (MAOI): Phenelzine, Tranylcypromine, Selegiline, Isocarboxazid, moclobemide; b. Use of iodinated contrasts during the treatment until 05 days after the end; c. Use of Antiretroviral Agents (Treatment of Acquired Immune Deficiency Syndrome – AIDS) 9. Patients with severe psychiatric disorders or major depression not controlled or controlled with any of the prohibited drugs (item above); 10. Pregnant or nursing patients; 11. History of severe ventricular cardiac arrhythmia (ventricular tachycardia, recovered ventricular fibrillation patients) or Long QT Syndrome; 12. History of diabetic ketoacidosis or a clinical condition that maintains persistent metabolic acidosis; 13. Surgical or contrast use planned to occur during treatment or within 5 days of the last dose of study medication; 14. Current daily and/or uncontrolled alcoholism; 15. History of seizures in the last month or an uncontrolled convulsional condition; 16. Clinical history of Liver Cirrhosis or Child-Pugh C classification; 17. Patients with known severe degenerative neurological diseases and/or severe mental illness; 18. Inability of the patient or representative to give consent or adhere to the procedures proposed in the protocol; 19. Hypersensitivity and/or known intolerance to Fluvoxamine, Ivermectin or Metformin; 20. Inability to take oral medications;
Primary and Secondary Outcomes:	<u>Primary endpoint:</u> • To evaluate the effect of fluvoxamine, ivermectin, and metformin in reducing the need for emergency care AND observation for longer than 06h due to worsening COVID-19; • To evaluate the effect of fluvoxamine, ivermectin and metformin in reducing the need for Hospitalization due to complications and/or worsening of COVID-19 <u>Co-primary Outcome:</u>

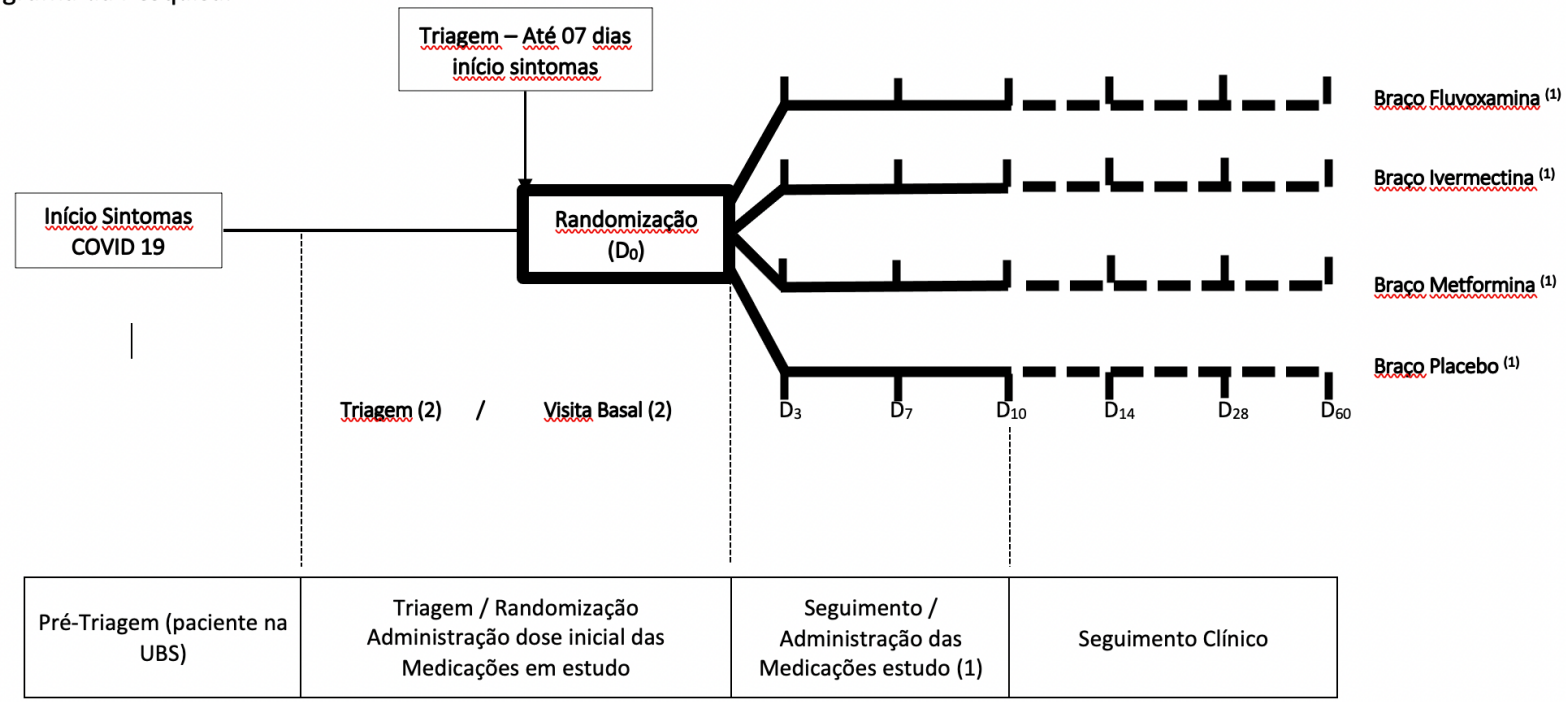
	To evaluate the effect of Fluvoxamine, Ivermectin and Metformin in reducing mortality associated with COVID-19 up to 28 days from randomization. <u>Secondary outcomes:</u> The secondary endpoints will assess, relative to the placebo group: • Change in viral load on day 03 and 07 after randomization (Evaluation to be performed on the first 600 randomized patients – 150 patients in each stratum); • Time to clinical improvement (up to 28 days from randomization), defined as greater than 50% improvement in reference to symptoms at the time of randomization; • Time to clinical failure, defined as the time until hospitalization due to clinical progression of COVID-19 (lower respiratory tract viral infection associated with dyspnea requiring oxygen therapy; hospitalization due to progression of COVID-19) or complications directly associated with COVID-19; • Number of days with respiratory symptoms since randomization • Hospitalization for any cause • Hospitalization due to progression of COVID-19 • Mortality due to pulmonary complications • Cardiovascular mortality • Mortality from any cause • Adverse events (up to 28 days); • COVID-19 symptom scale assessment (D_1 to D_{28}) • WHO Clinical Worsening Scale Assessment (D_1 to D_{10}) • Assessment of the PROMIS Global Health Scale (“Global-10”) days 14 and after60 randomization • Mortality rate of patients at day 14 and 28 days; • Proportion of non-adherent patients with the product under investigation; • Specific adverse reactions to the study medications: fluvoxamine, ivermectin and metformin.
Procedures	See study procedure schedule for details and applicable visits. <u>Visit 1 – screening visit (D_1).</u> Patients seen in the primary care network or in SUS emergency care units or patients seen in supplementary medicine emergency care units with clinical criteria for presumptive diagnosis of COVID-19, without fulfilling hospitalization indication criteria, will be invited to participate in this research. • obtaining the informed consent form (ICF) for potentially eligible subjects prior to any procedures related to this protocol • checking the inclusion/exclusion criteria

Procedures (continued)	• documentation of screening procedures (demographics, high-risk criteria for covid-19, and concomitant medications) as described in the protocol. Serious adverse events observed will be reported within 24 hours of knowledge of the event • sample collection for rapid antigen testing for SARS-CoV2 in undiagnosed patients. Patients with a confirmed diagnosis of COVID-19 within 7 days of screening do not need to be tested at screening <u>Visit 2 – baseline visit, randomization, and administration of the first dose of the investigational drug (D_1)</u> • The randomization visit should be performed immediately after the screening visit, at the same assessment • Performing the baseline visit procedures, according to the research flowchart: ○ airway secretion sample for RT-PCR for Sars-CoV2 in the first 800 patients (viral load assessment – expected in the first 200 patients in each stratum) • Urinary pregnancy test for women with at least one menstrual period in the last 12 months • Checking the inclusion/exclusion criteria • Randomization in the IWRS system • Completion of the WHO acute influenza syndrome questionnaire • Digital oximetry measurement • Randomization and delivery of the investigational drug as allocated by the IWRS. All patients will receive the standard treatment for COVID-19 as adopted by the health units to which they are linked, as defined by the medical team. All patients will also receive 24-hour telephone contact, to be activated in case of need and will be oriented about the daily telephone contact that will be carried out by the research team until D_{10}. The 800 initial patients will have their own nasal swab and saliva swab collected for RT-PCR at randomization, $_3$ from D_7 to treatment. The patients will be oriented about this home collection and logistics for collecting the samples at their homes <u>Evaluations after randomization</u> • all patient assessments will be conducted by telephone contact, social media applications, video calls, or telemedicine. No in-person visits are planned, especially due to the fact that the virus is highly transmissible, following the guidelines of the health authorities regarding recommendations for confinement and distancing from cases. • Daily evaluations by telephone contact: between D_1 and $D_{10,}$ the patient will be monitored daily by telephone and/or video calls, and the WHO flu symptoms questionnaire will be carried out. In the initial 600 patients, there will be additional information on the occasion of telephone contact on days D_2 and D_6, when the patient will be oriented about the self-collection of samples for viral load research (nasal swab + saliva) to be performed the next day.

	• Assessment of D_{14} – telephone contact/video call to assess the evolution of the clinical picture and verify outcomes. • Evaluation of D_{28} – telephone/video call contact for evaluation of the evolution of the clinical picture and verification of in-person outcomes. Possible persistence of symptoms that appeared at the time of COVID-19 diagnosis will be evaluated. <u>Research Monitoring Committee</u> A research steering committee, an independent data and safety monitoring committee, and an endpoint monitoring committee will be established in a blinded manner until the end of the study is defined. The research steering committee will ensure the scientific integrity of the study in addition to operational care for the proper conduct of the research. The safety monitoring committee will consist of experienced external researchers to ensure the overall safety of the participating research subjects and group data in a blinded manner. The endpoint monitoring committee will reassess identified clinical endpoints and ensure that they indeed fall within the intended endpoints of the trial, using predefined event classification criteria.
Sample Size	It is planned to randomize a total of 2,724 patients distributed in the four treatment arms
Statistical Methods	This study will be conducted in two phases: (1) Internal pilot phase, which will be considered for the first 100 patients. This phase is necessary due to the rapidly evolving scientific information, requiring responses from the public health systems, and considering the need for eventual adjustments in order for the study to be successful. At this time, there will be no analysis, and the patients' data will be included for analysis as planned; and (2) Main Study, which involves the full implementation of the research protocol with hospitalization as the primary endpoint of the study. This phase is also an adaptive phase, where there will be three (3) interim analyses to assess the effects of the interventions compared to the placebo arm, at 25, 50 and 75% of the total planned sample. Critical adjustments involve (a) withdrawing the placebo arm if there is great benefit from the others and (b) withdrawing any arm that does not show benefit or meets futility criteria. The sample size was calculated at 681 participants per group, for a total of 2,724, maintaining a power of 80% and a two-sided alpha of 0.05 to demonstrate a statistical significance ratio of 0.80 (20% reduction in hospitalization between groups and reduction in deaths compared with the COVID-19 population). The statistical software SAS version 9.4 was used for this sample calculation.

	The protocol design will be adaptive, with provision for blinded interim analyses comprising 25, 50 and 75% of the initially projected sample of participants. The sample size will be revised based on the outcomes that occurred in the placebo group at the time of the interim analyses. Blinded outcome analysis will be performed with simulations to limit type I errors within the 5% tolerance range (97.5% or greater probability of superiority over the control group). Decisions may be made at this point to terminate arms of the study if there are not acceptable projections of benefit over futility.

Fluxograma da Pesquisa:



1. Tratamento: Fluvoxamina, Ivermectina e Metformina em grupos paralelos pelo período planejado. Interromper se sintomas ou reações adversas.
2. Triagem e Randomização devem ser realizadas na mesma visita. Assegurar que o paciente seja randomizado por ocasião do atendimento.
3. As visitas subsequentes: D_3, D_7, D_{10}, D_{14}, D_{28}, D_{60} serão realizadas através de contato telefônico. Em qualquer momento visitas extras de segurança poderão ser realizadas. As visitas D_{14} e D_{28} são consideradas visitas de desfecho para a pesquisa. As visitas D_{28} e D_{90} são consideradas visitas pós estudo de acompanhamento de complicações tardias relacionadas ao COVID-19 e avaliação eventual de reações adversas tardias aos medicamentos da pesquisa e serão realizadas através de contato telefônico. Não há previsão de visitas presenciais nesta pesquisa em atenção às recomendações regulatórias emitidas pela autoridade de saúde pública no contexto da pandemia. Em qualquer momento visitas extras de segurança poderão ser realizadas.
4. Contato diário por telefone (não assinaladas acima) serão realizadas entre os Dias 1 a 9 de tratamento, à exceção dos dias acima descritos, os quais serão presenciais.

Table 4 – Procedure Flowchart

FLOWCHART		STUDY VISIT SCHEDULE						
	V1Triage [1]	V2Basal/ Randomization[2]	V3 Day 3	V4 Day 7	V5 Day 10	V6 Day 14	V7 Day 28	V8 Day 60 (EoS or Early Termination
			V3+1[3] day	V4+1[3] day	V5 ± 2 days	V6 [3] ±2 days	V7[3] ± 3 days	V8 ± 5 days
Free and Informed Consent	X							
Revision of Eligibility Criteria	X	X						
Demography	X							
Medical History		X						
Physical Exam		X						
Weight		X						
Height		X						
Vital Signs (Pulse Rate, Temperature)		X						
ECG (QT measurement)		X						
Oximetry		X						
Pregnancy Test	X[4]							
Adverse Events		X[5]	X	X	X	X	X	X
Previous pulmonary medications		X	X	X	X			
WHO Clinical Worsening Scale	X[6,7]	X[6,7]	X[6,7]	X[6,7]	X[6,7]	X[6,7]		
PROMIS Global Health Scale (Global-10)		X[6,7]				X[6,7]		X[6,7]

FLOWCHART		STUDY VISIT SCHEDULE						
	V1Triage [1]	V2Basal/ Randomization[2]	V3 Day 3	V4 Day 7	V5 Day 10	V6 Day 14	V7 Day 28	V8 Day 60 (EoS or Early Termination
			V3+1[3] day	V4+1[3] day	V5 ± 2 days	V6 [3] ±2 days	V7[3] ± 3 days	V8 ± 5 days
Randomization		X[8]						
Administration Investigational Treatment [9]		X[10]	X[11]	X[11]	X[11]			
Verification of clinical outcomes		X[12]	X	X	X	X	X	X[13]
Viral Load Evaluation (200 patients/ stratum – 800 patients total)		X	X	X				
Rapid Test for SARS-CoV2	X[1]							
Patient Identification Card		X						

1 Screening and baseline visit: must be performed at the same time, at the time of attendance at the UBS. Rapid antigen test for COVID-19 at the screening visit

2 Patients can be included in the survey IF he/she is already diagnosed with COVID-19 at the time of the baseline visit and has had flu symptoms for less than 7 days

3 Visits made by telephone, video call, telemedicine, calculated in relation to the randomization date

4 Must be performed on women of childbearing age and/or potential for pregnancy. Women of childbearing age must necessarily use contraception during the first 15 days of the study.

5 After signing the Informed Consent Form.

6 Questionnaires must be completed BEFORE any procedures of the proposed visit. Only a person unrelated to the research may assist the patient during the questionnaire. For telephone visits, the patient must answer directly at the time of contact.

7 Remind the patient that he/she will answer the questionnaire in the telephone contact at the pre-procedure visit.

8 After completing the screening/baseline visit procedures and presenting all inclusion/exclusion criteria, patients should be immediately randomized.

9 The study medication will be administered as prescribed. Patients should be observed for 30 minutes after the start of medication, where the first dose should be administered immediately after randomization to capture immediate adverse events with the administration of study medication and then released home.
10 The First dose of the treatment under investigation should be administered on the same day of randomization (immediately after randomizing)
11 Maintain the administration of the product under investigation as scheduled. Discontinue it if adverse events prevent the continuation of the medication.
12 As soon as I start the product under investigation.
13 Evaluation of late complications associated with COVID-19.

1 INTRODUCTION

1.1 Background

In December 2019, a series of cases of unknown etiology and with symptoms similar to that of a viral pneumonia began to be reported in Wuhan City, Hubei Province, China[1]. These initial cases were reported among people connected with a local seafood market, Huanan ("wet market")[2]. Patients were hospitalized with this viral pneumonia, bronchoalveolar lavage fluid samples were collected from three patients, and a novel coronavirus, termed 2019-nCoV, was isolated. Evidence for the presence of this virus included identification in bronchoalveolar lavage fluid in three patients by genome sequencing, direct PCR, and culture. The disease that was probably caused by this CoV was termed "new coronavirus-infected pneumonia." The complete genomes were submitted to GISAID. Phylogenetic analysis revealed that 2019-nCoV fell into the beta coronavirus genus, which includes the coronaviruses (SARS-CoV, bat SARS-like CoV, and others) discovered in humans, bats, and other wildlife[2].

Since then, the number of cases has increased, and on January 30, 2020, the outbreak was declared a Public Health Emergency of International Concern. As of January 31, 2020, there were, worldwide, 9826 confirmed cases of 2019-nCoV[3]. On that same day, the first two cases of 2019-nCoV were reported in Italy, and both had a travel history to the city of Wuhan, China. There were also already confirmed cases in 18 other countries besides Italy, making a total of 19 countries outside of China[3].

As of February 11, 2020, 43,103 cases were confirmed (42,708 of which were in China) and 1,018 deaths. On this same day, the World Health Organization (WHO), in collaboration with its departments (World Organization for Animal Health and the United Nations Food and Agriculture Organization), named the disease COVID-19 (short for "coronavirus disease 2019"[4]. On this same day, the Coronavirus Study Group (CSG) of the International Committee on Viral Taxonomy proposed to name the new Coronavirus as SARS-CoV-2 (severe acute respiratory syndrome Coronavirus 2)[5].

On March 11, 2020, the World Health Organization declared COVID-19 a global pandemic[6,7].

1.2 Transmission

Initial cases resulted from contact with the original seafood market[2,8]. Soon cases of transmission between humans were identified, through close contact, apparently without related epidemiology, configuring community transmission, with several cases occurring among medical professionals[9,10,11].

Evidence from initial epidemiological studies conformed that COVID-19 has higher levels of transmissibility and pandemic risk than SARS-CoV since the effective reproductive number (R_0) of COVID-19 was identified as close to 3.0, higher than that observed for SARS (R_0= 1.77)[10]. Considering the various epidemiological studies currently available, it is considered that the R of$_0$ COVID-19 is situated somewhere between 2.6 and 4.71[12]. The estimated mean incubation period until the first symptoms appear is 4.8 ± 2.6 days (CI 4.1-7.0; median 5.2)[9,10]. The most recent guidelines from the Chinese health authorities stated a mean incubation duration of 7 days, ranging from 2 to 14 days[12].

Current data reinforce the concern about asymptomatic transmission. About 86% of all infections were undocumented (95% CI: [82% -90%]) before the Chinese government's proposed travel restrictions in Wuhan. There is evidence that 55% of people acquire the virus and transmit it asymptomatically, without subsequently developing COVID-19, which may explain rapid transmission and the difficulty in containing its spread[9].

1.3 Clinical manifestations and risk profile

From the onset of the first cases of COVID-19 to the present day, a number of epidemiological data have been compiled as cases have emerged; however, most of these have not been adjusted. Initially, the following signs and symptoms were identified as most prevalent: Fever (98%), cough (95%), dyspnea (55%), myalgias (44%), sputum (28%)[11]. Currently, after the epidemiological knowledge of tens of thousands of cases of CODID-19, the following signs/symptoms are considered to be the most common: Fever (87.9%), Dry cough (67.7%), Dyspnea (40%) [13]. These same series identified subgroups of patients with a higher risk of mortality, and the following are currently considered to be quantitative:

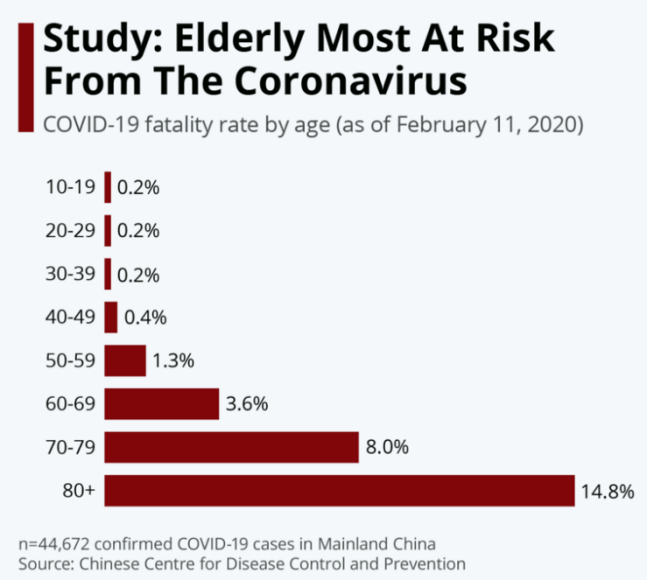


Figure 1 - Age-adjusted mortality rate

Mortality is also high in some disease strata, as initially suggested by early epidemiological studies conducted on cases in Wuhan. Patients who contracted COVID-19 and had stable chronic cardiovascular diseases such as clinically manifest heart failure, coronary artery disease, LV dilated cardiomyopathy had high mortality over the course of the disease. Similarly, patients with diabetes, chronic respiratory disease, and hypertension had an elevated mortality rate compared with subjects with COVID-19 and without these comorbidities.[13].

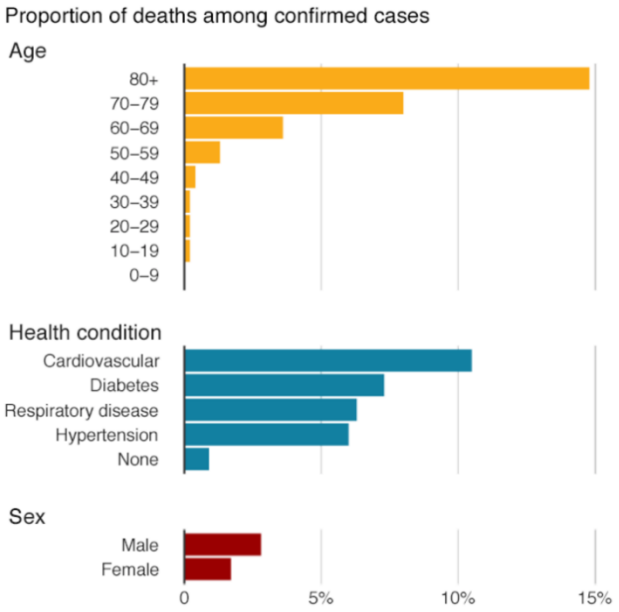


Figure 2 - Global mortality by age group - COVID-19

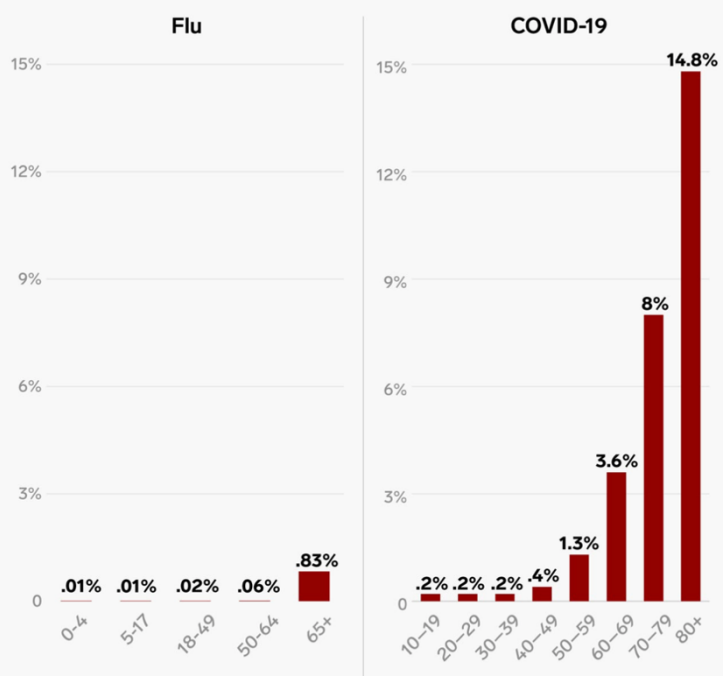


Figure 3 - Influenza and COVID-19 mortality

1.4 Mechanisms of infectivity

This global health emergency has intensified research efforts to better understand the pathogenesis, clinical manifestations, and outcomes of people affected by this new viral strain. It is known that the “spike proteins” of coronaviruses, including SARS-CoV2, interact with Angiotensin-converting enzyme 2 (ACE2) and type II transmembrane serine proteases to invade cells[14,15]. Thus, cells expressing ACE2, including pneumocytes and lung ciliated cells of the tracheobronchial tree, cardiac endothelial cells, intestinal mucosal cells, and renal epithelial cells, can be affected and could explain in part the multiple organ dysfunction observed in patients[16]. Under physiological circumstances, ACE2 acts as a natural antagonist of the renin/ angiotensin/ aldosterone system (RASA) pathways by degrading angiotensin II and then producing Angiotensins 1-7, which act by limiting the vasoconstrictor capacity of angiotensin I. Angiotensins 1-7 have pulmonary protective effects by attenuating the inflammatory response[17]. Indeed, as observed in recent SARS-CoV epidemics (SARS epidemic and MERS) and identified recently in genetic studies of SARS-CoV2, the inhibition of ACE2 transmembrane receptor expression resulting from viral infection occurs by blocking these through “spike proteins”. This abrupt reduction of ACE2 activity in lung cells is a critical point for the resulting pulmonary complications, given its important inhibitory effect related to pulmonary inflammatory mediators and thus reducing pulmonary Edema and the unwanted amplification of the inflammatory drive resulting from COVID-19[5].

1.5 Need for studies to treat COVID-19

Nowadays, the world is increasingly faced with a number of complex problems, especially with regard to emerging diseases. Thus, there is an increasing need for joint efforts to address acute health problems that one group, health system, or country cannot deal with alone. In this context, the pulmonary system is particularly vulnerable to all sorts of inoculums and contaminants, especially the airborne transmission of pathogens that often cause lung infections, affecting individuals of various age groups. Respiratory viruses represent in this scenario a continuous pandemic risk, among which the *Betacoronavirus*, belonging to the *Coronaviridae* family, is a known subgroup.

In recent decades we have been surprised by a significant number of emerging respiratory viral diseases of major pandemic potential, including the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) that emerged in China in 2002[18,19], the HN_{11} Swine Flu that first appeared in Mexico in 2009[20], and the Midwestern Respiratory Syndrome Coronavirus (MERS-CoV) that emerged in Saudi Arabia in 2012[21].

Within this continuum of emerging diseases, a new subtype of coronavirus emerged in December 2019 in Wuhan, initially causing an outbreak of viral pneumonia and then turning into an epidemic in China and globally thereafter[11,22,23]. The mortality associated with COVID – 19 is apparently associated with Adult Respiratory Distress Syndrome, which, when associated with comorbidities, significantly elevates mortality[24,25].

Despite all the efforts from basic and translational research associated with understanding influenza and coronavirus infections, to date, there are no effective treatments to combat this important disease and no vaccines to prevent infection in humans[26,27]. Data about COVID-19 continues to grow at alarming rates. From January 31 to March 23, 2020, 332,930 cases and 14,510 deaths have been confirmed, with community transmission present in virtually every country around the globe[28].

To date, there are no specific treatments for COVID-19. Since the emergence of this disease to the present day, there has been a myriad of proposed treatment protocols for this disease; however, none have shown good clinical response. On the Clinicaltrials.gov website, there are currently 4,125 registered clinical trials for the treatment of COVID-19, with 907 trials still in the preparatory phase, 2,120 trials with the recruitment phase initiated, and 546 trials completed. Several studies have been instrumental in highlighting the virtual lack of efficacy of various treatments in patients with moderate to severe disease, as well as in mild[29] disease. Given the high mortality expected in this pandemic and the high potential for transmission of infection affecting entire populations and countries, it is imperative that treatments be sought for this disease, for which, to date, there are supportive treatments.

2 OBJECTIVES OF THE STUDY

The objective of this study was to evaluate the efficacy, safety, and benefit of the use of Fluvoxamine, Ivermectin, and Metformin in patients acutely affected with COVID-19 and presenting mild respiratory symptoms, seen at emergency care units and/or Basic Health Units of the Brazilian Unified Health System, through a research protocol designed with 04 treatment arms: (1) Fluvoxamine; (2) Ivermectin; (3) Metformin and (4) Placebo.

The research subject's participation in the protocol is for 60 days, with the first 10 days being the treatment phase and the remaining period for follow-up after the end of treatment.

2.1 Objectives/primary endpoint

- Reducing the need for emergency department visits due to clinical worsening of COVID-19 and keeping the participant under observation for > 06hours in acutely affected patients with evidence of high risk for complications.
- Reducing the need for hospitalization due to progression of COVID-19 (worsening viral pneumonia) and/or complications in acutely affected patients with evidence of high risk for complications.

Goal/co-primary endpoint:

- To evaluate the effect of Fluvoxamine, Ivermectin and Metformin in reducing mortality associated with COVID-19 up to 28 days from randomization.

2.2 Objectives/secondary outcomes

The proposed secondary objectives are:

- Viral load change on day 03 and 07 after randomization (Evaluation to be performed on the first 600 randomized patients – 150 patients in each stratum)
- Time to clinical improvement (up to 28 days from randomization), defined as greater than 50% improvement in reference to symptoms at the time of randomization
- Time to clinical failure, defined as the time until hospitalization due to clinical progression of COVID-19 (lower respiratory tract viral infection associated with dyspnea requiring oxygen therapy; hospitalization due to progression of COVID-19 or complications directly associated with COVID-19
- Number of days with respiratory symptoms since randomization
- Hospitalization for any cause
- Hospitalization due to progression of COVID-19
- Mortality due to pulmonary complications

- Cardiovascular mortality
- Mortality from any cause
- Adverse events (up to 28 days)
- COVID-19 symptom scale assessment (D_1 to D_{28})
- WHO clinical worsening scale assessment (D_1 to D_{10})
- Assessment of the PROMIS Global Health Scale ("Global-10") days 14 and 60 after randomization
- Mortality rate of patients at day 14 and 28 days
- Proportion of non-adherent patients with the product under investigation
- Specific adverse reactions to the study medications: fluvoxamine, ivermectin and metformin

2.3 Exploratory Objectives

- Complication rate stratified by age
- Corticotherapy use rate
- Rate of use of antibiotic therapy
- Rate of complications observed in patients using nonsteroidal anti-inflammatory drugs
- Concomitant medications used by the patient from 30 days prior to screening until D_{14}

3 INVESTIGATIONAL PLAN

3.1 Study design

This is a multicenter, adaptive, double-blind, randomized, placebo-controlled study to evaluate the effect of fluvoxamine, ivermectin, and metformin in reducing hospitalization in patients with mild COVID-19 and high risk for complications.

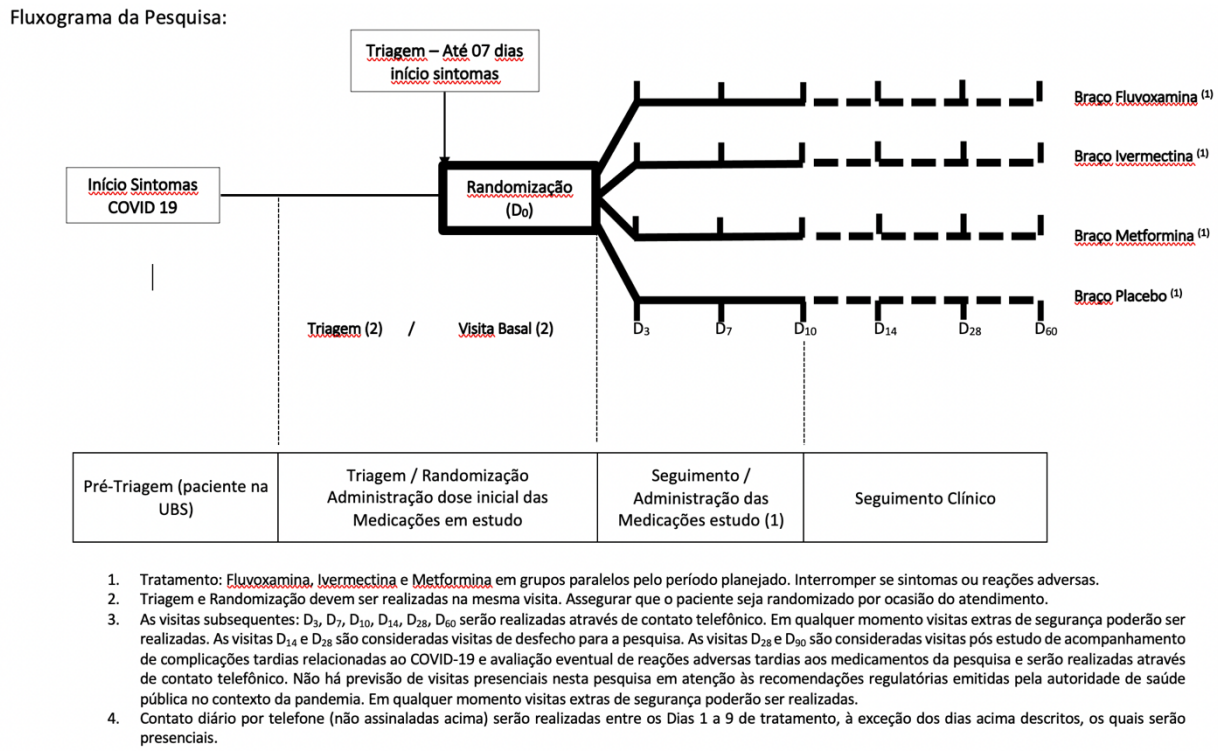
The groups will be as follows:

1. Placebo
2. Fluvoxamine
3. Ivermectin
4. Metformin

Patients will be randomized to one of the 4 study arms via an automated web-based randomization system (IWRS). The protocol provides for an adaptive phase to accommodate any pre-specified modification needs.

The protocol is designed to reach 800 patients in each of the 4 groups above in a 1:1:1:1 randomization ratio. The protocol has an adaptive phase with blinded interim analysis to control type I errors at a 5% tolerance level (97.5% or more probability of superiority over the placebo group), which will occur when 25, 50 and 75% of the number of participants proposed in the protocol are included, respectively. At this stage, blinded analysis of the proposed outcomes between the 4 groups will be performed by a committee independent of the research. This interim analysis includes an analysis of the futility of any research arm. If any arm is found to be futile, it will be removed from the study, the blinded condition of this arm will be released, and the study will continue with the remaining arms. Decisions regarding the need to readjust the number of participants can be made based on estimates of projections of actual events occurring in the protocol. Any decisions to discontinue a treatment arm will be subject to immediate notification to the regulatory authorities and the ministry of health, according to current regulations.

These interim assessments will be conducted by the Data Safety Review Committee, supported by statisticians, with decisions communicated to the study Steering Committee.



1. Tratamento: Fluvoxamina, Ivermectina e Metformina em grupos paralelos pelo período planejado. Interromper se sintomas ou reações adversas.
2. Triagem e Randomização devem ser realizadas na mesma visita. Assegurar que o paciente seja randomizado por ocasião do atendimento.
3. As visitas subsequentes: D_3, D_7, D_{10}, D_{14}, D_{28}, D_{60} serão realizadas através de contato telefônico. Em qualquer momento visitas extras de segurança poderão ser realizadas. As visitas D_{14} e D_{28} são consideradas visitas de desfecho para a pesquisa. As visitas D_{28} e D_{90} são consideradas visitas pós estudo de acompanhamento de complicações tardias relacionadas ao COVID-19 e avaliação eventual de reações adversas tardias aos medicamentos da pesquisa e serão realizadas através de contato telefônico. Não há previsão de visitas presenciais nesta pesquisa em atenção às recomendações regulatórias emitidas pela autoridade de saúde pública no contexto da pandemia. Em qualquer momento visitas extras de segurança poderão ser realizadas.
4. Contato diário por telefone (não assinaladas acima) serão realizadas entre os Dias 1 a 9 de tratamento, à exceção dos dias acima descritos, os quais serão presenciais.

Figure 3 - Flowchart of the research

3.2 Justification of the study design

The DMC for COVID19_MG_AMB_2 reviewed data from the current literature regarding possible efficacy treatments of the drugs proposed in this research

3.3 Rationale for the use of fluvoxamine

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) and an SR receptor$_1$ agonist[30]. The rationale for considering using fluvoxamine in patients with COVId-19 is that $_1$SR receptor agonists may attenuate excessive inflammation in patients with COVID-19. This and other potential mechanisms by which fluvoxamine may act in COVID-19 are summarized below.

3.3.1 Anti-inflammatory effects via SR$_1$-IRE

SR$_1$ is an endoplasmic reticulum (ER) chaperone protein involved in many cellular functions, including regulation of the ER stress response / unfolded proteins response (UPR) and inflammation[31]. SR protein$_1$ has been shown to inhibit the ER stress sensor enzyme 1α that requires inositol (IRE$_1$) mediated splicing of XBP$_1$, a key regulator in cytokine[32] production. These anti-inflammatory effects may be the most likely explanation for the beneficial effects of

fluvoxamine. In COVID-19, an excessive inflammatory process is known as a "cytokine storm" can contribute to worsening symptoms and cardiopulmonary complications, which can sometimes occur around the second week of the disease. Fluvoxamine may attenuate this excessive inflammatory response.

In a 2019 study by Rosen, fluvoxamine showed benefit in preclinical models of inflammation and sepsis[33]. In one model, mice were exposed to Toll-like receptor ligand 4 (TLR_4), lipopolysaccharide (LPS), which can trigger an inflammatory response. In another model, a fecal concentrate was injected, which triggers a generally sublethal infection and inflammatory response. Mice lacking $_1$SR receptors showed excessive increases in cytokine levels and greatly reduced survival under either of these conditions, suggesting that these receptors inhibit the exacerbated inflammatory response. Mice not genetically manipulated and exposed to the same inflammatory triggers showed reduced cytokine levels and increased survival when treated with fluvoxamine (an SR agonist$_1$). By investigating the mechanism underlying this effect, the authors demonstrated that $_1$SR receptors inhibit IRE_1 activity, which in turn prevents excessive cytokine production. In an experiment using human peripheral blood, they also showed that fluvoxamine could reduce LPS-induced cytokine production by human cells. In the case of COVID-19, the S1R agonist action of fluvoxamine may have a similar ability to reduce the excessive inflammatory response induced by a viral infection, thereby reducing inflammation-mediated organ damage.

3.3.2 Antiviral action through effects on lysosomes, autophagy and/or endocytosis.

Coronaviruses utilize cathepsin-like proteases present in the late endosome to facilitate entry into the cell and remodel phagosomes and endoplasmic reticulum membranes, turning them into sites of "viral replication"[34,35]. Both processes require stimulation of the endocytosis and autophagy-phagosome mediated pathways and then terminate autophagy prior to lysosomal fusion. SARS-CoV-2 proteins Nsp6, Nsp2, Orf7b and Orf9b have been shown to localize and modulate components of the autophagy pathway[36,37]. Additional Nsp6 has been shown to physically associate with SR_1[38]. Critically, SR_1 not only drives early-stage autophagy via the IRE/UPR_1 pathway but is also essential for lysosomal fusion and to complete autophagy, likely accompanying components of the SNARE complex[39]. It is possible that $_1$SR activation with fluvoxamine may overcome Nsp6 inhibition of S1R to allow autophagy to eliminate SARS- CoV2. Others have also recognized targeting the autophagy pathway as a promising strategy to treat SARS-CoV2[40,41].

Chemically, fluvoxamine is a cationic amphiphilic drug (ACD) with log P 3.1 and pKa 9.4 and, along with a variety of antipsychotic and antihistaminic drugs, accumulates preferentially in the lysosome. Perhaps because of this, fluvoxamine reaches higher concentrations in the lungs

(which are rich in lysosomes) than in the brain[42]. In the case of COVID-19, this may increase the effects of the treatment on the airway[43] epithelium. At high doses (10 μM), CADs, including fluvoxamine, have been shown to inhibit lysosomal acid sphingomyelinase and cause drug-induced phospholipidosis. This non-specific activity may globally dysregulate lipid homeostasis, which in turn modulates autophagy via the mTOR nutrient-sensing pathway[44,45].

3.3.3 Antiviral effects and prevention of organ damage through regulation of the ER/UPR stress response

Some viruses hijack the ER / UPR stress response to achieve viral functions, and a number of studies have suggested that drugs targeting the ER / UPR stress response may be beneficial in treating COVID-19[46,47,48]. SR agonists$_1$ (such as fluvoxamine) regulate ER-associated stress. SR ligand$_1$ effects during ER-mediated stress and other ER functions may reduce organ dysfunction/damage[49,50].

3.3.4 Antiplatelet effects (common to all SSRIs).

Platelet hyperactivity may contribute to pathophysiological processes leading to thrombotic complications in COVID-19. SSRIs may inhibit platelet activation, which may reduce the risk of thrombosis, and these antiplatelet effects may be cardioprotective[51,52].

3.3.5 Elevation of melatonin levels in the body.

The SARS-CoV2 virus can activate the NLRP343 inflammasome, which may contribute to the cytokine storm[53,54]. Melatonin may act on this NLRP3 pathway to reduce inflammation[55,56]. Fluvoxamine inhibits melatonin metabolism, so it may increase the level of melatonin in the body, which may be beneficial in COVID-19[57].

3.4 Rationale for the use of ivermectin

In vitro studies have shown that ivermectin inhibits the replication of many viruses, including influenza, zika, dengue and others. It has also been seen to inhibit the replication of SARS-CoV2 in infected cell cultures, leading to the absence of almost all viral material within 48h. In addition to these, in several animal models, when infected with SARS-CoV2 or similar coronaviruses, the use of ivermectin in several preclinical and clinical studies resulted in a significant drop in viral load and blocked several inflammatory pathways associated with proteolysis, cell lysis, and consequent reduction of organ[58,59,60,61,62,63,64,65,66] damage.

Similarly, several *in vivo* studies with animal models using ivermectin resulted in activation of several anti-inflammatory pathways, potentiating these mechanisms by inhibiting both several cytokines associated with inflammatory activation as well as transcription of nuclear factor-κB (NF-κB), a factor involved in an uncontrolled inflammatory response[67,68,69].

Some observational studies and open randomized trials with small numbers of patients using ivermectin in patients with COVID-19 suggest that (1) ivermectin prevents transmission and development of COVID-19 disease in healthy persons exposed to infected patients[70,71,72,73]; (2) accelerates clinical recovery, minimizing the progression to complications in patients with mild to moderate clinical picture if treated soon after symptoms[74,75,76]; (3) accelerates recovery and avoids ICU admission and death in hospitalized patients[77,78,79,80], and in regions where its use has been widespread, it indicates a possible reduction in mortality, however, these studies have not adjusted for covariates nor have they performed a sample size calculation to support the conclusions obtained[81,82].

Such evidence shows the need to study this drug using an adaptive design model and to use a robust methodology to verify the real role of this drug in the context of COVID-19 treatment.

3.5 Rationale for the use of metformin

Since the appearance of the first cases of viral pneumonia associated with SARS-CoV2 until today, several clinical conditions have been definitely associated with the complications that have occurred, progression of lower respiratory tract infection, respiratory failure, and death. It is believed that these conditions enable the virus to develop an exacerbated inflammatory response. These clinical conditions are now considered to be risk factors for the worsening of COVID-19. Among these, advanced age is one of the most important, and associated with it are hypertension, diabetes, coronary artery disease, smoking, and obesity. In this context, obesity stands out since after being adjusted for the other risk factors, obesity appears as an important factor associated with ventilatory worsening and the need for artificial ventilatory assistance[83]. Patients with body mass index > 25 kg/m^2 or men with excess visceral adipose tissue have a high risk of needing invasive ventilatory support in the course of COVID-19[84].

Visceral adipocytes secrete several inflammatory pro-mediators and pro-coagulant molecules, including interleukin (IL)-6, tumour necrosis factor α (TNF-α) adipokines, and D-dimer, and in patients with COVID-19, high production of inflammatory and pro-coagulant chemokines was observed, which were identified and associated with the lung inflammatory picture of these patients[85,86]. In patients with type e diabetes mellitus, TNF-α and IL-6 are elevated, and IL-10 levels are reduced, with a direct relationship between these changes and the intensity of insulin resistance observed in these patients[87].

Metformin, a type 2 diabetes drug, decreases levels of TNFα, adipokines, and IL-6 and increases levels of IL-10, and these changes have been observed in both experimental studies and studies in patients with type 2 diabetes mellitus and are more evident in women[88,89,90]. These effects associated with the reduction of circulating adipokines may contribute to minimize the degree of inflammatory response and thus reduce the severity of the disease[91].

Clinical studies have suggested that clinical complications and mortality in patients with COVID-19 may be lower in patients taking metformin; however, the observational and retrospective nature (analysis of medical records), as well as other studies not confirming this association, makes it difficult to adopt this as part of inpatient treatment[92,93,94,95]. Recently, an observational study identified metformin as a potential mortality reducer in women[96].

Considering this conflicting evidence in the literature and the safety of metformin use, acquired through decades of use in clinical practice, the need for randomized, prospective studies with this drug in patients with COVID-19 arises.

3.6 Justification of the dose/regimen, route of administration, and duration of treatment

3.6.1 Fluvoxamine

The STOP COVID 2 study evaluated fluvoxamine in patients with COVID-19 and showed potential benefit in reducing complications associated with the disease, suggesting the need for randomized, placebo-controlled studies, since the objective of the study was to explore this therapeutic possibility and, therefore, with a small number of patients involved[97]. Considering contacts made with the researchers of the STOP COVID study, we chose to adopt the dosage of (100 mg twice a day), which is different from the initial study, which adopted the dosage of 100 mg three times a day, considering the maximum dosage allowed by the American drug regulatory agency (FDA). According to the authors, 96% of the participants who used fluvoxamine reached the dose of 200 mg/day (86 out of 90), but only 50% of the patients increased the dose to 300 mg/day, and this occurred only after 5-6 days of treatment, which may already be outside the risk period for complications. In other words, the study result suggests that it is not necessary to reach 300 mg/day of fluvoxamine. Reviewing the pharmacokinetics and activity of fluvoxamine to SR receptors$_1$, apparently, the dose of 200 mg/ day is sufficient for the expected $_1$SR agonist effect. Thus, we chose to consider treatment with fluvoxamine at a dose of 100 mg twice daily for 10 days, which will cover the period of highest risk of worsening COVID-19.

3.6.2 Ivermectin

Several studies using ivermectin for both prophylaxis and treatment have used a single dose of the drug ranging from 150 to 250µg/kg.

Initially, we proposed in this clinical trial to use a treatment scheme with ivermectin at the dose commonly proposed for treatment of ectoparasites, intestinal parasitoses and parasitic infestations. Thus, we chose to use the fixed-dose regimen by weight range. Thus, patients weighing less than 60 kg will receive 12 mg of ivermectin, between 60 and 80 kg will receive a dose of 18 mg, and patients weighing more than 80 kg will receive a dose of 24 mg of ivermectin. This dose has been shown to be safe in these studies and in studies in patients with COVID-19.

The literature data have been reviewed recently, taking into account the published articles about ivermectin, the experience of using the medication at doses up to 600 mcg/kg/day in some diseases, the experience of using the medication at high doses in lice infestations, and the experience of using doses up to 800 mcg/kg/day in patients with onchocerciasis in several countries where this disease has high endemicity.

We also conducted an extensive review of the effects of ivermectin as an antiviral agent and as a regulator of the inflammatory process in several diseases and also reviewed the pharmacokinetic data of the medication at commonly used doses and at high doses, aiming to evaluate the safety of the use of these doses (see document "IVERMECTIN_REVISION_SUMARIA_FARMACOLOGIA_FARMACOKINETICS_CLINICAL_ENSEALS" attached to this protocol amendment).

Considering the available evidence, including in patients with COVID-19, we are proposing the administration of ivermectin at an average dose of 400 mcg/kg/day, not to exceed a dose of mcg/kg/day470 in a single dose for 03 consecutive days.

3.6.2.1 Justification of the change of dosage regimen of ivermectin in the clinical trial

In the present study, we initially proposed the mean dose of 400 mcg/ kg in a single dose. Considering the availability of ivermectin in Brazil (06 mg tablets), we stipulated the following dosage based on patient weight:

- from 40 to 60 kg: 03 tablets - 18 mg
- from 60 to 80 kg: 04 tablets - 24 mg
- > 80 kg: 05 tablets - 32 mg

Such a dosing regimen was discussed extensively between the co-authors and the study steering committee a few weeks before the original version of this clinical trial was finalized. Moreover, the data made available by the authors of the ongoing clinical trials did not contain a

significant number of participants. Even though pharmacokinetic studies evaluating higher doses in other clinical conditions are already in the public domain, we have chosen to initially maintain the dose of 400 mcg/ kg in a single dose in the trial.

Since then, a number of clinical studies have been published in peer-reviewed scientific journals and posted on pre-publication sites evidencing that the average dose of 400 mcg/kg/day in a single daily dose taken consecutively over three to five days is safe in the COVID-19 population, confirming the previous pharmacokinetic studies with high doses of ivermectin in three takes over 7 days where doses up to 60 mg/kg per taking were used (cumulative weekly dose: 180mg as reviewed above) and with no evidence of adverse events compared to the placebo group. Furthermore, the accumulated experience with single doses of 800 mcg/kg taken every 12 weeks in studies conducted in the African continent for the treatment of onchocerciasis and the clinical trials conducted in DENV where the dose of 400 to 600 mcg/kg/day was administered orally for 03 consecutive days allow us to conclude that both doses are safe and the adverse events resulting from this dosage are comparable to the adverse events occurring in the placebo[98] group.

Data obtained from clinical trials using ivermectin in patients with COVID-19 were compiled according to meta-analysis, where studies published in peer-reviewed scientific journals, submitted for publication, and made available on online platforms and ongoing studies where authors shared ongoing data were compiled and summarized by Hill et al[99]. Considering only the randomized trials (data as of February 05, 2021), the author identified more than 600 patients assigned to the active treatment arm, where the observed adverse reactions were similar to those observed in the placebo group.

There were approximately 240 patients treated with 400 mcg/kg/day ivermectin for 2-3 days and 230 patients treated with the same dose for 05 consecutive days. In this meta-analysis, there is the suggestion that the use of ivermectin 400 mcg/kg/day for 2-3 takes translates into a lower incidence of relevant clinical outcomes. While this may be open to criticism, such a dosage is in line with experimental studies in LPS-mediated sepsis models, where an intermediate dose of this drug (350-400 mcg/kg) apparently resulted in lower mortality than a higher dose[100]. Similarly, previous studies have shown a reduction in inflammatory cytokines and other important mediators in the inflammatory cascade using the average dose of 400 mcg/kg/day for 03 consecutive days[101].

Thus, in order to obtain the best clinical results with the use of the drug within the safety observed in several clinical trials conducted using ivermectin for Malaria, Dengue and COVID-19, we are proposing to extend the treatment in this clinical trial to use for 03 days, instead of a single dose, according to the table below:

Weigh t (kg)	Number of pills 06 mg	Total dose mg	Dose (mcg kg)
40 - 45	3	18	400 - 450
46 -	3	18	360 - 391
51 -	4	24	436 - 470
56 -	4	24	400 - 428
61 -	4	24	369 - 393
66 -	5	30	428 - 450
71 -	5	30	422 - 375
80 -	6	36	400 - 450
> 91	6	36	Up to 400

Table 2 - Dosage considering ivermectin 06 mg tablets

Considering some available formulations of ivermectin in sublingual administration, if this is used in the protocol, we will adopt the following prescription table:

Weight (kg)	20 mg Wafer	05 mg Wafer	Total dose mg	Dose (mcg kg)
40 - 45	01 (20 mg)	not	20	444 - 500
46 - 50	01 (20 mg)	not	20	400 - 434
51 - 55	01 (20 mg)	01 (05 mg)	25	454 - 490
56 - 60	01 (20 mg)	01 (05 mg)	25	416 - 446
61 - 65	01 (20 mg)	01 (05 mg)	25	384 - 409
66 - 70	01 (20 mg) + 01 (10	not	30	428 - 454
71 - 80	01 (20 mg) + 01	not	30	375 - 422
80 - 90	01 (20 mg) + 01	01 (05 mg)	35	388 - 437
> 91	01 (20 mg) + 01	01 (05 mg)	35	Up to 384

Table 3 - Posology considering ivermectin sublingual formulation (05 and 20 mg pills)

3.6.3 Metformin

At the time of the design of this protocol, there were no registered clinical trials (randomized and double-blind) for the treatment of early-stage COVId-19 containing metformin. We chose to use the 750 mg dose in two daily takes of metformin since in virtually all clinical studies where anti-inflammatory effects are clinically relevant used the 500 mg dose in two takes or 750 mg dose in two daily takes.

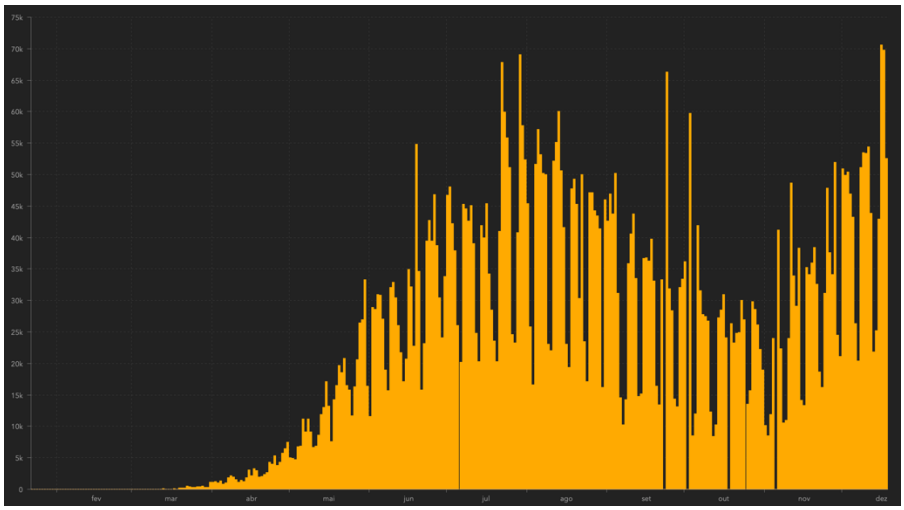
We chose to use the extended-release formulation because it causes fewer gastrointestinal adverse effects, and the bioavailability is more consistent and stable, which becomes an advantage by providing a uniform serum dose.

3.7 Justification for the study

The World Health Organization has been following this disease since the beginning of the first cases, compiling data from virtually every country on the progress of COVID-19. Considering the high mortality of this disease and the absence of effective treatment, the academic community worldwide has made an unprecedented effort in recent scientific history in an attempt to find an alternative to alleviate this high mortality. On the www.clinicaltrials.gov platform alone, there are currently 4,195 clinical trials targeting COVID-19, many of which have been conducted under less than ideal conditions or with inadequate designs[102].

From the beginning of the pandemic until now, the Brazilian scientific community has made an unprecedented effort through hundreds of research programs directed towards tackling COVID-19, and so far, there are 777 approved clinical trials in Brazil[103]. Many of these studies brought important information that impacted the way in which COVID-19 is approached, causing changes in care in several countries.

However, both morbidity and mortality have been reduced little, making it imperative to continue this academic effort in order to cope with the ongoing pandemic. Today, December 17, the pandemic still shows signs of exuberance, with increasing rates of cases, hospitalizations, and mortality (Figure 4, 5).



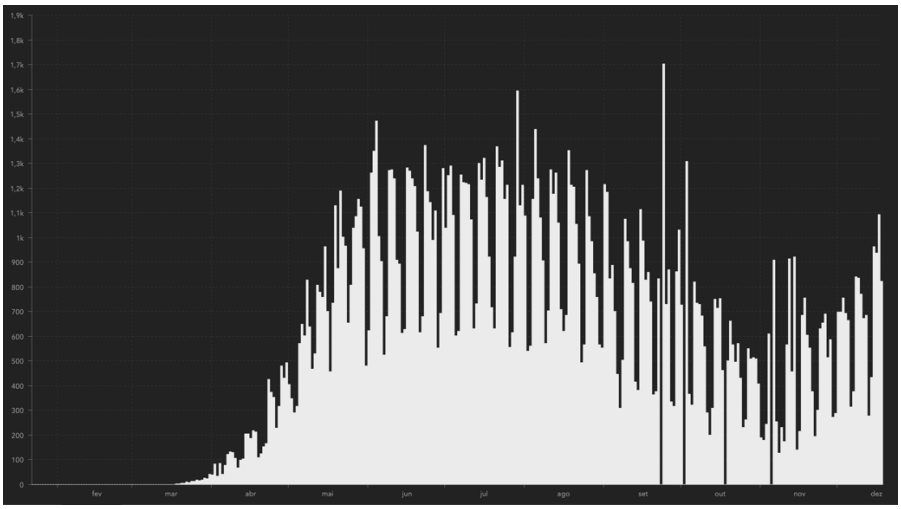


Figure 5 and 6 - Number of cases (yellow) and deaths (white) diaries associated with COVID-19
Source: Johns Hopkins University Data Center (12/17/2020)

There is, therefore, the need to provide an answer to an epidemic that has been raging in our country since March 2020, coupled with the fact that the exuberance of contemporary data from patients with CODIV-19 and the need to find an effective treatment for this pandemic would in itself justify foregoing a study containing a placebo arm.

Currently, the absolute number of deaths exceeds the epidemics of EBOLA (1976), SARS (2002) and MERS (2012).

The world health organization has been following this disease since the first cases began, compiling data from virtually every country on the progress of COVID-19. The world academic community has made an unprecedented effort in recent scientific history in an attempt to find an alternative to alleviate this high mortality rate. On the www.clinicaltrials.gov platform alone, there are currently 4,195 clinical trials targeting COVID-19, many of which have been conducted under less than ideal conditions or with inadequate designs[104].

From the beginning of the pandemic until now, the Brazilian scientific community has made an unprecedented effort, through hundreds of research programs directed to the confrontation of COVID-19, existing until now 777 clinical studies approved in Brazil[105]. The need to offer a rapid response to an epidemic that has been ravaging our country since March 2020, coupled with the exuberance of contemporary data from patients with CODIV-19 and the need to find an effective treatment for this pandemic would in itself justify foregoing a study containing a placebo arm.

Nevertheless, considering the absence of efficient treatments in patients with initial and acute presentation of COVID-19, the presence of the placebo group becomes an important tool to ensure that we have a control group being exposed to the same behaviours, concomitant medications, procedures and medical attitudes, something complex to obtain in clinical protocols, where it is not possible to obtain data with the same temporal nexus. Such attributes, which

demand a control group with standard treatment, are fundamental to verifying the real usefulness of treatments and interventions. However, it is necessary to consider the pandemic involving a deadly disease for which there are no treatments. In this context, the adaptive research design is inserted, for which, if there is evidence of the superiority of some arm or even of futility, measures will be adopted during the course of the research aiming to avoid either unnecessary exposure to some treatment or the non-reporting of an effective treatment for this disease. Thus, the assumptions of the contemporaneity of treatments and conduct of health professionals in relation to the disease, exposure to health resources and access to resources will be present. Patients treated in the health network that will not be participating in this research will not be conducted with treatment knowledge bias. The primary outcome to be observed is the need for hospitalization due to disease progression.

4 RESEARCH PLAN

4.1 Overall study design

The study consists of an in-person screening and randomization visit that will occur simultaneously and visits conducted via telephone contact and social media applications using video teleconferencing:

- V1 (D_0) - Screening visit
- V2 (D_0) - Baseline Visit + Randomization (Start of treatment phase)
- V3 (D_3) - Day 3 Telephone Contact (+ 1 day)
- V4 (D_7) - Day 7 Telephone Contact (+ 1 day)
- V5 (D_{10}) - Day 10 Telephone Contact (±days2; End of treatment phase)
- V6 (D_{14}) - Day 14 Telephone Contact (±days2)
- V7 (D_{28}) - Day 28 Telephone Contact (±days3)
- V8 (D_{60}) - Telephone Contact of the Day (60±5 days)

Note: Participants who prematurely discontinue the investigational product open treatment remain in the trial.

- Unscheduled visit (during the treatment period, at any time in case of adverse events.
-

Visit V1 and V2 - Screening visit/baseline visit/randomization

At the screening visit, potentially eligible patients will be offered the possibility of participating in a research program to approach experimental treatments for COVID-19. Patients will be presented with the Informed Consent Form, and after they agree to participate and sign the written consent, screening procedures for the study will begin. Eligibility criteria, demographics, concomitant medications, and sample collection for rapid testing for COVID-19 will be verified.
Patients tested negative for COVID-19 will be considered screening failures, and positive patients will be invited to perform visit 2 in sequence when all the procedures in the research flowchart are performed.
Participants who already have a positive RT-PCR test for SARS-CoV2 at screening and meet all the research inclusion criteria will not require further confirmatory testing for COVID-19 and can be considered eligible for the randomization/treatment phase.

Treatment phase (Randomization):

After all baseline visit procedures have been performed, all inclusion criteria have been checked, and it has been identified that the patient does not meet any exclusion criteria for the study, the participants will be considered eligible for the treatment phase and then randomized to one of the four arms of the trial in a 1:1:1:1 ratio for treatment with the investigational product(s).
This randomization process will be performed centrally using the IWRS system, and treatment kits will be allocated and identified by random numbering. The KITs will be made available in such a way that no individual will be able to identify the study medication.
Participants will start their assigned treatments (Fluvoxamine; Ivermectin; Metformin or placebo).

4.2 Duration of participation in the study

Participation for each eligible research subject includes a screening visit (D_0), followed by the treatment phase (lasting up to 10 days per participant), which will end on D_{09}. The trial will continue into a follow-up phase after completion of the investigational product, with telephone contact anticipated on days 28 and after60 the randomization date.
For verification of the primary endpoint, follow-up up to 14 and 28 days, respectively, will be used.
For assessment of late complication outcomes of COVID-19, post-study follow-up by telephone contact on the day after 60randomization will be used.
Patients who discontinue the investigational product prematurely will remain in the study for the collection of data on the events of the composite endpoint and will receive usual care.

5 SELECTION AND WITHDRAWAL OF PARTICIPANTS

5.1 Number of participants

For detailed information about the justification of the sample size, please refer to Section**12**.

5.2 Inclusion criteria

1. Patients over the age of 18 with the capacity to provide informed consent;
2. Patients seen at a Primary Care Unit of the Brazilian National Health System (SUS), or patients seen at SUS or supplementary care units with an acute clinical picture compatible with COVID 19 and symptoms beginning within 7 days of the screening date;
3. Patients over 18 years of age and with at least ONE of the following criteria
    a) Age 50≥ years (no other risk criteria needed)
    b) *Diabetes mellitus* requiring oral medication or insulin
    c) Hypertension requiring at least 01 oral medication for treatment
    d) Known cardiovascular diseases (heart failure, congenital heart disease, valve disease, coronary artery disease, myocardiopathy under treatment, clinically manifest heart diseases with clinical repercussions)
    e) Lung disease symptomatic and/or under treatment (emphysema, fibrosing diseases)
    f) Patients with symptomatic asthma requiring chronic use of agents for symptom control
    g) Smoking
    h) Obesity defined as BMI > 30 kg/m^2 on weight and height information provided by the patient
    i) Transplant Patients
    j) Patient with stage IV chronic kidney disease or on dialysis.
    k) Immunosuppressed patients/in use of corticotherapy (equivalent to at least 10 mg prednisone per day) and/or immunosuppressive therapy)
    l) Patients with a history of Cancer in the past 05 years or currently undergoing oncological treatment
4. Patient with a positive rapid test for SARS-CoV2 antigen performed at the time of screening or patient with a positive diagnostic test for SARS-CoV2 within 7 days of symptom onset.

5. Willingness to use the proposed investigational treatment and follow the procedures foreseen in the research

5.3 Exclusion criteria

Participants who meet any of the following criteria during screening will be excluded:

1. Diagnostic test for negative SARS-CoV2 associated with acute influenza symptoms (patient with a negative test taken early and becomes positive a few days later is eligible, provided he/she is < 07 days from the onset of influenza symptoms);
2. Patients with an acute respiratory condition compatible with COVID-19 seen in the primary care network and with a decision to hospitalize;
3. Patients with an acute respiratory condition due to other causes;
4. Patients vaccinated for SARS-CoV-2
5. Dyspnea secondary to other acute and chronic respiratory causes or infections (e.g., decompensated COPD, acute bronchitis, pneumonia, primary pulmonary arterial hypertension);
6. Acute influenza presenting at least ONE of the criteria below:
    a) Respiratory Rate > 28/min;
    b) SaO2 < 90% or < 93% on nasal oxygen therapy at 10 l/ min;
    c) $PaO/_2$ IOF $_2$< 300 mmHg;
7. Patients taking serotonin reuptake inhibitors: Donepezil, sertraline;
8. Use of the following medications in the last 14 days:
    a) Monoamine-Oxiety Inhibitors (MAOI): Phenelzine, Tranylcypromine, Selegiline, Isocarboxazid, moclobemide;
    b) Use of iodinated contrasts during the treatment until 05 days after the end;
    c) Use of Antiretroviral Agents (Treatment of Acquired Immune Deficiency Syndrome - AIDS);
9. Patients with severe psychiatric disorders or major depression not controlled or controlled with any of the prohibited drugs (item above);
10. Pregnant or nursing patients;
11. History of severe ventricular cardiac arrhythmia (ventricular tachycardia, recovered ventricular fibrillation patients) or Long QT Syndrome;
12. History of diabetic ketoacidosis or a clinical condition that maintains persistent metabolic acidosis;

13. Surgical or contrast use planned to occur during treatment or within 5 days of the last dose of study medication;
14. Current daily and/or uncontrolled alcoholism;
15. History of seizures in the last month or an uncontrolled seizure condition;
16. Clinical history of Liver Cirrhosis or Child-Pugh C classification;
17. Patients with known severe degenerative neurological diseases and/or severe mental illness;
18. Inability of the patient or representative to give consent or adhere to the procedures proposed in the protocol;
19. Hypersensitivity and/or known intolerance to Fluvoxamine, Ivermectin or Metformin;
20. Inability to take oral medications;
21. Inability or unwillingness to follow research guidelines and procedures

1.

5.4 Randomization criteria

Participants can be randomized when they meet the inclusion criteria and have no exclusion criteria for the study.

5.5 Discontinuation of the product under investigation or withdrawal of participants

5.5.1 Discontinuation of the product under investigation

During the treatment phase of the research, the participant may discontinue the investigational product at any time and at his discretion. Likewise, the investigator may discontinue the investigational product whenever he/she deems it necessary, whether due to an adverse event or to preserve patient safety.

Participants who discontinue treatment of the investigational medicinal product without an apparent justification after randomization and prior to trial completion will be encouraged to return on their medication and continue in the trial as normal. If medication is discontinued, the patient will continue in the trial for the collection of composite endpoint events. These participants will be treated according to the standard of care according to the investigator's judgment.

5.5.2 Withdrawal from the study

5.5.2.1 Withdrawal of consent

Within the provisions of informed consent and good clinical judgment regarding participant safety, every effort should be made for participants to complete the treatment phase and visits after the treatment phase. Participants will be informed that they are free to withdraw from the study at any time. However, should a participant withdraw from the study, every effort will be made to determine why the patient has withdrawn their consent. Although participants are not required to give a reason for withdrawal of consent, the investigator will make every effort to obtain the reason while fully respecting the participant's rights. Reasons for withdrawal of consent, when provided by the participant, will be recorded in the clinical record, and the center should make every effort to ensure that the participant completes the early termination (EP) procedures described. Every effort will be made to contact a participant who fails to attend and/or attend a study visit by phone to ensure that the participant is in satisfactory health.

The participant who wishes to withdraw consent will be offered the opportunity to consent with the following:

- Provide information about your own health status by phone or other means by the date of the common EoS
- Allow family physicians or the family to be contacted to provide information about the participant's health status
- Allow a final contact at the end of the study (at or after the EoS)
-

5.5.2.2 Participant withdrawn by the researcher

The investigator and designated staff may use their medical judgment to terminate the participant's participation in the trial if they determine that the participant's continuation in the trial is a potential safety concern. The investigator must immediately inform the medical monitor of plans for the early withdrawal of a participant from the study. Participants withdrawn by investigators will also be offered the opportunity to consent to the three options described above. All participants withdrawn early from the study for any reason must complete the Early Study Termination procedures described and be followed up for safety after receiving the last dose of study medications. Randomized participants who are withdrawn from the trial for any reason will not be replaced.

5.5.2.3 All early withdrawal participants

For any participants who leave the study early (including participants who withdraw their consent), survival information can be verified via a public database search at the end of the study.

6 STUDY TREATMENTS

6.1 Concealment of treatment

The initial phase is blind to the participant and the research team.

To minimize the potential for bias during the treatment phase, the treatment randomization information will be kept confidential by a non-blinded biostatistician and will not be released to third parties until the study database has been locked. The study is blinded, and both the patient and the investigator and staff will not have access to the contents of the vials, which are sealed and hermetically sealed. Likewise, the sponsor and designee will not have access to the randomization data. Treatment vials will be dispensed using codes, maintained with a biostatistician who is not blinded and not involved with the research. The Data Safety Monitoring Committee (DSMC) and medication safety team will not have access to patient allocation during interim evaluations for appropriate decisions about the continuation of the research protocol, except in anticipated situations (decision to discontinue any arm of the research, termination of the research, or for reasons of global safety of the participants).

The clinical research supply management team will have access to the overall use of investigational products at the center level for managing packaging and distribution activities, as well as overseeing inventory levels of investigational products in drug depots and study centers.

The investigator, study site staff, or study pharmacist should make every effort not to disclose treatment assignments to other health care professionals, outside participants in the participant's care, or caregivers.

6.2 Dosage form/formulation administration

6.2.1 Fluvoxamine

It will be provided to the participant in the form of mg100 tablets for oral use.

6.2.2 Ivermectin

It will be provided to the participant in the form of mg06 tablets for oral use or tablets for sublingual use in dosages of 05 and 20 mg.

6.2.3 Metformin

It will be provided to the participant in the form of 750 mg Extended Release (XR) tablets for oral use.

All products under investigation will be supplied to patients from companies approved by ANVISA and certified to produce them or by means of an import license for products destined for clinical research.

6.3 Dosage and administration

6.3.1 Treatment groups

- Fluvoxamine:
  - Dose of 100 mg twice a day for a period of 10 days, always at 7 a.m. and 7 p.m.

- Ivermectin:
  - Doses to be administered over three days, according to the table below:

Peso (kg)	Número de comprimidos de 06 mg	Dose total mg	Dose (mcg kg)
40 - 45	3	18	400 – 450
46 – 50	3	18	360 - 391
51 - 55	4	24	436 - 470
56 – 60	4	24	400 - 428
61 – 65	4	24	369 - 393
66 – 70	5	30	428 - 450
71 - 80	5	30	422 - 375
80 - 90	6	36	400 - 450
> 91	6	36	Até 400

Tabela 2 – Posologia considerando comprimidos de ivermectina 06 mg

Peso (kg)	20 mg Wafer	05 mg Wafer	Dose total mg	Dose (mcg/ kg)
40 – 45	01 (20 mg)	não	20	444 - 500
46 – 50	01 (20 mg)	não	20	400 - 434
51 - 55	01 (20 mg)	01 (05 mg)	25	454 - 490
56 – 60	01 (20 mg)	01 (05 mg)	25	416 - 446
61 – 65	01 (20 mg)	01 (05 mg)	25	384 – 409
66 – 70	01 (20 mg) + 01 (10 mg)	não	30	428 – 454
71 – 80	01 (20 mg) + 01 (10 mg)	não	30	375 – 422
80 – 90	01 (20 mg) + 01 (10 mg)	01 (05 mg)	35	388 – 437
> 91	01 (20 mg) + 01 (10 mg)	01 (05 mg)	35	Até 384

Tabela 3 – Posologia ivermectina formulação sublingual (comp. de 05 e 20 mg)

- Metformin:
  - Dose 750 mg twice daily for a period of 10 days, always at 7 a.m. and 7 p.m.

6.3.2 Dosage and administration guidelines

6.3.2.1 Fluvoxamine

The dose on the day of randomization will be 100 mg to be taken at the end of the visit, followed by 100 mg every 12 hours until completing 10 days of treatment (If the randomization is with an interval of less than 6 hours from the subsequent dose, the same will not be administered. Example: Patient randomized at 2 pm will not take the 7 pm dose foreseen. If the patient is randomized at 11:00 am, he will take the 7:00 pm dose)

6.3.2.2 Ivermectin

The dose on the day of randomization will be 18 mg once if the patient's reported weight is < 80 kg. If the patient's weight is > 80 kg, the dose will be 24 mg once. In the eventual case of a patient weighing < 60 kg, the dose will be 12 mg. The medication should be taken at the end of the randomization visit.

6.3.2.3 Metformin

The dose on the day of randomization will be 750 mg to be taken at the end of the randomization visit, followed by 100 mg every 12 hours until completing 10 days of treatment (If the randomization is with an interval of less than 6 hours from the subsequent dose it will not be administered. Example: Patient randomized at 2 pm will not take the 7 pm dose. If the patient is randomized at 11:00 am, he will take the 7:00 pm dose)

6.4 Packaging and labelling

The products under investigation will be provided to the participant at no cost to him/her, with the guidance to use only for the purpose of the research. Identically shaped vials will be provided with the amount of medication sufficient for use as scheduled. The patient must return with the cartridges/blisters for an accounting of the medication delivered.
The study medication used will come from pharmaceutical plants that hold a commercial authorization for their production, already approved by ANVISA.

6.5 Study treatment allocation

Each eligible participant will be allocated to 1 of the 4 treatment groups via an internet-accessible remote randomization system (IWRS), namely:

- Fluvoxamine
- Ivermectin
- Metformin
- Placebo (pills without medicine)

After inclusion in the initial phase of the study, each participant will receive instructions on the proper dosing of medications and individualized instructions on when to take them and other concomitant medications after considering the participant's current medication regimen. The participant will be instructed to follow the agreed-upon dosing instructions throughout the remainder of the study to encourage adherence. The investigator will determine if the study medication administration instructions require changes at each planned telephone contact visit, and any changes will be communicated to the participant.

Participants who qualify for the treatment phase will be randomized to receive the investigational products as allocated to one of the study arms.

Participants will also be instructed to keep the empty/unused medication blister packs which will be collected by research staff in D_{10} for compliance assessment in the treatment phase. Participants will be instructed to return the empty/unused medication blister packs to the containers in which they were originally provided.

Adherence will be documented. Adherence will be assessed based on the prescribed number of medications, the duration of treatment, and the amount of medications dispensed and returned (used and unused). Research subject reported adherence would also be considered.

6.6 Delivery, storage, and accounting by the study center

6.6.1 Delivery from the study center

Once a study site has been approved to receive the study drug, it will receive an initial shipment of sufficient study medication for participants20. The need for drug replenishment will be assessed regularly, taking into account the number of participants enrolled, the number of participants being screened at the study site, and overall study participation.

6.6.2 Storage

The pharmacist or his representative will verify and acknowledge receipt of each shipment of the drugs. They will be shipped and stored at room temperature, no higher than 30°C and out of direct sunlight. All study medications will be stored in a secure location. No participants other than those included in this specific clinical trial should take the medications provided for this trial. The medications provided for this study may not be used in any animal or laboratory research.

6.6.3 Accounting

All investigational products dispensed to participants should be accurately recorded in the investigational product accounting record maintained at the study site by the study pharmacist or qualified representative. Participants should be instructed to return all investigational products dispensed to them (blister packs and containers, used or unused), which will be collected by research staff at D_{14}. All used investigational product blister packs and containers will be retained at the site by the study pharmacist/qualified representative for verification by the study monitor. Accounting and investigational product adherence verification for all investigational products will be performed by the study pharmacist or qualified representative at each scheduled study visit.

6.7 Changing the dose of the drug

6.7.1 Adverse reactions during the use of medications

The research participant should contact you when he/she presents any adverse reactions that he/she feels may be associated with the product under investigation. Likewise, the patient will be monitored daily by safety telephone contacts to ascertain the presence of any undesirable symptoms, adverse reactions, and other signs/symptoms that may be present. The participant may be scheduled for an extra safety consultation whenever the investigator deems it necessary, with reference to the information obtained during the telephone contact.

The decision to temporarily discontinue medication can be made at any time by either the participant or the investigator. Return to investigational products should be attempted whenever possible.

6.7.2 Usual care

During the treatment phase, all participants will receive usual care according to the recommendations in the guidelines. Usual care includes recommendations for all aspects of treatment for patients with an acute upper airway infection condition (i.e., recommendations for antipyretics if T. Ax > 38.0C^0, frequent hydration, analgesics for intense myalgias, and seeking medical help if fatigue). Usual care may also include educating the patient.

6.8 Prohibited therapy, special considerations, and concomitant treatment

6.8.1 Prohibited medications

Throughout the study, the following medications will be prohibited while the patient is being treated with the study medications:

- Monoamine-Oxiety Inhibitors (MAOI): Phenelzine, Tranylcypromine, Selegiline, Isocarboxazid, moclobemide;
- Use of iodinated contrasts during the treatment until 05 days after the end;
- Use of Antiretroviral Agents (Treatment of Acquired Immune Deficiency Syndrome - AIDS);
- Sertraline, Donepezil

6.8.2 Concomitant medications

Information on concomitant medications (prescription drugs, over-the-counter medications, herbal, and naturopathic medications, etc.) will be collected starting at screening and throughout the study (including at the Early Termination/ EoS visit, follow-up phone call).
In general, participants should continue the same medications and regimens that were ongoing at the time of study entry. The doses of these concomitant medications should be kept as stable as possible during the study. Medications that the investigator considers indicated for the treatment of any intercurrent disease or a preexisting condition that are not on the list of prohibited medications or do not form an exclusion criterion for participation in this study will generally be allowed.

7 RISKS AND PRECAUTIONS

7.1 Precautions

The investigator should be aware of the administration of investigational drugs in the following situations:

- Depression or psychiatric conditions: Such patients should be carefully evaluated, and participation may be allowed if there is no evidence of uncontrolled, worsening, or major depression. Patients with severe psychiatric conditions should not participate in this research program.
- Patients taking verapamil should be observed carefully because there may be an increase in the serum bioavailability of metformin.
- Patients should consume food after the use of medications. It is inadvisable to ingest them while fasting and to maintain the same immediately after the medications.
- Patients with a history of seizures can participate if they have not manifested in the last 60 days and are stable, under pharmacological control.

7.2 Adverse reactions

7.2.1 Fluvoxamine

Most adverse reactions reported in clinical studies conducted with Fluvoxamine are gastrointestinal symptoms, usually of mild intensity (nausea, dyspepsia, mild diarrhea, abdominal pain). Other adverse reactions: agitation, anxiety, insomnia, headache, anorexia, palpitations, hyperhidrosis, malaise. Apart from gastrointestinal symptoms, the manifestation of other symptoms is not common in treatments lasting less than 30 days.

7.2.2 Ivermectin

Most adverse reactions reported in clinical studies conducted with ivermectin are related to the digestive system, usually mild gastrointestinal symptoms (nausea, dyspepsia, mild diarrhea, abdominal pain). Other adverse reactions: dizziness, drowsiness, lightheadedness, allergic skin reactions, which may occur in less than 1% of patients.

7.2.3 Metformin

Most adverse reactions reported in clinical studies conducted with Metformin are gastrointestinal symptoms, usually of mild intensity (dysgeusia, nausea, dyspepsia, mild diarrhea, abdominal pain, inappetence). Other adverse reactions: reduced absorption of vitamin $_{12}$ Be and lactic acidosis, both very rare (incidence less than 1: 10,000).

8 STUDY PROCEDURES

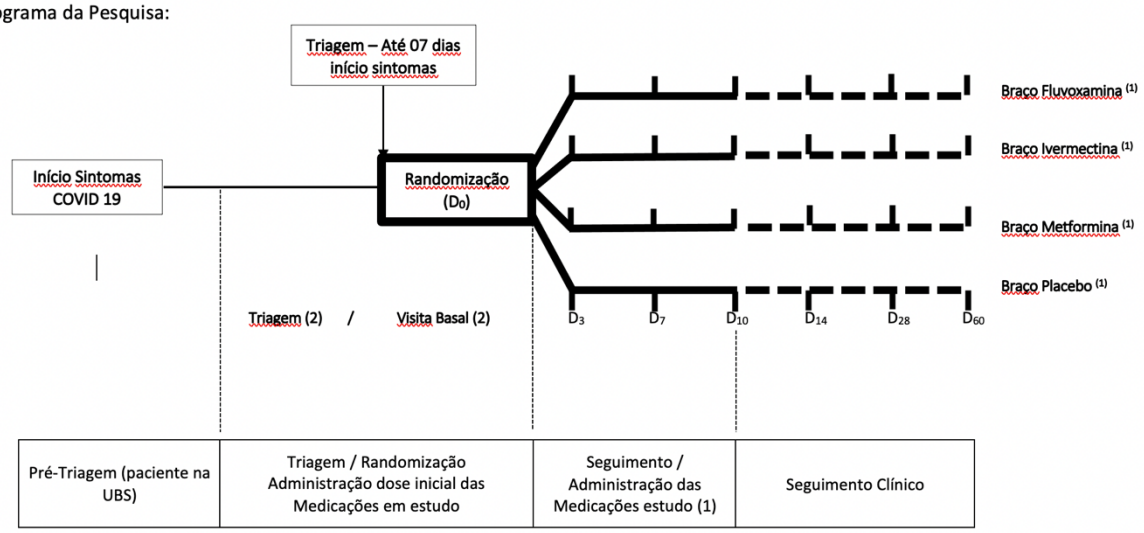
For a detailed evaluation schedule (with all the evaluations, visits and visit windows required by the protocol), see the study flowchart

8.1 Screening procedures

8.1.1 Screening procedures

Before any specific procedure of the study, the participant will receive an explanation of all the procedures of the study and must date and sign an informed consent form (ICF) approved by a Research Ethics Committee (REC). The screening visit will be performed (1) in Basic Health Units / Outpatient Clinics or (2) in Emergency Room Units either from SUS or supplementary medicine and will follow the flowchart below:

Fluxograma da Pesquisa:



1. Tratamento: Fluvoxamina, Ivermectina e Metformina em grupos paralelos pelo período planejado. Interromper se sintomas ou reações adversas.
2. Triagem e Randomização devem ser realizadas na mesma visita. Assegurar que o paciente seja randomizado por ocasião do atendimento.
3. As visitas subsequentes: D_3, D_7, D_{10}, D_{14}, D_{28}, D_{60} serão realizadas através de contato telefônico. Em qualquer momento visitas extras de segurança poderão ser realizadas. As visitas D_{14} e D_{28} são consideradas visitas de desfecho para a pesquisa. As visitas D_{28} e D_{90} são consideradas visitas pós estudo de acompanhamento de complicações tardias relacionadas ao COVID-19 e avaliação eventual de reações adversas tardias aos medicamentos da pesquisa e serão realizadas através de contato telefônico. Não há previsão de visitas presenciais nesta pesquisa em atenção às recomendações regulatórias emitidas pela autoridade de saúde pública no contexto da pandemia. Em qualquer momento visitas extras de segurança poderão ser realizadas.
4. Contato diário por telefone (não assinaladas acima) serão realizadas entre os Dias 1 a 9 de tratamento, à exceção dos dias acima descritos, os quais serão presenciais.

Table 1 - Procedure flowchart

Identification of eligible patients will be made at the time of screening or during the clinical consultation. Patients identified with a clinical picture of acute influenza syndrome in the context of the pandemic of COVID-19 will be invited to learn about the research project. If they show interest, they will be directed to a previously designated and trained research member to present the proposed research program and present the Informed Consent Form (ICF), which will be presented according to current regulatory standards for clinical research. The research procedures will only begin if the participants who express interest in participating in the research program sign the ICF. At the screening visit, participants will receive a unique participant number, which will be generated during the registration of the screening visit in IWRS.

Participants are first screened to identify those who meet the eligibility criteria. Once a participant meets all eligibility criteria, he or she will begin the baseline visit phase.

The activities described below will be performed at the screening visit:

- The participant signs the ICF
- Review of eligibility criteria
- Demography
- Pregnancy test for women of childbearing age
- Respiratory signs and symptoms
- Perform the rapid test for COVID-19 using the nasopharyngeal sample to be collected at this time.

8.1.1.1 Retrying participants

In this study, retrying of the patient is only allowed if it occurs > 30 days from the first evaluation, in the case of a patient previously defined as a screening failure due to a negative rapid test for COVID-19.

8.1.2 Visit 2: Baseline visit procedures/randomization

The baseline visit/randomization should be performed immediately after confirmation of positivity for COVID-19 by rapid test. If the patient has difficulties or has a confirmatory test for COVID-19, randomization may be performed, provided that it occurs within 7 full days of the onset of acute flu symptoms. The following procedures will be performed at this visit

- IWRS Registration
- Review of eligibility criteria
- Medical History
- Weight (informed by the patient)
- Height (informed by the patient)
- Temperature
- ECG (Kardiamobile, 01 or 06 leads) for measurement of Heart Rate and QT interval.
- Adverse Events if applicable
- Concomitant medications
- WHO Flu Syndrome Questionnaire
- Eq-5D-5L Questionnaire
- Baseline pulse oximetry measurement
- Randomization
- Delivery of medications and orientation regarding the same
- Orientation regarding daily telephone contacts and subsequent visits
- Orientation regarding the D_3 and V_7 visits and the procedures associated with them (600 initial patients)
- COVID-19 guidelines and quarantine recommendations

8.2 Procedures of the treatment phase (double-blind character)

Participants who meet all inclusion criteria and do not have exclusion criteria will be randomized within 7 full days of symptom onset, preferably following the screening visit (both performed at the same time). The procedures to be performed from the randomization visit will be considered as procedures from the V2 visit. The medication allocated through randomization will be delivered to the patient, along with the swab kits in the case of the first 600 patients (nasopharyngeal SWAB associated with sputum/saliva collection to check viral load), and the patient will also receive orientation regarding daily telephone contacts and procedures associated with the next study visits. Considering the high degree of transmissibility of COVID-19 and the need for quarantine of identified cases as the only existing alternative, daily telephone contacts will be made between randomization through D7.

8.2.1 Daily telephone contacts (D_2 to D_7)

The patient will be contacted daily, either by phone or through social media. The following data will be evaluated:

- Tolerance to the product under investigation
- Adverse effects/adverse reactions which may arise
- Clinical progress regarding COVID-19 and any emergency room visits or hospitalizations
- WHO Ordinal Scale of Clinical Improvement Questionnaire
- For the first 600 patients in the study, during the contact made at the D_2 and D_6 visits, the participant will be instructed about the collection of nasopharyngeal SWAB or sputum/saliva, which will be performed by the participant himself on the following day (D_3 and D_7). In the D telephone contact, $_7$the participant will be oriented about the collection of the SWAB samples (it will be collected at the patient's home) or at a place to be arranged, in case of impossibility of access by the delivery service (hard to reach the place, area of high social vulnerability). In these cases, a designated person will go to a known point at an agreed time to collect the sample

8.2.2 Visit 3 and 4: D_3 and D_7 (+ 1 day)

At these visits, in addition to the procedures as described in the daily telephone contacts, nasopharyngeal or sputum/saliva SWAB will be performed by the participant himself. Such a procedure will be performed for the first 600 patients included in the trial (approx. 150 patients per treatment arm).
In addition to this, the following procedures will be checked in these visits:

- Adverse Events
- Concomitant Medications
- WHO Flu Symptoms Questionnaire
- Respiratory Symptoms
- Clinical outcomes
- Remote Product Accounting under Investigation
- WHO ordinal scale of clinical improvement

8.2.3 Visit 5 (D_{10})

A telephone/social media contact is planned a face-to-face evaluation of the patient, which is performed the day after the last day of administration of the medication under investigation. The following procedures are planned for this visit

- Assessment of AEs/special situations
- Registration of drugs and concomitant procedures
- Evaluation of secondary clinical outcomes
- Collecting the research medication KITs for accounting.
- Guidelines on Ending the Treatment Period
- Follow-up phone contact guidelines
- WHO ordinal Clinical Improvement Scale

8.2.4 Visits 6 (D_{14}), 7 (D_{28}), 8 (D_{60} - End of study)

These visits will be conducted via telephone contact, with the last visit being able to be conducted in person, at the discretion of the investigator (If it is necessary to verify some adverse event or participant initiative). The following procedures will be verified in these visits:

- IWRS Registration
- Evaluation of adverse events
- Evaluation of clinical outcomes
- Registration of drugs and concomitant procedures
- Orientations about the end of contacts and end of the research
- PROMIS V10 Questionnaire
- WHO ordinal Clinical Improvement Scale

At visit $D_{28,}$ an EQ-5D-5L questionnaire will be conducted over the phone.

8.3 Unscheduled visit procedures

An unscheduled visit may occur at the discretion of the investigator or by patient need and may occur during the treatment period until the final visit of the study (Visit 8).
On an unscheduled visit during any phase of the study, the following activities will be performed:

- IWRS Registration
- Assessment of AEs/special situations
- Registration of drugs and concomitant procedures
- Evaluation of the reason for the unscheduled visit and definition of conduct.

Any other study evaluations may be performed at the investigator's discretion during an unscheduled visit. In the case of clinical evolution of expected complications for COVID-19, the related adverse events will be considered as expected for the presented clinical problem.
The following activities are optional during an unscheduled visit:

- Performing a physical examination
- Collection of a blood sample for hematological evaluation (central laboratory)
- Referral to tertiary care services for continuity of treatment at the hospital level.

8.4 Proceedings of the D_{28} visit

The date for the evaluation of the primary and secondary endpoints for the study is set to be the date of the D_{28} visit. We will conduct telephone follow-up after the final study endpoint visit (D_{28}), as we consider it important to check for any late complications both from study participation and from COVID-19 disease. This post-study visit is scheduled to occur on D_{90} post-randomization.

8.5 Early termination procedures (ET)

For participants who withdraw prematurely from the trial (before the scheduled date of the final trial endpoint assessment - D_{28}), the site should do its best to ensure that the participant completes the PT visit, which should be conducted on the day of withdrawal or as soon as possible after withdrawal. The assessments performed at the TP visit should be the same as those at the D_{28} visit.

9 EVALUATIONS OF THE STUDY

9.1 Laboratory examinations

In this clinical research protocol, there is no provision for laboratory tests, except for the rapid test for COVID-19 and the RT-PCR tests, both using nasopharyngeal/saliva secretion as biological material for testing.
In women of childbearing age, pregnancy testing is planned, and the biological material to be used is urine.
Laboratory tests may be performed to elucidate adverse events or changes for which the investigator deems laboratory evaluation necessary.

9.2 Vital signs

Considering the extreme transmissibility nature of SARS-CoV2 and the recommendations for isolation of positive individuals, the only vital data to be observed are:

- Respiratory Rate
- Arterial oxygen saturation using a digital oximeter.
- Temperature.
- Weight and height (informed by the patient)

9.2.1 Heart rate and blood pressure

Considering the highly transmissible nature of COVID-19 and risks of contamination of the research team and considering the profile of patients to participate in the research (patients with mild symptoms, without any major physiological system complications at the time of participation), we understand that blood pressure, and heart rate data will not contribute to any COVID-19-related risk assessment. Furthermore, the heart rate can be obtained when performing the ECG via the Kardiamobile®. Therefore, it is a procedure that adds transmission risks for the research team without a direct benefit of the data for patient orientation towards COVID-19. Thus, we will not measure blood pressure or heart rate in the classical way during this research, except in situations in which the research team identifies the need to know the blood pressure levels for immediate action

9.3 Physical examination

There is no provision for a complete physical examination by systems in this research for the same reasons listed in item 9.2.

9.4 ECG evaluation

Evaluation of an ECG tracing should be performed to check for any changes due to COVID-19 and will be performed at the Screening visit. We will not monitor the QT interval in this research since the medications being used do not alter the QT interval.
The participant should rest at rest for a minimum of 5 minutes before the exam and the procedure to be performed as per the Kardiamobile® manufacturer's guidelines.

9.5 Patient-reported outcomes

Patient-reported outcome questionnaires (EQ-D-5L5 and WHO Flu Syndrome Questionnaire) will be completed by participants before the study team conducts any further assessments during the telephone contact or face-to-face visit in order to avoid influencing participant responses. The study coordinators will review the participant's responses immediately after the participant completes the questionnaires to ensure that all questions are answered.

Clinical Worsening Questionnaire - WHO
We will assess the clinical condition of the participants using the WHO scale: 0-1: ambulatory (no clinical deterioration during the RCT phase), 2: activity limitation but no hospitalization; 3: hospitalization but no O2 required; 4: hospitalization, O2 required; 5: non-invasive ventilation or high-flow oxygen; 6: ventilator required; 7: ventilation plus organ support required; 8: death. The scale can be found on page 6 at the following link: https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf.
Since ordinal scales have proven useful in studies of hospitalized patients with respiratory illness, this measure will be particularly useful as an outcome measure for the subset of study participants requiring hospitalization.

PROMIS Global Health Questionnaire (Global-10)

We will assess the patients' global health status on days 0, 14 and day 60 using the 10-item PROMIS global health scale (Patient-Reported Outcomes Measurement Information System 10)[106]. The items on this scale assess general domains of health and functioning, including overall

physical health, mental health, social health, pain, fatigue, and overall perceived quality of life. The 10 questions on the Global-10 were largely adapted from older measures, such as the SF-36 and the EQ-5D, with modifications that resulted in greater sensitivity and accuracy than the questions originally formulated.

9.6 Contraception in women of childbearing potential

For women of childbearing potential, a urinary or serum pregnancy test will be performed at the randomization visit.

Fluvoxamine is considered a "C" risk medication, and there have been reports of primary pulmonary hypertension, especially when used in the 3rd trimester of pregnancy. These drugs can cause neurological withdrawal symptoms in newborns of mothers taking fluvoxamine. It is excreted in breast milk in small amounts and therefore should not be used by nursing mothers. Ivermectin is considered a "C" risk medication in pregnancy, and there are no studies evaluating its effect in this population. The recommendation of use is only under medical advice and after risk/benefit evaluation. It is excreted in small quantities through breast milk. Metformin is considered a B risk medication in pregnancy and is excreted in minimal amounts through breast milk.

Considering the above data, pregnant and breastfeeding women cannot participate in this research.

Pregnancy testing will be performed on all women of childbearing age (childbearing age being defined in this protocol as at least one episode of menstruation occurring in the last 12 months in women between the ages of 18 and 55).

Any pregnancy occurring during the treatment phase of the trial will be monitored until birth for possible complications and adverse events.

10 EVALUATION, RECORDING AND REPORTING OF ADVERSE EVENTS

10.1 Definition of adverse events

An adverse event is any unfavorable medical occurrence experienced by a patient or a clinical trial participant who has received a drug that does not necessarily have a causal relationship to that treatment[107]. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding) or symptom or disease temporally related to the use of an (investigational) drug product, whether related to the (investigational) drug product or not. This includes:

(1) any new clinical picture, sign or symptom, clinically significant physical examination abnormality, or newly diagnosed event occurring during the AE reporting period, including signs or symptoms associated with an underlying condition that were not present prior to the AE reporting period;

(2) a pre-existing condition that worsened in severity or frequency or changed in character after the participant signed the RCT during the AE reporting period; and

(3) complications that occur as a result of protocol-required interventions. An AE can arise from any use of the investigational drug (e.g., off-label use, use in combination with another drug) and with the use of any route of administration, formulation, or dose, including an overdose. Also, any side effects, harm, toxicity, or sensitivity reactions that may be presented by a participant in this clinical trial may also be AEs.

For the purposes of this protocol, events that will not be considered EAs include:

- Expected fluctuating signs or symptoms of a preexisting medical condition (e.g., tremor in a participant with Parkinson's disease; migraine episodes) that did not worsen in severity or frequency or change in character during the AEs reporting period;
- Surgeries or medical procedures are not AEs; however, the clinical condition (new or worsening) that led to the surgery or medical procedure is the reported AE (e.g., for appendicitis resulting in appendectomy, the appendicitis should be reported as the AE);
- Overdosage without clinical signs or symptoms;
-

10.2 Adverse event reporting period

AEs, including serious adverse events (SAEs), will be collected throughout the study period, from the time the participant signs the WIC until the EoS visit. All AEs still present at the conclusion of the trial will be followed up by the investigator by contacting the participant until their resolution or stabilization or until the participant is lost to follow-up and can no longer be contacted. The outcome should be documented in the participant's source documents. The investigator should report all SAEs occurring after the reporting period specified in the protocol if, according to the investigator's judgment, there is a reasonable possibility that the SAE is related to the test article or any trial procedure.

10.3 Obtaining adverse events

If the participant reports an AE, it is the investigator's responsibility to obtain sufficient information to assess causality. This may require additional laboratory tests, physical examinations, telephone contact, etc.

To avoid bias in the collection of AEs, participants should be asked to answer a neutral question, such as "How are you feeling?" It is also important to ask the participant in a non-biased manner about changes in their health or use of concomitant medication since their last visit. This information should be collected prior to conducting assessments at all study visits. In addition, any symptoms/conditions reported during assessments and deemed clinically significant by the investigator will be assessed as AEs.

10.4 Evaluation of adverse events

10.4.1 Intensity/severity

The medical assessment of intensity will be determined using the following definitions:

- Mild: The AE is easily tolerated and does not affect normal activities.
- Moderate: The AE affects daily activities, but the participant is still able to perform them.
- Severe: The AE is disabling, and the participant is unable to work or perform his or her usual activities.

A new event will be documented whenever the intensity of an event changes.

It is important to note the distinctions between severe AEs and severe AEs (SAGs). Severity is a rating of the intensity of a specific event (such as mild, moderate, severe); however, the event itself may be of relatively minor clinical significance (such as severe headache). An SAE, however, is an AE that meets any of the specified regulatory criteria required for severity designation (e.g., a headache may be severe [significantly affects the participant's usual functions] but would not be classified as severe unless it is met any of the criteria for SAEs).

10.4.2 Causality and reporting

The investigator will provide a causality assessment for all AEs using their best clinical judgment based on available medical information about the event being reported. The causality assessment will be reassessed as new information becomes available. If the investigator's assessment of causality is not reported, the event will be considered "related" until that information is received. Each investigator will assess the degree to which the AE is related to the drugs under investigation using the following definitions:

Unrelated: There is no reasonable possibility that the product under investigation caused or contributed to the AE.

- The event is related to an etiology other than the investigational drug, such as underlying disease, study or procedures not included in the study, concomitant medications, or the participant's medical condition
- The timing of the AE is not reasonably related to the administration of the study drug
-

Related: There is a reasonable possibility that the product under investigation caused or contributed to the AE.

- There is no compatible temporal association between the event and the administration of the investigational drug
- Is there a biologically plausible mechanism by which the study treatment may have caused or contributed to the AE
- The event improves or decreases after discontinuation of the study drug without initiation of any event-specific treatments (exposure withdrawal) and/or the event recurs or worsens upon reintroduction of study therapy
- The event cannot be reasonably attributed to the concomitant or underlying disease or other medications or procedures
-

For purposes of causality assessment, "reasonable possibility" means that, based on the investigator's medical judgment of the available information, there are facts or arguments that suggest a positive causal relationship.

10.4.3 Outcome categorization

The outcome can be classified as: recovered/resolved (e.g., no sequelae); recovered/resolved with sequelae; not recovered/unresolved; fatal; or unknown (if follow-up is not possible).
If the outcome of an SAE is reported as recovered/resolved with sequelae, the investigator should specify the type of sequelae on the SAE form. If the outcome of an SAE is reported as unknown, the investigator should specify (on the SAE form) the rationale for why unknown was selected.
"Fatal" should be recorded as an outcome when the AE results in death. The cause of death is required when known. If a necropsy was performed, a necropsy report will be provided. If no necropsy was performed, a death certificate will be provided if obtainable. Death will be reported as a result and not as an event. If more than one AE is possibly related to the participant's death, the outcome of death should be indicated for the AE that, in the investigator's opinion, is the most plausible cause of death. All other ongoing AEs/SAEs should be recorded as unrecovered/unresolved at the time of death.

10.5 Recording and Reporting

10.5.1 Persistent or recurrent adverse events

AEs that continuously extend, without resolution, between clinical trial evaluations should be recorded. A new event will be documented whenever the intensity of an event changes.
AEs that resolve and then occur again should have each recurrence recorded separately in the medical record.

10.5.2 Diagnosis versus signs and symptoms

Whenever possible, the investigator should report a diagnosis rather than individual signs and symptoms or abnormal laboratory values. However, if a set of signs and/or symptoms cannot be characterized clinically in the form of a single diagnosis or syndrome at the time of reporting, each individual event should be recorded in the medical record. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be cancelled and replaced by 1 AE report based on that single diagnosis, with an onset date that corresponds to the date of onset of the first symptom of the eventual diagnosis.
The investigator should use standard medical terminology/concepts and avoid colloquial terms and abbreviations. Only one AE term should be recorded in each event field on the medical record.

10.5.3 Pre-existing clinical conditions

A pre-existing condition is one that is present at the screening visit for this study. Such a condition should be recorded on the medical history form. A pre-existing condition should be recorded as an AE only if the frequency, severity, or character worsens during the study. When recording these events on the AE clinical record, it is important to indicate the concept of change in the pre-existing condition, including applicable descriptors (e.g., "most frequent headaches").

10.5.4 Clinical laboratory analysis

Not all laboratory tests with results outside the reference range qualify as an AE. A laboratory investigation result should be reported as an AE if it meets any of the following criteria:

- Be accompanied by clinical symptoms
- Result in a change of study treatment (e.g., modification of dose administration, discontinuation of treatment, or discontinuation of treatment)
- Result in unanticipated medical intervention.
- Present the change of a parameter from a normal value to a pathological value or a new worsening of an already pathological value
- Is considered clinically significant in the opinion of the investigator

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment must be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. When evaluating such changes, the extent of the deviation from the reference range, the duration until return to the reference range, either during continuous treatment or after cessation of treatment with the investigational product, and the range of variation of the respective parameter within its range should be taken into consideration.
The investigator has the responsibility to determine the clinical significance of each abnormality.
If at the end of the treatment phase, pathological laboratory values exist that were not present at baseline, additional clinical or laboratory investigations should be carried out until the values return to the reference range or a plausible explanation (e.g., concomitant disease) is found for the pathological laboratory values. The investigator must decide, based on the above criteria and a participant's clinical picture, whether a change in a laboratory parameter is clinically significant and therefore represents an AE. If the investigator considers such an AE to be serious, it should be reported as an SAE.
If a laboratory abnormality that meets the above criteria is a sign of a disease or syndrome, only the diagnosis should be recorded on the medical record. If a laboratory abnormality that meets the above criteria is not a sign of a disease or syndrome, the abnormality itself should be recorded on the medical record, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "potassium elevated" rather than "potassium abnormal"). If the laboratory abnormality can be characterized by a precise clinical term according to standard definitions, the clinical term should be recorded as the AE, e.g., hypercalcemia or hypoglycemia. The initial severity of the event should be recorded, and the severity or severity should be updated at any time if the event worsens.

All pathological laboratory values/achievements diagnosed throughout the treatment period should be analyzed by the investigator to provide a final clinical assessment in view of the dynamics of the laboratory changes/abnormalities.

10.5.5 Abnormal vital signs and other abnormalities

Non-standard laboratory results, ECGs, vital signs, and other safety assessments will be considered AEs if they meet at least one of the following criteria:

- Are associated with symptoms or result in a diagnosis (in which case the symptom or diagnosis will be recorded as an AE)
- Lead to discontinuation of the product under investigation
- Require treatment or referral of the participant for additional off-protocol testing (retesting or titration are within protocol procedures)
-

It is the investigator's responsibility to review all vital signs, ECG, and other safety findings. Medical and scientific judgment must be exercised to decide whether an isolated laboratory abnormality should be classified as an AE. If a clinically significant abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded in the medical record.
Observations on the same clinically significant laboratory abnormality between visits should not be recorded repeatedly unless there are changes in etiology. The initial severity of the event should be recorded, and the severity or severity should be updated at any time if the event worsens.

10.6 Adverse drug reaction and reference safety information

10.6.1 Adverse drug reaction

An adverse drug reaction (ADR) is an undesirable, unintended response to a drug product related to any dose administered. This definition implies a reasonable possibility of a causal relationship between the event and the drug under investigation. This means that there are facts (evidence) or arguments to suggest a causal relationship.

Considering that the medications under investigation have been approved commercially by ANVISA for decades, in this study, only the adverse reaction not yet described in the ANVISA drug dossier and evaluated by the investigator as a reasonable causal relationship with a medicinal product (under investigation) will be considered ADR.

Thus, it is not expected that there will be an ADR report related to the drugs used in this research.

10.6.2 Reference safety information

Baseline safety information (RSI) presents the basis for assessing the predictability of an ADR for accelerated reporting and annual safety reports, as well as for safety surveillance of the participant in a clinical trial by regulatory agencies (or ethics committees).

In the context of this study, ADR reporting is not expected because it is expected that potential adverse reactions are already described in the SIR of the medications under investigation (ANVISA Dossier on

Medication, package insert registered at ANVISA), unless in exceptional cases, for the medical products under investigation in this research.

10.7 Serious Adverse Event

10.7.1 Definition of serious adverse event

An SAE is defined as any unfavourable medical occurrence that, at any dose:

- Result in death
- Be life-threatening (the term life-threatening in the definition of seriousness refers to an event during which the participant was at risk of death; it does not refer to an event that hypothetically could have caused death if it were more severe)
- Require hospitalization or prolongation of existing hospitalization. Hospitalizations for elective surgery (i.e., a planned, non-emergency medical procedure), social hospitalizations, and hospitalizations lasting less than 24 hours are not considered SAEs
- Result in persistent or significant disability/incapacity
- Either a congenital anomaly/birth defect
- Be a major medical event (i.e., clinically significant)
-

Medical and scientific judgment must be exercised to decide whether expedited reporting is appropriate in other situations, such as in the case of major medical events that may not be immediately life-threatening or result in death or hospitalization but may place the participant at risk or may require intervention to prevent one of the other outcomes listed in the definition above. These events must also be considered serious.

Any worsening of a pre-existing condition or any new condition that meets the above SAE criteria should be considered an SAE, and the investigator is encouraged to discuss with the research coordinator any AE for which the severity assessment is uncertain or questionable.

10.7.1.1 Situations that are not considered serious adverse events

The following situations are not considered SAEs:

- Elective or pre-planned surgery for a pre-existing condition that has not worsened
- Routine health assessments requiring hospitalization not associated with a deteriorating clinical picture
- Social hospitalization (homelessness, family circumstances, etc.)
- Adverse reactions associated with the drugs under investigation, which can be expected for the same, according to the drug dossier registered at ANVISA
- Outcomes under investigation (Hospitalization, worsening of COVID-19)

10.7.2 Serious adverse event reporting

The SAE reporting period begins at the time the TCLE is signed by the participant. The SAE reporting period ends at the visit ($7D_{28}$).

The occurrence of an SAE must be reported immediately to the research coordinating committee within 24 hours of its notification by fax, e-mail, or telephone. This includes all SAEs (regardless of the relationship to the study treatment).

A death that occurs during the study (up to visit D_{28}) or that is reported to the investigator by visit ($8D_{90}$), whether considered treatment-related or not, must be reported to the study's follow-up committee.

Any SAE deemed to bear a causal (e.g., related) relationship to the product under investigation and discovered by the investigator at any time after the study should be reported. A rationale for assessing a causal relationship should be provided by the investigator. All safety information that is obtained after the clinical database has been closed shall be documented in the safety database, and the implications for handling the data in the clinical database assessed on a case-by-case basis.

The SAE start date is defined as the date when the signs/symptoms/diagnosis became severe (i.e., meet at least one of the severity criteria). If the participant presents with an AE and it progresses to an SAE, a new SAE should be recorded. The resolution date of the original AE should be the same as the start date of the SAE. However, when the SAE resolves, and the pre-existing EA is still in progress, this should be recorded as a new EA. The date of the resolution of an SAE is defined as the time when the symptoms resolve or when the event is considered chronic (e.g., sequelae) or stable and/or if the severity criteria are no longer applicable.

The investigator should complete the SAE report form and verify the accuracy of the information recorded on the SAE pages with the source documents. The sponsor's SAE report form will be completed in capital letters, in medical terms, in English, and as best as possible given the time constraints. Any supporting documentation (e.g., hospital discharge summary, necropsy report/death certificate, etc.) should be sent/transmitted along with the SAE (follow-up) reporting form. The supporting information provided should not reveal the identity of the participant beyond the agreed study identifier. The investigator should ensure that the reported information is accurate and consistent.

At a minimum, the following information should be provided at the time of the initial SAE report:

- Study name and/or number
- The number, age, and gender of the participant
- The literal description/term of the event (including the date the SAE started, its outcome, and the reason it was considered serious)
- Relationship to the medical product under investigation (e.g., causality)

- Dose of the medical product under investigation (number of packages) and administration dates
- Measure taken with respect to the medical product under investigation
- Severity of the event
- Name and address of the investigator
- Name of the reporter (including center name or number and country) e,
- Dated signature of researcher or sub/co-researcher
-

When using electronic methods of reporting SAEs, some of the information in the list above may be generated by the electronic system. Since SAEs are also AEs, the information for the AE clinical record and the SAE form should be consistent.

Follow-up information should be handled in the same manner and reported at the same time interval as the initial SAE report. A safety contact sheet will be provided to the Investigator (prior to the first participant providing informed consent) detailing all applicable contact information for safety reporting. This contact sheet will be kept up to date with any changes being provided to the Investigator immediately.

Whenever possible, the investigator should report a diagnosis rather than individual signs and symptoms or abnormal laboratory values.

Death should be considered an outcome and not a separate event. In the case of a fatal outcome, the investigator should provide a working diagnosis (an event that caused the outcome, e.g., death due to fatal heart attack) rather than reporting only death, and a necropsy report should be provided when possible. If the cause of death becomes known later (e.g., after the autopsy), this working diagnosis should be replaced by the established cause of death.

All registered SAEs, regardless of the relationship to the experimental product, will be followed up until their resolution or stabilization or until the participant is a follow-up loss and can no longer be contacted. At the D_8 visit, updates should be recorded and submitted. In circumstances where the investigator is unable to contact the participant (or their relatives), the investigator should provide a written statement (recorded in the participant's source documents) to the trial steering committee confirming that the participant is not being followed up.

10.7.2.1 Composite study endpoints

All events potentially related to the primary outcome (i.e., emergency department care and observation stay for a period > 12 hours associated with hospitalization for worsening of a lower respiratory tract infection [LTRI]) will be collected from the date informed consent was signed. For the purposes of this protocol, the following events are considered Study Outcomes and should be reported as previously described.

- Change in viral load on days 03 and 07 after randomization (first 600 patients);
- Time to clinical improvement (up to 28 days), defined as normalization of temperature, respiratory F, SaO_2, and relief of flu-like symptoms (defined as improvement > 50% from baseline as measured by the WHO Flu Syndrome Questionnaire) within the last 72 hours;
- Time to clinical failure, defined as the time until hospitalization due to progression of COVID-19 or emergency room care with a stay for treatment of progression of COVID-19 for > 12 hours;
- Hospitalization for any cause
- Hospitalization due to progression of COVID-19
- Mortality due to pulmonary complications
- Cardiovascular mortality
- Adverse events (up to 28 days);
- Mortality rate of patients at day 14, 28 and 90 days;
- Proportion of non-adherent patients with the product under investigation;
- Specific adverse reactions to fluvoxamine;
- Specific adverse reactions to ivermectin;
- Metformin-specific adverse reactions;

Based on the specific study design and the advanced state of the underlying disease in the recruited participant population, events suggestive of study outcomes would automatically qualify to meet the severity criteria in this study. These events include known consequences of the underlying disease and are expected to occur in the study population regardless of drug exposure (see above). These events should be reported, collected, and monitored during the course of the trial, just like all other SAEs, but will not be reported individually on an immediate basis. Although these SAEs should meet the definition of unexpected, these events do not require a safety report, accelerated as in individual cases, because it is not possible on a single case basis to determine that there is a reasonable possibility that the study drug caused the event. As a result, they would not meet the definition of suspected adverse reaction.
The DSMC will monitor events identified during the conduct of the trial and alert if there is evidence of a causal relationship between the product under investigation and the event after its analysis.

10.7.3 SUSARs

The definition of a suspected unexpected serious adverse reaction (SUSAR) is any ADR (Adverse Drug Reaction) that is serious and unexpected.
For the purposes of this protocol, the occurrence of SUSARs is not expected since the medications have been approved for several years by ANVISA and used in hundreds of thousands of patients, where possible adverse reactions from and/or idiosyncrasies are already widely known to the regulatory authorities.

10.8 Special Situations

10.8.1 Definition of special situations

The following situations are defined as special:

- Medication abuse: persistent or sporadic intentional and excessive use of study medication by the participant (not for therapeutic purposes)
- Medication error: an unintentional error in the prescription, delivery, or administration of an EFP during the study. (Medication error is any preventable event that can cause or lead to inappropriate use of medication or harm to the patient while the medication is under the control of the health care provider or patient.)
- Medication misuse: intentional and inappropriate use of an EFP by the participant for therapeutic purposes that is not in accordance with the dose, route of administration, and/or protocol indication(s) (e.g., participant deliberately took the medication twice a day instead of once a day)
- Medication overdose: the administration of an amount of the study drug equivalent to three times the maximum dose allowed by the protocol per administration or per day.
- Drug interaction involving study medication
- Unexpected therapeutic or clinical benefit from the use of study medication
-

Suspected AEs associated with medication errors or off-label use (e.g., overdose) should be reported and documented in the medical record.

10.8.2 Registration and special situation reporting

All special situations must be documented in the participant's source documents.
If any special situation leads to an SAE, the event must be reported immediately within 24 hours of its notification, by fax, e-mail, or phone.

10.8.3 Exposure during pregnancy and birth events

10.8.3.1 Definition of exposure during pregnancy and birth events

The experience accumulated over decades with the use of Fluvoxamine, ivermectin and metformin allows us to conclude that these medications should not be prescribed to pregnant patients without a careful evaluation of the risks and benefits of their use during this phase. Therefore, pregnancy is not expected to occur during the treatment phase (10 days), and women should use contraceptive methods to avoid pregnancy (if necessary, we will provide an effective method of contraception for use during the medication period).

When a female participant becomes pregnant during the trial and study, treatment has been administered to the participant, the pregnancy outcome needs to be monitored, and the safety of the mother and the unborn child needs to be monitored. Therefore, the outcome of all such pregnancies (including normal births) should be tracked and documented, even if the participant has been withdrawn from the trial or the trial has been terminated.

A female participant should immediately inform the investigator if she becomes pregnant during the study. The investigator should counsel the participant and discuss the risks and benefits of continuing the research medication and advise the patient about follow-up until the birth of the child.

The investigator is responsible for monitoring the participant and the pregnancy outcome and for reporting this information to the sponsor. Every effort should be made to collect information about the pregnancy outcome by 90 days after delivery (or, if not, as appropriate).

10.8.3.2 Exposure during pregnancy and recording and reporting of birth events

Pregnancies should be reported throughout the conduct of the study, including up to 4 weeks after the last dose of the study drug received. Pregnancy reporting includes exposure of the female partner of a male participant. Although pregnancy is not considered an SAE, it must be reported within 24 hours of its notification by the participant. Complications of pregnancy are reported as AEs or SAEs (if applicable). Any pregnancy will be followed up until delivery to note any SAEs. Deaths, spontaneous or elective abortion, congenital abnormalities/congenital defects, and AEs/SAEs occurring in newborns should be reported as SAEs. Newborns potentially exposed to the study drug through maternal or paternal sources who present with an SAE before, during, or after delivery (including those who received breastfeeding from the participating mother) will be followed until resolution of the event (or for a period of 1 year).

11 STUDY COMMITTEES

11.1 Data Security Monitoring Committee (DSMC)

An independent DSMC will be established, consisting of scientists of unimpeachable reputation and expertise who have no involvement with this research protocol. The DSMC will act as a research advisor to monitor the safety of participants who participate in this trial.
The DSMC is governed by a charter that explains the working procedures and responsibilities of the DSMC.
The research steering committee will define the working procedures and responsibilities of the DSMC. The charter will be agreed upon in advance by the DSMC and will follow good research practice.

11.2 Event Adjudication Committee

The independent Event Adjudication Committee (EAC) will evaluate all events related to the trial endpoints based on pre-established criteria and in a prospective, blinded manner.
CAT members should not be direct research members, and among them should be at least two qualified members. The CAT will operate on a blinded basis for trial treatment allocations to assess events. Outcome adjudication will occur continuously throughout the treatment phase of the blinded trial.

12 STATISTICAL CONSIDERATIONS

12.1 Study Design

The study will be conducted in two phases:

12.1.1 Internal pilot phase

Due to the rapidly evolving pandemic of COVID-19 and the challenge that public health systems will face in responding to this devastating infection, there are several aspects related to the feasibility of the study that needs to be evaluated once we begin implementing it.
The goal of the internal pilot phase is to assess any unforeseeable feasibility issues and address them to improve the overall success of the research. In particular, we will assess issues related to recruitment, consent, drug availability and administration, data collection and recording. There will be no analysis of clinical outcomes at the end of this phase - as these patients will be transferred to the main study. This will involve about 10% of the target sample size.

12.1.2 The main clinical trial

This involves implementation, with the primary clinical endpoint being hospitalization and emergency room visits with observation for more than 6 hours. This phase is also an adaptive phase, with two interim analyses to evaluate effects against the placebo arm. The main adaptations include:

i) Discard the placebo arm if there is strong evidence of benefit;
ii) possibly discard active arms of the trial, which may show statistically significant unfavorable outcomes
iii) introduction of mortality as a co-primary outcome.

12.2 Randomization

Patients will be randomly assigned to one of four treatment arms:

a. Fluvoxamine
b. Ivermectin
c. Metformin
d. Placebo.

We will use a computer-generated, centralized random allocation schedule implemented using a remote access online system. Randomization will be stratified by participating primary health care facilities. The randomization system will use an allocation rate in the ratio of 1: 1: 1: 1, which will be blocked using variable patient set sizes.

The randomization system will be programmed to block the randomization of diabetic patients in the metformin arm if:

- Patients taking metformin at a dose > 1.5 g/day
- Patients with clinically important renal insufficiency or documented creatinine > 1.8 mg%.

These patients may be randomized to the other arms of the study.

12.3 Sample Calculation

The sample size calculation is based on testing for the hypothesis that each of the treatments: i) fluvoxamine; ii) ivermectin; and iii) metformin, will be better than placebo in reducing the risk of hospitalization and 12-hour emergency room visits for complications directly related to COVID-19. The main effect measure is hospitalization for COVID-19-related complications. The significance criterion (alpha) was set at 0.05. The test is two-tailed, meaning that an effect in either direction will be interpreted. The sample size was calculated using SAS statistical software (Version 9.4). With the proposed sample size of 681 participants in each group (assuming an allocation ratio of 1: 1:1:1), the study will have a power of 80% to produce a statistically significant result using a logistic regression (assuming an intention-to-treat principle of analysis) of the reduction in the odds of hospitalization at alpha = 0.05.

These estimates used in the design of this study are based on global and Brazilian data of patients infected with COVID as of December 10, 2020. It is important to note that this is an evolving situation. Therefore, we calculated the sample size table showing the sensitivity of sample size estimates based on different baseline risks for hospitalization and expected treatment effects (see Table 4 below).

Table 5- Sample calculation using paired samples in relation to the control group. For these calculations, we focused on a paired comparison between Treatment 1 and Treatment 2 (Fluvoxamine, Ivermectin, Metformin). The treatment group proportions were estimated by the baseline risk change and assumed relative risk reduction. We used these simulations considering the following breakdown:

Baseline Risk	Treatment 1* (minimum hospitalization)	Treatment 1 Hospitalization	Risk Difference (T2-T1)	RRR (T2-T1)/T2	Sample (group)	Total sample
0.10	0.05	0.09	0.04	44.4 %	638	2552
		0.08	0.03	37.5 %	1059	4236
		0.07	0.02	28.6 %	2213	8852
		0.06	0.01	16.7 %	8158	32632
0.15	**0.075**	0.135	0.06	44.4 %	409	1636
		0.12	**0.045**	**37.5 %**	**681**	**2724**
		0.105	0.03	28.6 %	1428	5712
		0.09	0.015	16.7 %	5280	21120
0.20	0.1	0.18	0.08	44.4 %	295	1180
		0.16	0.06	37.5 %	492	1968
		0.14	0.04	28.6 %	1035	4140
		0.12	0.02	16.7 %	3841	15364
0.25	0.125	0.225	0.1	44.4 %	226	904
		0.2	0.075	37.5 %	379	1516
		0.175	0.05	28.6 %	800	3200
		0.15	0.025	16.7 %	2978	11912
0.30	0.15	0.27	0.12	44.4 %	180	720
		0.24	0.09	37.5 %	304	1216
		0.21	0.06	28.6 %	643	2572
		0.18	0.03	16.7 %	2402	9608

- Basal Risk (10%, 15%, 20%, 25% and 30%)
- Risk reduction (10%, 20%, 30%, 40% and 50%).

Considering a 50% reduction in relative risk (baseline = control group), we evaluated the calculated risks of the treatment group in order to identify the minimal risk of hospitalization. These treatment comparisons were used to derive sample size calculations, keeping power (80%) and significance level (0.05) constant. SAS statistical software (Version 9.4) was used to perform the calculations.

12.4 Statistical Analysis

The analysis and reporting of the results follow the CONSORT guidelines (www.consort-statement.org). The statistician/data analyst will be blinded to the study group. The process of patient selection and flow throughout the study will be summarized using a flow chart. The results of the analysis of patient demographics and baseline (primary and secondary) outcome variables will be summarized using descriptive summary measures: expressed as mean (standard deviation) or median (minimum-maximum) for continuous variables, as appropriate, and number (percentage) for categorical variables. We will adopt an intention-to-treat principle to analyze all results. We will also use multiple imputations to deal with missing data. All statistical tests will be performed using two-tailed tests at the 0.05 significance level. For all models, results will be expressed as effect reported as hazard ratio [HR] or *"odds ratio"* [OR] for binary outcomes and mean difference for continuous outcomes, corresponding 95% confidence intervals on both sides and associated p-values. P-values will be reported to three decimal places with values less than 0.001 reported as <0.001. All analyses will be performed using SAS 9.4 (Cary, NC). A detailed analysis plan will be developed prior to locking the database.

12.5 Analysis of the feasibility results

Analysis of feasibility results at the end of the internal pilot phase will be based on descriptive statistics reported as percentages (95% confidence intervals).

12.6 Analysis of primary and secondary results

We will use Cox regression to analyze the primary outcome as the length of hospitalization for CVID-19 or Hospitalizations due to COVID-19 related complications. This analysis will adjust for death before hospitalization as a competing risk. We will also use logistic regression if the proportional hazard assumption is not met. For all binary outcomes, we will use logistic regression for analysis. We will also use linear regression for all continuous outcomes. All secondary outcome analyses will be exploratory in nature, without adjustment for alpha for various secondary analyses.

12.7 Sensitivity analysis

We will conduct several sensitivity analyses to assess the robustness of the results, mainly on the primary outcome. This includes:

i) per-protocol analysis based only on patients who adhered to the protocol as described;
ii) ii) Competing risk analysis: this analysis will adjust for death as a competitive increase for any binary outcome;
iii) (iii) missing data analysis: This analysis will assess the impact of missing data on key findings.
iv) vi) Bayesian analysis: We will also perform sensitivity analyses using Bayesian methods to assess the impact of including data in other studies as before.
v) v) We will also perform sensitivity analyses to account for any unforeseen problems that will arise during the process of the study that may affect the main conclusions.

12.8 Subgroup analysis

We will perform some subgroup analyses to evaluate the consistency of effects in patient subgroups by:

a. Age - assumption that younger patients will benefit more than older patients
b. Gender - we think that women will benefit more than men.
c. Comorbidity in screening:

- Diabetes mellitus (yes or no);
- Cardiovascular disease (yes or no);
- Lung disease (yes or no);
- Immunosuppressed patients / use of corticotherapy (Yes or No)
- Other special categories (solid organ transplantation, end-stage renal disease)

Our hypothesis is that patients without the clinical comorbidities described above will benefit more than those without these clinical data. All subgroup hypotheses are based on emerging data from other countries indicating the differential impact of COVID-19 by age, sex, and the existence of clinical comorbidity under baseline conditions. The subgroup effects will be evaluated by including an interaction term between the treatment group and the subgroup variables. These interaction effects will be exploratory in nature and will be evaluated using alpha = 0.05.

12.9 Lost data

Due to the study design and short duration, we expect to obtain data from all participants. However, in the unlikely event of missing data, they will be considered.

12.10 Combined studies analysis policy

It is hoped that individual patient data from similar studies can be pooled in a combined study analysis. De-identified data from the present study may be made available for these purposes after discussion by the study Steering Committee and in line with a policy of academic-scientific cooperation to find solutions for the treatment of this pandemic.

12.11 Summary table of events

Outcome	Hypothesis	Outcome Measurement	Statistical Analysis Method
1) **Primary** a) Emergency room attendance and observation time > 06 hours b) Hospitalization for complications of COVID-19 2) Co-Primary	Treatment with medications will be better than placebo	Hospitalization due to COVID-19 or related complications Mortality due to complications of COVID-19	Cox Regression/Logistic Regression
2) **Secondary** Negative/viral load reduction on days 03 and 07 (150 patients per stratum)	Negative viral load treatment with medications	Negative/viral load reduction	Descriptive Analysis
Time to clinical improvement (28 days)	Treatment will shorten time to clinical improvement	Interval of days between randomization and clinical improvement	Cox Regression/Logistic Regression
Time to clinical failure (28 days)	Treatment will prevent clinical failure	Interval of days between randomization and hospitalization	Cox Regression/Logistic Regression
Number of days with respiratory symptoms since randomization	Treatment will shorten the number of days with respiratory symptoms	Interval of days between randomization and normalized WURSS scale	Cox Regression/Logistic Regression
Change in EQ-5D-5L quality of life scale	Treatment will improve quality of life	EQ-5D-5L scale improvement in 28 days	Cox Regression/Logistic Regression
Hospitalization for any cause	Treatment will prevent hospitalizations for any cause	Measurement of hospitalization in the groups	Cox Regression/Logistic Regression
Safety of Fluvoxamine, Ivermectin and Metformin in patients with COVID-19	Drugs are safe in patients with COVID-19	Measurement of adverse events in the treatment groups	Descriptive Analysis
Cardiovascular mortality	Treatment will prevent cardiovascular mortality	Measurement of cardiovascular deaths in the groups	Cox Regression/Logistic Regression

Mortality from any cause	Treatment will prevent global mortality	Measurement of deaths in the groups	Cox Regression/Logistic Regression
3) **Subgroup Analysis:** i) age (young vs. old) ii) Sex (male vs. woman) iv) Diabetes v) Hypertension vi) Chronic kidney disease KDIGO IV or hemodialysis vii) Chronic lung disease viii) Solid-organ transplantation ix) Heart Failure	The elderly have a higher risk of complications Men have a higher risk Diabetes has a higher risk Hypertensives have a higher risk Kidney disease carries a higher risk Lung disease has a higher risk Transplantation has a higher risk Heart failure carries a higher risk	Risk Measurement	Regression methods with appropriate interaction terms.
4) **Sensitivity Analysis**	Results remain robust	The primary and co-primary outcome	

IMPORTANT REMARKS:

- In all analyses, results will be expressed as estimated effect (corresponding to 95%) and associated p-values.
- The quality of fit will be assessed by examining the residuals for the model assumptions and chi-square test of goodness of fit

13 ETHICAL CONSIDERATIONS OF THE STUDY

13.1 Ethical conduct of the study

The study will be conducted in accordance with the principles of the World[108] Medical Association's Declaration of Helsinki, and the International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, as amended[107].

The investigator must ensure the anonymity of all participants taking part in the trial. Each participant will receive a unique participant number, which should be used on all forms associated with the participant's documents or samples that will be provided to the sponsor or any party performing tests on behalf of the sponsor (e.g., blood for assessments at the central laboratory). All anonymous data remains the property of the research Steering Committee

13.2 Informed consent

Individual participant medical information obtained as a result of this study is considered confidential, and disclosure to unauthorized persons is prohibited. The confidentiality of the participant will be ensured by the use of unique participant numbers rather than names. If the results of this study are reported in medical journals or at meetings or are sent to the appropriate regulatory authorities in connection with regulatory proceedings, such as applications for marketing authorization for pharmaceutical products, the identity of the participant will not be revealed.

With the participant's permission, medical information may be provided to the participant's personal physician or other appropriate medical staff responsible for the participant's well-being. In accordance with BPC guidelines, all participants will be informed of the purpose of the research, the possible risks, and their right to withdraw at any time from the study without any harm and without risk to their future medical care at the center. Each participant must agree to cooperate in all aspects of the study and must provide written confirmation (signed informed consent form) to the investigator prior to participation in the study. If the informed consent form is modified during the course of the trial, active participants must sign the new version in order to continue trial participation. For any updated or revised informed consent form, if applicable, the participant's record should state that written informed consent has been obtained for the use of the updated/revised consent form for continued participation in the clinical trial. The ICF should be revised whenever there are changes to the procedures in the protocol amendment associated with the procedures in the ICF or when new information becomes available that may affect the participant's willingness to participate. Each participant will receive a copy of each version of the form that he or she signs before and during the trial.

No participant should participate in study activities until informed consent has been obtained. Documentation of the process of obtaining informed consent and discussion of the information provided to the participant should appear in the participant's medical record and include a statement that informed consent has been obtained prior to participation in the trial. Signed forms (TCLEs) should remain in the participant's files and should be available for verification by monitors, auditors, and/or regulatory agency inspectors at any time.

13.3 REB

All investigators participating in this study must be governed by an appropriate REB. The REB/CONEP system must review and approve this protocol, the SCT, study documents, and any information to be given to the participant before a site can begin to conduct any study-related activities.

Subsequently, the investigator is responsible for obtaining a new REB approval annually or more frequently in accordance with regulatory requirements and established REB policies and procedures. Copies of the investigator's annual report and other reports are required to be submitted to the REB, and copies of continuing REB approval must be provided to the Steering Committee. The investigator must also inform the REB of any changes or amendments to the protocol, expedited SAE reports submitted to regulatory authorities, and other significant safety concerns in accordance with REB policy. Written documentation of approval of protocol amendments by the REB must be received prior to implementation. Upon completion or termination of the trial, investigators should notify their REBs. The investigator will be in compliance with the REB policies for the duration of the trial.

14 QUALITY CONTROL AND QUALITY ASSURANCE

Participant data integrity and quality will be ensured through the process of training and instruction for completing clinical records, quality control checks, performing ongoing clinical data analysis (including medical history and safety reviews), and performing source data verification and data reconciliation.

The investigator will also permit the research steering committee or its auditor's representative, the REB, ANVISA or other regulatory authority inspectors to review and inspect facilities, procedures, and all records relevant to this trial. These records include but are not limited to: the participant's signed informed consent form, source documentation, regulatory and essential documents, medical records, and drug accounting records.

The following steps will be taken to ensure that the study is conducted by the research center in compliance with the study protocol, GCP, and other applicable regulatory requirements:

- Meeting with the researcher and/or
- Initiation of the Investigator Center
- Routine monitoring of the plant, if applicable
- Protocol training and documented BPC
- Review of medical records and questionnaires against source documents
- Collection of normal intervals from the local laboratory

14.1Quality management: critical processes and data

The following processes and data were identified during the risk management activities for this trial as critical to ensuring the protection of the human patient and the reliability of the trial results.

14.1.1 Critical processes

Throughout the study, the clinical trial team will work to ensure that the clinical trial is operationally feasible, with a focus on the study and activities essential for the protection of human participants and the reliability of the study results, including, but not limited to, the following:

- Study protocol design and implementation
- Supporting data collection and processing tools and procedures
- Tools and procedures to ensure the rights and protection of human participants
- Essential activities for study decision making and adherence

15 REPORTING AND RECORDING DATA

Source documents are original documents, data, and records (e.g., case histories, physician's progress notes, nurse's notes, medical records, hospital records, clinical and office charts, laboratory notes, evaluation memos or checklists, pharmacy dispensing records, automated instrument data records, copies or transcripts certified after verification as accurate and complete, records kept in the pharmacy or laboratories, and participant records). Source data are contained in source documents and should be adequate to reconstruct all of the data transcribed to the clinical records and to evaluate the study. Examples of source data include clinical findings, observations, a summary of inclusion information and RCT procedures, assessment of clinical significance for laboratory results, AE severity and severity, and investigator opinion on the relationship of AE to study medications.

The investigator should prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation for all participants.

Source documentation should be available at the monitoring visit to verify data entered into eCRFs as needed. Source documentation should also be available for verification by auditors and/or inspectors as needed.

15.1 Source documentation

The investigator should keep adequate and accurate source documents on which the case reports for each participant are based. They should be separate and distinguished. These records should include detailed notes on:

The medical history, prior to participation in the study;

The basic identifying information, such as demographic data which links the participant's source documents;

- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data about the participant's condition;
- The participant's exposure to the study treatment;
- All EAs and pregnancies;
- All special situations;
- The participant's exposure to any concomitant therapy;
- All relevant observations and data about the participant's condition throughout the study;
- Verbal and written communication with the participant about the study treatment (including the risks and benefits of the study); the date of informed consent should be recorded in the source documentation;

All data for the study must be available in the source documentation.

15.2 Medical records

A clinical record is designed to record all protocol-required information to be reported about each clinical trial participant. The investigator is responsible for ensuring the accuracy, completeness, legibility, clarity, and timeliness of the data reported on the participants' clinical records. Reported data that is transcribed from the source documents should be consistent with the source documents, or discrepancies should be explained. An explanation should be provided for any missing data.

All clinical trial data and visit resolutions should be recorded only by clinical trial staff designated by the investigator. Site staff will have appropriate training before accessing the EDC system.

Any changes or corrections to a medical record will be tracked through an audit trail within the EDC system. The audit trail will contain the original data value, new data value, the date it was changed, the user who made the change, and the reason(s) for the change.

Medical records should be completed in time for the respective visit (e.g., the center should not wait for a monitoring visit before entering the data). The data from the medical records and visits will be tracked and entered into a clinical database. The database system will be a password-protected secure system with the full audit trail utility.

Participant data will be reviewed through scheduled quality checks and manually by reviewing data listings. Data that appear inconsistent, incomplete, or inaccurate will be queried for clarification by the center. Data corrections will be updated in the database and tracked in the audit trail. AEs and concomitant medications will be coded using standardized healthcare industry dictionaries (e.g., MedDRA and World Health Organization Medication Dictionary).

The investigator is responsible for reviewing, verifying, and approving all participant data (e.g., medical records and questions answered).

15.3 Records Retention

The investigator should maintain adequate records for the trial, including completed clinical records, medical records, laboratory reports, signed TCTs, drug distribution records, adverse experience reports, information about participants who discontinued the trial, all correspondence with the REB and research steering committee, and other pertinent data.

The investigator should retain all records at the health care facility. The investigator will notify them in writing of the transfer of any study records out of the research institution after the study is closed.

15.4 Plant documentation

The investigator should keep adequate and accurate records to allow the conduct of the study to be fully documented and the study data to be subsequently ascertained.

16 PROCEDURES FOR PROTOCOL MODIFICATION OR PREMATURE TERMINATION OF THE STUDY

16.1 Protocol Deviation

The investigator should not deviate from the protocol without prior written approval, except in medical emergencies. In the event of a medical emergency, the investigator should notify the medical monitor as soon as possible. Any other changes to the protocol should be implemented as an amendment to the protocol. The criteria for describing protocol deviation(s) and how they will be handled will be documented in the Study Manual.

16.2 Protocol Amendments

Amendments to the protocol, except as necessary to eliminate an immediate hazard to participants, should be made only with the prior approval of the steering committee. Each applicable regulatory authority/CEP should review and approve the amendments prior to their implementation. Regulatory authority/CEP approval does not need to be obtained prior to the removal of an immediate hazard to participants.

16.3 Study Closure

The Steering Committee reserves the right to terminate the study in its entirety or at a site at any time. Reasons for termination may include (among others) unsatisfactory participant enrollment with respect to quality and/or quantity, the site cannot meet protocol or GCP requirements, or data recording is inaccurate and/or incomplete.

In the event of study termination, the steering committee and the investigator should ensure that due consideration is given to protecting the interests of the participant. Both parties will organize the proceedings individually after the review and visit and in accordance with the study contract.

Based on its analysis of the data, the DSMC may provide recommendations to stop the study as directed in the DSMC bylaws. The steering committee will determine whether the study should be stopped early.

The study can be terminated or suspended at the request of regulatory authorities.

17 DATA SUBMISSION AND PUBLICATION POLICY

The data generated through this research protocol belong to the steering committee. No data may be disclosed or published without the prior consent of the steering committee. The confidentiality agreement to be established with the participating research centers will establish the publication policy.

In compliance with applicable laws and regulations, the sponsor will publicly record and provide all mandatory information regarding this trial, including, to the extent and by the required deadlines, a summary of the clinical trial data and results.

18 REFERENCES

1 WHO. Novel Coronavirus-China. 2020a.Available at: https://www.who.int/csr/don/12- january-2020-novel-coronavirus-china/en/. Accessed: 21 March 2020.

2 ZHOU P, YANG XL, WANG, XG, HU B, ZHANG L, ZHANG W, et al. Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin. bioRxiv. 2020; doi: https://doi.org/10. 1101/2020.01.22.914952

3 WHO. Novel Coronavirus (2019-nCoV) Situation Report - 11. 2020b. Available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200131-sitrep-11-ncov.pdf?sfvrsn=de7c0f7_4 . Accessed: March 21, 2020.

4 WHO. Novel Coronavirus(2019-nCoV) Situation Report - 22. 2020. Available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200211-sitrep-22-ncov.pdf?sfvrsn=fb6d49b1_2 . Accessed: March 21, 2020.

5 GORBALENYA, Alexander E.; BAKER, Susan C.; BARIC, Ralph S.; GROOT, Raoul J. de; DROSTEN, Christian; GULYAEVA, Anastasia A.; HAAGMANS, Bart L.; LAUBER, Chris; LEONTOVICH, Andrey M; NEUMAN, Benjamin W.; PENZAR, Dmitry; PERLMAN, Stanley; POON, Leo L.M.; SAMBORSKIY, Dmitry; SIDOROV, Igor A.; SOLA, Isabel; ZIEBUHR, John. Severe acute respiratory syndrome-related coronavirus: The species and its viruses - a statement of the Coronavirus Study Group. Available from: bioRxiv 2020.02.07.937862; doi: https://doi.org/10.1101/2020.02.07.937862 .

6 WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [Internet]. World Health Organization. World Health Organization; 2020 [cited 2020Mar19]. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks -at-the-media-briefing-on-covid-19---11-march-2020 Accessed 21 March 2020.

7 WHO Coronavirus disease 2019 (COVID- 19) Situation report - 62. Searched March 23, 2020 and available at https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200322-sitrep-62-covid-19.pdf?sfvrsn=f7764c46_2

8 LI Q, GUAN X, WU P, WANG X, ZHOU L, TONG Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020. https://doi.org/10.1056/NEJMoa2001316

9 LI R, PEI S, CHEN B, et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2) [published online ahead of print, 2020 Mar 16]. Science. 2020;eabb3221. doi:10.1126/science.abb3221

10 LIU T, HU J, KANG M, LIN L, ZHONG H, XIAO J, et al. Transmission dynamics of 2019 novel coronavirus (2019-nCoV). 2020; doi: https://doi.org/10.1101/2020. 01.25.919787.

11 HUANG C, WANG Y, LI X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [published correction appears in Lancet. 2020 Jan 30;:]. Lancet. 2020;395(10223):497–506. doi:10.1016/S0140-6736(20)30183-5

12 ADHIKARI SP, MENG S, WU YJ, et al. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. Infect Dis Poverty. 2020;9(1):29. Published 2020 Mar 17. doi:10.1186/s40249-020-00646-x.

13 Wu, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA *https://doi.org/10.1001/jama.2020.2648*

14 Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. https://doi.org/10.1038/s41586-020-2012-7

15Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, Zhong W, Hao P (2020) Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its Spike protein for risk of human transmission. Sci China Life Sci. https://doi.org/10.1007/s11427-020-1637-5

16 Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Medicine. 2020 Mar 3:1-5. https://doi.1org/0.1007/s00134-020-05985-9 .

17 Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nature medicine. 2005 Aug;11(8):875-9.

18 Drosten C. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N. Engl. J. Med. 2003;348(20):1967-1976. [PubMed] [Google Scholar]

19 Peiris J., Guan Y., Yuen K. Severe acute respiratory syndrome. Nat. Med. 2004;10(12):S88-S97.[PubMed] [Google Scholar]

20 Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, Dawood F.S., Jain S., Finelli L., Shaw M.W., Lindstrom S., Garten R.J., Gubareva L.V., Xu X., Bridges C.B., Uyeki T.M. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N. Engl. J. Med. 2009;360(25):2605-2615.[PubMed] [Google Scholar]

21 Zaki A.M. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N. Engl. J. Med. 2012;367(19):1814-1820. [PubMed] [Google Scholar]

22 US CDC Confirmed 2019-nCoV Cases Globally. https://www.cdc.gov/coronavirus/2019-ncov/locations-confirmed-cases.html#map Availabe at. Accessed March 21, 2020.

23 Geographical Distribution of 2019-nCov Cases Globally. European Centre for Disease Prevention and Control; 2020. https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases Accessed March 23, 2020.

24 Zhu N., Zhang D., Wang W. A novel coronavirus from patients with pneumonia in China, 2019. N. Engl. J. Med. 2020;382(8):727-733. [PubMed] [Google Scholar]

25 Zhu N., Zhang D., Wang W. A novel coronavirus from patients with pneumonia in China, 2019. N. Engl. J. Med. 2020;382(8):727-733. [PubMed] [Google Scholar]

26 Hui D.S., Zumla A. Severe acute respiratory syndrome: historical, epidemiologic, and clinical features. Infect. Dis. Clin. 2019;33(4):869-889. [PubMed] [Google Scholar]

27 Abdirizak F., Lewis R., Chowell G. Evaluating the potential impact of targeted vaccination strategies against severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) outbreaks in the healthcare setting. Theor. Biol. Med. Model. 2019;16(1):16.[PMC free article] [PubMed] [Google Scholar]

28 WHO. Novel Coronavirus (2019-nCoV) Situation Report - 63. Available at https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200323-sitrep-63-covid-19.pdf?sfvrsn=d97cb6dd_2 Accessed March 23, 2020.

29 National Institutes of Health, US National Library of Medicine. ClinicalTRials.gov. Available at https://clinicaltrials.gov/ct2/results?cond=Covid+19 Accessed March 23, 2020.

30 Narita N, Hashimoto K, Tomitaka S, Minabe Y. Interactions of selective serotonin reuptake inhibitors with subtypes of sigma receptors in rat brain. *Eur J Pharmacol.* 1996;307(1):117-119.

31 Delprat B, Crouzier L, Su TP, Maurice T. At the Crossing of ER Stress and MAMs: A Key Role of Sigma-1 Receptor? *Adv Exp Med Biol.* 2020;1131:699-718.

32 Mori T, Hayashi T, Hayashi E, Su TP. Sigma-1 receptor chaperone at the ER-mitochondrion interface mediates the mitochondrion-ER-nucleus signaling for cellular survival. *PLoS One.* 2013;8(10):e76941

33 Rosen DA, Seki SM, Fernandez-Castaneda A, et al. Modulation of the sigma-1 receptor-IRE1 pathway is beneficial in preclinical models of inflammation and sepsis. *Sci Transl Med.* 2019;11(478).

34 Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell.* 2020;181(2):271-280 e278

35 Knoops K, Kikkert M, Worm SH, et al. SARS-coronavirus replication is supported by a reticulovesicular network of modified endoplasmic reticulum. *PLoS Biol.* 2008;6(9):e226.

36 Gassen NC, Papies J, Bajaj T, et al. Analysis of SARS-CoV-2-controlled autophagy reveals spermidine, MK-2206, and niclosamide as putative antiviral therapeutics. *bioRxiv.* 2020:2020.2004.2015.997254.

37 Laurent EMN, Sofianatos Y, Komarova A, et al. Global BioID-based SARS-CoV-2 proteins proximal interactome unveils novel links between viral polypeptides and host factors involved in multiple COVID19-associated mechanisms. *bioRxiv.* 2020:2020.2008.2028.272955

38 Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature.* 2020;583(7816):459-468.

39 Yang H, Shen H, Li J, Guo LW. SIGMAR1/Sigma-1 receptor ablation impairs autophagosome clearance. *Autophagy.* 2019;15(9):1539-1557.

40 Gorshkov K, Chen CZ, Bostwick R, et al. The SARS-CoV-2 cytopathic effect is blocked with autophagy modulators. *bioRxiv : the preprint server for biology.* 2020:2020.2005.2016.091520.

41 Homolak J, Kodvanj I. Widely available lysosome targeting agents should be considered as potential therapy for COVID-19. *Int J Antimicrob Agents.* 2020;56(2):106044.

42 Daniel WA, Wojcikowski J. Contribution of lysosomal trapping to the total tissue uptake of psychotropic drugs. *Pharmacol Toxicol.* 1997;80(2):62-68.

43 Fung TS, Liu DX. The ER stress sensor IRE1 and MAP kinase ERK modulate autophagy induction in cells infected with coronavirus infectious bronchitis virus. *Virology.* 2019;533:34-44.

44 Kornhuber J, Tripal P, Gulbins E, Muehlbacher M. Functional inhibitors of acid sphingomyelinase (FIASMAs). *Handb Exp Pharmacol.* 2013(215):169-186.

45 Breiden B, Sandhoff K. Emerging mechanisms of drug-induced phospholipidosis. *Biol Chem.* 2019;401(1):31-46.

46 Chan SW. The unfolded protein response in virus infections. *Front Microbiol.* 2014;5:518.

47 Jheng JR, Ho JY, Horng JT. ER stress, autophagy, and RNA viruses. *Front Microbiol.* 2014;5:388.

48 Nabirotchkin S, Peluffo AE, Bouaziz J, Cohen D. Focusing on the Unfolded Protein Response and Autophagy Related Pathways to Reposition Common Approved Drugs against COVID-19. *Preprints.* 2020.

49 Hosszu A, Antal Z, Lenart L, et al. sigma1-Receptor Agonism Protects against Renal Ischemia-Reperfusion Injury. *J Am Soc Nephrol.* 2017;28(1):152-165.

50 Tagashira H, Bhuiyan MS, Fukunaga K. Diverse regulation of IP3 and ryanodine receptors by pentazocine through sigma1-receptor in cardiomyocytes. *Am J Physiol Heart Circ Physiol.* 2013;305(8):H1201-1212.

51 Manne BK, Denorme F, Middleton EA, et al. Platelet gene expression and function in patients with COVID-19. *Blood.* 2020;136(11):1317-1329.

52 Schlienger RG, Meier CR. Effect of selective serotonin reuptake inhibitors on platelet activation: can they prevent acute myocardial infarction? *Am J Cardiovasc Drugs.* 2003;3(3):149-162.

53 Van den Berg DF, Te Velde AA. Severe COVID-19: NLRP3 Inflammasome Dysregulated. *Front Immunol.* 2020;11:1580.

54 Ratajczak MZ, Kucia M. SARS-CoV-2 infection and overactivation of Nlrp3 inflammasome as a trigger of cytokine "storm" and risk factor for damage of hematopoietic stem cells. *Leukemia.* 2020;34(7):1726-1729.

55 Garcia JA, Volt H, Venegas C, et al. Disruption of the NF-kappaB/NLRP3 connection by melatonin requires retinoid-related orphan receptor-alpha and blocks the septic response in mice. *FASEB J.* 2015;29(9):3863-3875.

56 Volt H, Garcia JA, Doerrier C, et al. Same molecule but different expression: aging and sepsis trigger NLRP3 inflammasome activation, a target of melatonin. *J Pineal Res.* 2016;60(2):193-205.

57 Hartter S, Wang X, Weigmann H, et al. Differential effects of fluvoxamine and other antidepressants on the biotransformation of melatonin. *J Clin Psychopharmacol.* 2001;21(2):167-174.

58 S. C. Atkinson, M. D. Audsley, K. G. Lieu, G. A. Marsh, D. R. Thomas, S. M. Heaton, J. J. Paxman, K. M. Wagstaff, A. M. Buckle, G. W. Moseley, D. A. Jans and N. A. Borg. Recognition by host nuclear transport proteins drives disorder-to-order transition in Hendra virus V. Scientific Reports. 8, 358 (2018).

59 S. N. Y Yang, S. C. Atkinson, C. Wang, A. Lee, M. A. Bogoyevitch, N. A. Borg and D. A. Jans. The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. Antiviral Research. 177, 104760 (2020).

60 V. G.tz, L. Magar, D. Dornfeld, S. Giese, A. Pohlmann, D. H.per, B.-W. Kong, D. A. Jans, M. Beer, O. Haller and M. Schwemmle. Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import. Scientific Reports. 6, 23138 (2016).

61 C. Lv, W. Liu, B. Wang, R. Dang, L. Qiu, J. Ren, C. Yan, Z. Yang and X. Wang. Ivermectin inhibits DNA polymerase UL42 of pseudorabies virus entry into the nucleus and proliferation of the virus in vitro and vivo. Antiviral Research. 177, 104760 (2020).

62 E. Mastrangelo, M. Pezzullo, T. De Burghgraeve, S. Kaptein, B. Pastorino, K. Dallmeier, X. de Lamballerie, J. Neyts, A. M. Hanson, D. N. Frick, M. Bolognesi and M. Milani. Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. Journal of Antimicrobial Chemotherapy. 67, 1884-1894 (2012).

63 M. Y. F. Tay, J. E. Fraser, W. K. K. Chan, N. J. Moreland, A. P. Rathore, C. Wang, S. G. Vasudevan and D. A. Jans. Nuclear localization of dengue virus (DENV) 1-4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin. Antiviral Research. 99, 301-306 (2013).

64 F. S. Varghese, P. Kaukinen, S. Gl.sker, M. Bespalov, L. Hanski, K. Wennerberg, B. M. Kümmerer and T. Ahola. Discovery of berberine, abamectin and ivermectin as antivirals against chikungunya and other alphaviruses. Antiviral Research. 126, 117-124 (2016).

65 K. M. Wagstaff, H. Sivakumaran, S. M. Heaton, D. Harrich, D. A. Jans. Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Biochemical Journal. 443, 851-856 (2012).

66 C. R. King, T. M. Tessier, M. J. Dodge, J. B. Weinberg, J. S. Mymryk, Inhibition of Human Adenovirus Replication by the Importin α/β1 Nuclear Import Inhibitor Ivermectin. Journal of Virology. 94, e00710-20 (2020).

67 X. Zhang et al, Inhibitory effects of ivermectin on nitric oxide and prostaglandin E2 production in LPS-stimulated RAW 264.7 macrophages. Int Immunopharmacol. 9, 354-359 (2009).

68 X. Ci et al, Avermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen-activated protein kinase activation pathway. Fundam Clin Pharmacol. 23, 449-455 (2009).

69 X. Zhang, Y. Song, X. Ci, N. An, Y. Ju, H. Li, X. Wang, C. Han, J. Cui and X. Deng. Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice. Inflamm Res. 57, 524-529 (2008).

70 Carvallo H. https://clinicaltrials.gov/ct2/show/NCT04425850 (2020).

71 Shouman W. https://clinicaltrials.gov/ct2/show/NCT04422561 (2020).

72 P. Behera et al., https://www.medrxiv.org/content/10.1101/2020.10.29.20222661v1.full (2020).

73 A. Elgazzar et al., https://www.researchsquare.com/article/rs-100956/v2 (2020).

74 Robin RC, Alam RF, Saber S, Bhiuyan E, Murshed R, Alam MT. A case series of 100 COVID-19 positive patients treated with combination of ivermectin and doxycycline. Journal of Bangladesh College of Physicians and Surgeons. 38, Supp 10-15 (2020).

75 Mahmud R. https://clinicaltrials.gov/ct2/show/NCT04523831 (2020).

76 M. S. I. Khan, C. R. Debnath, P. N. Nath, M. A. Mahtab, H. Nabeka, S. Matsuda and S. M. F. Akbar. Ivermectin treatment may improve the prognosis of patients with COVID-19. Archivos de Bronconeumología. 10.1016/j.arbres.2020.08.007 (2020).

77 J. C. Rajter, M. S. Sherman, N. Fatteh, F. Vogel, J. Sacks, J. J. Rajter. Use of ivermectin is associated with lower mortality in hospitalized patients with COVID-19 (ICON study). Chest. 10.1016/j.chest.2020.10.009 (2020).

78 Hashim HA et al,
https://www.medrxiv.org/content/10.1101/2020.10.26.20219345v1 (2020).

79 M. S. Niaee et al., https://www.researchsquare.com/article/rs-109670/v1 (2020).

80 A. Portmann-Baracco, M. Bryce-Alberti, R. A. Accinelli. Antiviral and anti-inflammatory properties of ivermectin and its potential use in Covid-19. Arch Broncopneumol. July 7, doi: 10.1016/j.arbres.2020.06.011 (2020)

81 A. Portmann-Baracco, M. Bryce-Alberti, R. A. Accinelli. Antiviral and anti-inflammatory properties of ivermectin and its potential use in Covid-19. Arch Broncopneumol. July 7, doi: 10.1016/j.arbres.2020.06.011 (2020)

82 J. J. Chamie. https://www.researchgate.net/publication/344469305 (2020).

83 Simonnet A, Chetboun M, Poissy J, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obesity 2020; 28: 1195-99.

84 Bosch TA, Steinberger J, Sinaiko AR, et al. Identification of sex-specific thresholds for accumulation of visceral adipose tissuein adults. Obesity 2015; 23: 375-82.

85 Bray GA. Medical consequences of obesity. J Clin Endocrinol Metab 2004; 89: 2583-89.

86 Tufan A, Avanoğlu Güler A, Matucci-Cerinic M. COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. Turk J Med Sci 2020; 50: 620-32.

87 Blüher M, Fasshauer M, T.njes A, Kratzsch J, Sch.n MR, Paschke R. Association of interleukin-6, C-reactive protein, interleukin- 10and adiponectin plasma concentrations with measures of obesity, insulin sensitivity and glucose metabolism. Exp Clin Endocrinol Diabetes 2005; 113: 534-37.

88 Matsiukevich D, Piraino G, Lahni P, et al. Metformin ameliorates gender-and age-dependent hemodynamic instability and myocardial injury in murine hemorrhagic shock. Biochim Biophys Acta Mol Basis Dis 2017; 1863: 2680-91.

89 Quan H, Zhang H, Wei W, Fang T. Gender-related different effects of a combined therapy of exenatide and metformin on overweight or obesity patients with type 2 diabetes mellitus. J Diabetes Complications 2016; 30: 686-92.

90 Park JW, Lee JH, Park YH, et al. Sex-dependent difference in the effect of metformin on colorectal cancer-specific mortality of diabetic colorectal cancer patients. World J Gastroenterol 2017; 23: 5196-205.

91 Chen X, Guo H, Qiu L, Zhang C, Deng Q, Leng Q. Immunomodulatory and Antiviral Activity of Metformin and Its Potential Implications in Treating Coronavirus Disease 2019 and Lung Injury. Front Immunol. 2020 Aug 18;11:2056. doi: 10.3389/fimmu.2020.02056.

92 Scheen AJ. Metformin and COVID-19: From cellular mechanisms to reduced mortality. Diabetes Metab. 2020 Nov;46(6):423-426. doi: 10.1016/j.diabet.2020.07.006.

93 Luo P, Qiu L, Liu Y, et al. Metformin treatment was associated with decreased mortality in COVID-19 patients with diabetes in a retrospective analysis. Am J Trop Med Hyg 2020; 103: 69-72.

94 Cariou B, Hadjadj S, Wargny M, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia 2020; 63: 1500-15.

95 Pérez-Belmonte LM, Torres-Peña JD, López-Carmona MD. Mortality and other adverse outcomes in patients with type 2 diabetes mellitus admitted for COVID-19 in association with glucose-lowering drugs: a nationwide cohort study. BMC Med. 2020 Nov 16;18(1):359. doi: 10.1186/s12916-020-01832-2.

96 Bramante CT, Ingraham NE, Murray TA. Metformin and risk of mortality in patients hospitalised with COVID-19: a retrospective cohort analysis. Lancet Health Longevity 2020 Dec 3, S2666-7568 (20) 30033-7. doi: https://doi.org/10.1016/S2666-7568(20)30033-7

97 Lenze EJ, Mattar C, Zorumski CF. Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19: A Randomized Clinical Trial. JAMA. 2020 Dec 8;324(22):2292-2300. doi: 10.1001/jama.2020.22760.

98 Smit MR, Ochomo EO, Aljayyoussi G et al. Safety and mosquitocidal efficacy of high-dose ivermectin when co-administered with dihydroartemisinin-piperaquine in Kenyan adults with uncomplicated malaria (IVERMAL): a randomised, double-blind, placebo-controlled trial. Lancet Inf Dis 2018, 18(6): 615-626. DOI:https://doi.org/10.1016/S1473-3099(18)30163-4

99 Hill A, Abdulamir A, Ahmed A et Al. Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection. Research Square, 2020, doi: 10.21203/rs.3.rs-148845/v1. Available at https://www.researchsquare.com/article/rs-148845/v1 , Accessed 07 February 2021.

100 Zhang X, Song Y, Ci X et al. Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice. Inflammation Research 2.008, 57(11): 524-9. Doi: 10.1007/s00011-008-8007-8.

101 Suputtamongkol Y, Avirutnan P, Mairiang D et al. Ivermectin Accelerates Circulating Nonstructural Protein 1 (NS1) Clearance in Adult Dengue Patients: A Combined Phase 2/3 Randomized Double-blinded Placebo Controlled Trial, *Clinical Infectious Diseases*, 2021;, ciaa1332, https://doi.org/10.1093/cid/ciaa1332

102 COVID-19 clinical trials listed as of Dec 15, 2020. https://www.clinicaltrials.gov/ct2/results?cond=COVID-19. Accessed December 15, 2020.

103 National Research Ethics Commission: Research Ethics Bulletin - December 2020. http://conselho.saude.gov.br/images/comissoes/conep/img/boletins/BE_DEZEMBRO_OFICIAL.pdf Accessed December 15, 2020.

104 COVID-19 clinical trials listed as of Dec 15, 2020. https://www.clinicaltrials.gov/ct2/results?cond=COVID-19. Accessed December 15, 2020.

105 National Research Ethics Commission: Research Ethics Bulletin - December 2020. http://conselho.saude.gov.br/images/comissoes/conep/img/boletins/BE_DEZEMBRO_OFICIAL.pdf Accessed December 15, 2020.

106 Hays RD, Bjorner JB, Revicki DA. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. *Qual Life Res. 2009 Sep; 18(7):873-80.*

1. 107 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Harmonised Guideline. E6(R2): integrated addendum to ICH E6(R1): guideline for good clinical practice. 2016 Nov 9.

108 World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. 2013 Oct.

MASTER CLINICAL TRIAL PROTOCOL

Repurposed Approved Therapies for Outpatient Treatment of Patients with Early-Onset COVID-19 and Mild Symptoms

Short Title	TOGETHER
Investigational Products	Repurposed therapies
Phase	Phase III
Indication	Mild infection with SARS-CoV-2
Sponsors	McMaster University
Study Protocol Version/Date	Version: 3.0; dated 13 Sept 2021

Reviewed and Approved by:		
Edward Mills	***Signature:***	***Date:***
Gilmar Reis	***Signature:***	***Date:***

Table of Contents

STUDY SUMMARY

Methodology	Multi-Center, Adaptive, Randomized, Portfolio Trial
Sponsor	McMaster University
Background	The discovery of effective and affordable treatments for preventing COVID-19 disease progression and subsequent hospitalization in outpatient settings is critical to minimizing limited hospital resources, particularly for resource-limited settings. As vaccine rollout has been slow in many countries and new variants of SARS-CoV-2 cause concern for their effectiveness, identifying therapeutics that are cheap, widely available and effective against COVID-19 is of prime importance. Repurposing existing treatments is an appealing approach as drugs currently used to treat other health conditions have known safety profiles. For this trial, we will assess the efficacy of a number of repurposed drugs, as treatment for early COVID-19 among outpatients at a high risk for complications.
Primary Objective	The primary objective is to determine if each investigational product (IP) reduces: • Emergency room visits due to the clinical worsening of COVID-19 (defined as participant remaining under observation for > 6 hours) within 28 days of randomization. • Hospitalization due to the progression of COVID-19 (defined as worsening of viral pneumonia) and/or complications within 28 days of randomization.
Secondary Objectives	The secondary objectives are to evaluate, in comparison with placebo, the effect of the IPs on the following parameters: • All cause, respiratory, and cardiovascular death • Viral clearance and viral load on day 3 and day 7 after randomization • Number of days with respiratory symptoms since randomization • Time to hospitalization/urgent care due to the progression of COVID-19 • Rate of all-cause and COVID-specific hospitalizations • Time to hospitalization for any cause • Time to death • Symptoms as assessed by the WHO Clinical Worsening Scale • Health-related quality of life as assessed by PROMIS global health scale (“Global-10”) scores • Telephone Interview for Cognitive Status (TICS)) memory scale at day 28

	Adverse events, adverse reactions to the IPs and the proportion of participants who are non-adherent with the IPs will also be assessed.
Diagnosis and Main Inclusion Criteria	Patients 18 years of age or older, presenting to an outpatient care setting with an acute clinical condition compatible with COVID-19 and symptoms beginning within 7 days of the screening date.
Treatment Groups	Each eligible participant will be randomized to receive one of the IPs or placebo. IP treatment arms may be discontinued or added during the course of the trial.
Duration of Treatment	Will vary depending on the IP.
Length of Follow-Up	Participants will be followed for 60 days, with the primary and secondary endpoints being assessed at 28 days.
Study Outcomes	Outcomes include: • Emergency room visits due to the clinical worsening of COVID-19 (defined as participant remaining under observation for > 6 hours) • Hospitalization due to the progression of COVID-19 (defined as worsening of viral pneumonia) or complications related to COVID-19 • Mortality and cause of mortality • Viral clearance and viral load • Respiratory symptoms • Hospitalization for any cause • WHO clinical worsening scale • PROMIS global health scale • TICS questionnaire • Adverse events • Adverse drug reactions • Serious adverse events
Sample Size	681 participants per treatment arm.

LISTING OF COMMON ABBREVIATIONS

ACE2	Angiotensin-Converting Enzyme 2
ADR	Adverse Drug Reaction
CAD	Cationic Amphiphilic Drug
DSMC	Data and Safety Monitoring Committee
eCRF	Electronic Case Report Form
EAC	Event Adjudication Committee
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EOS	End of Study
ER	Endoplasmic Reticulum
FPIC	Free, Prior and Informed Consent
GCP	Good Clinical Practice
ICH	International Council for Harmonization
ICU	Intensive Care Unit
IP	Investigational Product
IWRS	Interactive Web Response System
nCoV	New Coronavirus
PROMIS	Patient-Reported Outcomes Management Information System
RSI	Reference Safety Information
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SSRI	Selective Serotonin Reuptake Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction
TICS	Telephone Interview for Cognitive Status
WHO	World Health Organization

1.0 INTRODUCTION

1.1 Background

- In December 2019, a series of cases of unknown etiology and with symptoms similar to viral pneumonia were reported in Wuhan city, Hubei province, China[1]. These initial cases were associated with people linked to a local seafood market in Huanan ("wet market")[2]. Patients were hospitalized with this viral pneumonia and samples of bronchoalveolar lavage fluid were collected from three patients, and a new coronavirus, named 2019-nCoV, was isolated. Evidence for the presence of this virus included identification in bronchoalveolar lavage fluid in three patients by genome sequencing, direct PCR and culture analysis. The disease that this CoV probably caused was called "new coronavirus-infected pneumonia". The complete genomes were submitted to GISAID. Phylogenetic analysis revealed that 2019-nCoV fell within the genus *betacoronavirus*, which includes coronaviruses (SARS-CoV, CoV similar to bat SARS and others) discovered in humans, bats and other wildlife[2].

- Since then, the number of cases has markedly increased, and on January 30, 2020, the outbreak was declared a Public Health Emergency of International Concern. By January 31, 2020, there were 9826 confirmed cases of 2019-nCoV worldwide[3]. On that same day, the first two cases of 2019-nCoV were reported in Italy and both individuals had a history of traveling to Wuhan city, China. There were already confirmed cases in 19 countries besides China[3].

-

- On February 11, 2020, 43,103 cases were confirmed (42,708 in China) and 1,018 deaths. On the same day, the World Health Organization (WHO), in collaboration with its departments (World Organization for Animal Health and the Food and Agriculture Organization of the United Nations) called the disease COVID-19 (short for "2019 coronavirus disease")[4]. Also on the same day, the Coronavirus Study Group (CEG) of the International Committee on Taxonomy of Viruses proposed to name the new Coronavirus as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2)[5].

-

- On March 11, 2020, the World Health Organization declared COVID-19 to be a global pandemic[6,7].

1.2 Transmission

- Initially, the vast majority of cases were the result of contact with the seafood market[2,8]. Soon, cases of human-to-human transmission were identified through close contact, apparently not related, configuring community transmission, with several cases occurring among medical professionals[9-11].

-

- Evidence from initial epidemiological studies confirmed that COVID-19 has higher levels of transmissibility and pandemic risk than SARS-CoV, since the effective reproductive number (R0) of COVID-19 was identified as close to 3.0, higher than the observed risk in SARS (R0 = 1.77)[10]. Considering the various epidemiological studies currently available, the COVID-19 R0 is somewhere between 2.6 to 4.71[12]. The estimated average incubation period until the first symptoms appear is 4.8 ± 2.6 days (CI 4.1-7.0; median 5.2)[9,10]. The most recent guidelines from Chinese health authorities stated an average incubation duration of 7 days, ranging from 2 to 14 days[12].

- Current data reinforce the concern about asymptomatic transmission. About 86% of all infections were undocumented (95% CI: [82% –90%]) before the travel restrictions proposed by the Chinese government in Wuhan. There is evidence that 55% of people acquire the virus and transmit it, asymptomatically, without subsequently developing COVID-19 symptoms, which may explain rapid transmission and the difficulty in containing its spread[9].

1.3 Clinical Manifestations and Risk Profile

- From the identification of the first cases of COVID-19 until today, a set of epidemiological data has been compiled as the cases have emerged; however, most of these have not been adjusted. Initially, the following signs and symptoms were identified as the most prevalent: fever (98%), cough (95%), dyspnoea (55%), myalgia (44%), and expectoration (28%)[11]. Currently, the following signs/symptoms are most common: fever (87.9%), dry cough (67.7%), and dyspnea (40 %)[13]. These same series identified a subgroup of patients with a higher risk of mortality (Figure 1).

-

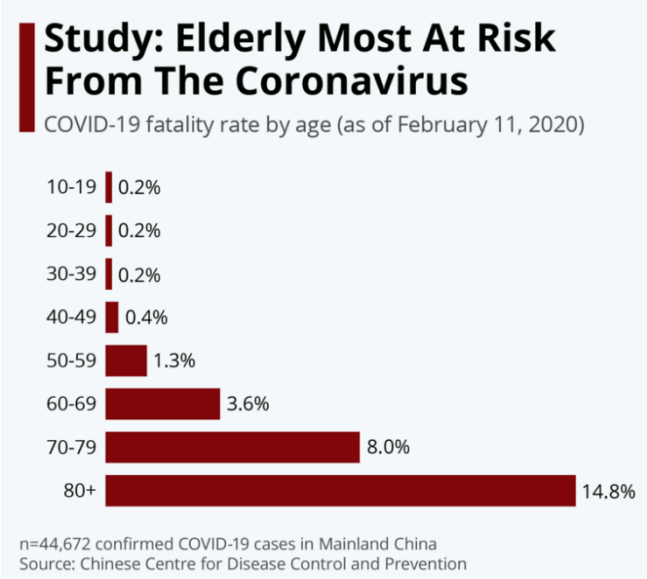


Figure 1 - Age-adjusted mortality

Mortality is also high in some strata, as initially suggested by the first epidemiological studies carried out in Wuhan. COVID-19 patients and those who had stable chronic cardiovascular diseases such as clinically overt heart failure, coronary artery disease, dilated LV cardiomyopathy had high mortality in the course of the disease. Likewise, patients with diabetes, chronic respiratory diseases and systemic arterial hypertension had high mortality, compared to individuals with COVID-19 without these comorbidities (Figure 2 and Figure 3)[13].

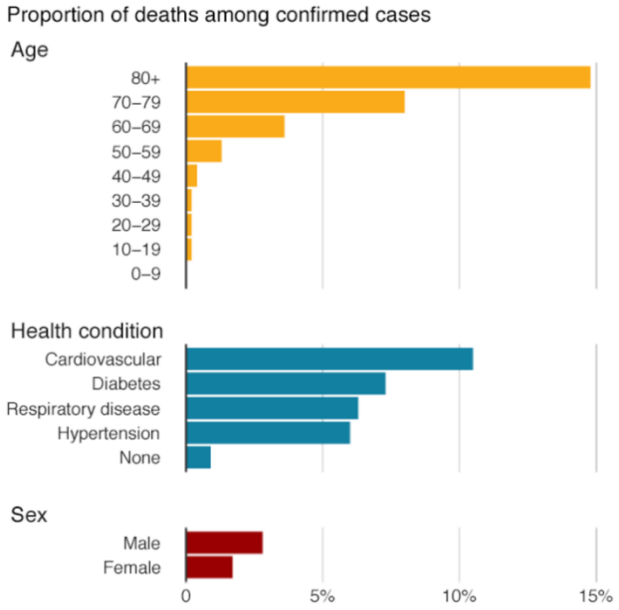


Figure 2 – Global Mortality by Age group – COVID-19

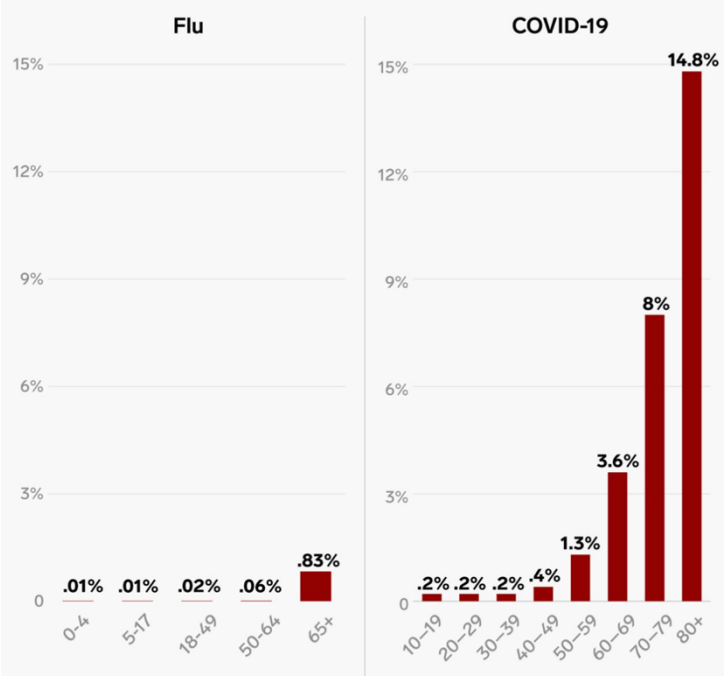


Figure 3 – Mortality from influenza and COVID-19

1.4 Mechanisms of Infectivity

This global health emergency has intensified research efforts to understand better the pathogenesis, clinical manifestations and outcomes of people affected by this new viral strain. Coronavirus spike proteins, including those from SARS-CoV2, interact with Angiotensin-Converting Enzyme 2 (ACE2) and with type II transmembrane serine proteases to invade cells[14,15]. In this way, cells expressing ACE2, including pneumocytes and hair cells in the tracheobronchial tree, cardiac endothelial cells, intestinal mucosa cells and renal epithelial cells are susceptible to infection and could partly explain the multiple organ dysfunction seen in patients[16]. Under physiological circumstances, ACE2 acts as a natural antagonist of the renin / angiotensin / aldosterone system (RAAS) pathways by degrading angiotensin II and then producing Angiotensin (1-7), which act by limiting the vasoconstrictive capacity of angiotensin I. Angiotensin (1-7) have protective pulmonary effects attenuating the inflammatory response[17]. In fact, as observed in the recent SARS-CoV epidemics (SARS and MERS epidemic) and recently identified in SARS-CoV2 genetic studies, inhibition of the expression of ACE2 transmembrane receptors resulting from viral infection occurs by blocking them through spike proteins. This abrupt reduction in the activity of ACE2 in lung cells is a critical point for the resulting pulmonary complications, given its important inhibitory effect related to pulmonary inflammatory mediators and thus reducing pulmonary edema and the unwanted amplification of the inflammatory response resulting from COVID-19[15].

1.5 Need for COVID-19 Treatment Studies

Currently, the world is increasingly faced with several complex problems, especially concerning emerging diseases. Thus, there is an increasing need for joint efforts to face possible acute health problems that a single group, health system or country cannot face alone. In this context, the pulmonary system is particularly vulnerable to all kinds of inoculants and contaminants, especially the airborne transmission of pathogens which often cause pulmonary infections, affecting

individuals of the most varied age groups. In this scenario, respiratory viruses represent a continuous pandemic risk, among which *Betacoronaviruses*, belonging to the *Coronaviridae* family, is a subgroup.

In the past few decades, we have been exposed to a significant number of emerging respiratory viral diseases of significant pandemic potential, including the coronavirus that causes Severe Acute Respiratory Syndrome (SARS-CoV), which appeared in China in 2002[18,19], Swine Flu H1N1, which first appeared in Mexico in 2009[20] and the Coronavirus that causes the Midwest Respiratory Syndrome (MERS-CoV) which appeared in Saudi Arabia in 2012[21].

A new coronavirus subtype emerged in Wuhan in December 2019, initially causing an outbreak of viral pneumonia and then turning into an epidemic in China and globally thereafter.[11,22,23] Mortality associated with COVID-19 is apparently associated with Adult Respiratory Distress Syndrome, which when associated with comorbidities, significantly increases mortality[24,25].

Despite all efforts arising from biomedical and translational research associated with understanding infections by influenza and coronavirus, there are currently no effective treatments for this disease or vaccines capable of preventing infection in humans.[26,27] Data on COVID-19 continues to grow at an alarming rate. Between January 31 and March 01, 2020, 332,930 cases and 14,510 deaths were confirmed, with community transmission in almost all countries of the globe[28].

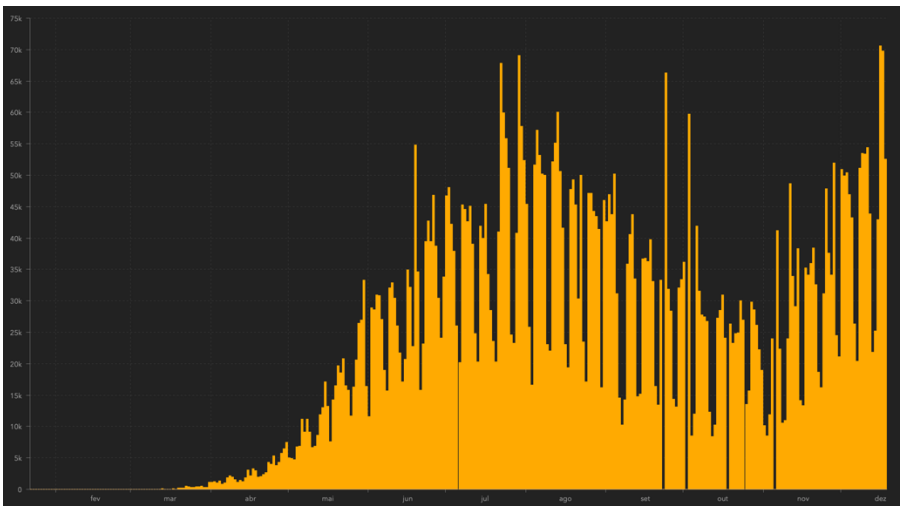
To date, there are no specific treatments for COVID-19. From the onset of this disease to the present, there are several proposed treatment protocols for this disease, however with no evidence of good clinical response. On the Clinicaltrials.gov website, there are currently 4,125 clinical studies registered for the treatment of COVID-19, 907 of which are still in the preparatory phase, 2,120 studies started the recruitment phase, and 546 studies are completed. Several studies highlighted the lack of effectiveness of different treatments in patients with moderate to severe illness, as well as in mild illness[29]. Given the high level of mortality expected for this pandemic and the high potential for transmission of the infection affecting populations and entire countries, it is imperative to seek treatments for this disease, for which there are supportive treatments so far.

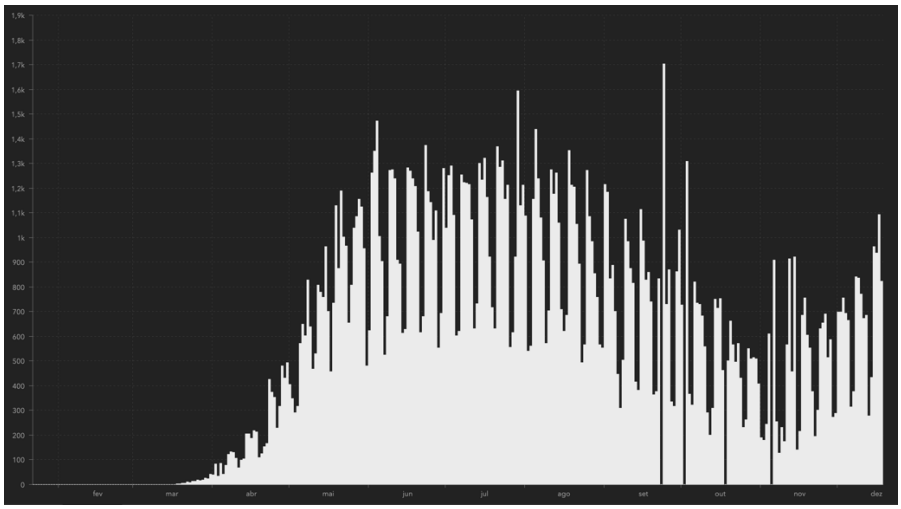
1.5.1 Justification for the Trial

The World Health Organization has been monitoring this disease since the first cases, compiling data from countries regarding the progress of COVID-19. The WHO declared on January 30, 2020 that COVID-19 was a global public health emergency[30]. By March 2020, the WHO declared COVID-19 a pandemic, with the vast majority of countries reporting COVID-19 infections and related deaths. Considering the high mortality of this disease and the lack of effective treatment, the academic community has made an unprecedented effort in recent scientific history attempting to seek an alternative to reduce this high mortality. In the platform www.clinicaltrials.gov there are currently 4,195 clinical studies targeting COVID-19, many of which have been carried out under non-ideal conditions or with inadequate designs[31].

Since the onset of the outbreak, both morbidity and mortality have been minimally impacted, and it is essential to continue academic efforts to face the current pandemic. As of December 17th,

2020, the pandemic still shows signs of exuberance, with increasing rates of cases, hospitalizations and mortality (Figures 4,5).





Figures 4 and 5 - Numbers of daily cases (yellow) and deaths (white) associated with COVID-19
Source: Johns Hopkins University data Center (12/17/2020)

There is, therefore, the need to offer a response to an epidemic that has been plaguing the globe since March 2020, associated with the fact that current data from patients with COVID-19 are exuberant and the need to find an effective treatment for this pandemic, would justify including a placebo arm. Currently, the absolute number of deaths exceeds the epidemics of EBOLA (1976), SARS (2002), and MERS (2012).

Nevertheless, considering the lack of efficient treatments in patients with initial and acute COVID-19, the presence of the placebo group becomes an important tool to ensure that we have a control group being exposed to the same conducts, concomitant medications, medical procedures and attitudes, something complex to obtain in clinical protocols, in which it is not possible to get data with the same temporal nexus. Such attributes, which demand a control group with standard treatment, are fundamental to verify the real usefulness of treatments and interventions. However,

we must consider the pandemic involving a deadly disease for which there are no treatments. In this context, it is important to highlight the adaptive design of the study. In case of evidence of superiority of some arm or even futility, measures will be adopted in the research to avoid either unnecessary exposure to some treatment or not to inform any effective treatment in this case. The assumptions of contemporary treatment and health professionals conduct concerning the disease, exposure to health resources, and access to resources will be present. Patients treated in the health care network which will not be participating in this research will not be conducted with the knowledge of treatment bias. The primary outcome to be observed is the need for hospitalization due to disease progression.

2.0 STUDY OBJECTIVES

There is currently no specific treatment appropriate for the outpatient setting with demonstrated efficacy against COVID-19. The Investigational Products (IPs) selected for this trial 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).

The objective of this study is to evaluate the efficacy, safety, and benefit of the use of IPs in patients acutely affected with COVID-19 presenting to outpatient settings with mild respiratory symptoms who are high-risk of experiencing complications. The patient's participation period in the protocol is 60 days, with up to 14 days being the treatment phase and the remaining period being follow-up after completion of treatment. The primary and secondary objectives will be assessed over 28 days following randomization. However, participants will continue to be followed for safety and late complications of COVID-19 until 60 days post randomization.

2.1 Primary objectives

The primary objective is to determine if each of the IPs reduces:

- Emergency room visits due to the clinical worsening of COVID-19 (defined as participant remaining under observation for > 6 hours) within 28 days of randomization.
- Hospitalization due to the progression of COVID-19 (defined as worsening of viral pneumonia) and/or complications within 28 days of randomization.

2.2 Secondary objectives

The secondary objectives are to evaluate, in comparison with placebo, the effect of the IPs in the following parameters:

- All cause, respiratory, and cardiovascular death
- Viral clearance and viral load on day 3 and day 7 after randomization
- Number of days with respiratory symptoms since randomization
- Time to hospitalization/urgent care due to the progression of COVID-19
- Rate of all-cause and COVID-specific hospitalizations
- Time to hospitalization for any cause
- Time to death
- Symptoms as assessed by the WHO Clinical Worsening Scale

- Health-related quality of life as assessed by PROMIS global health scale ("Global-10") scores
- Telephone Interview for Cognitive Status (TICS)) memory scale at day 28

Adverse events, adverse reactions to the study medications and the proportion of participants who are non-adherent with the study drugs will also be assessed.

2.3 Exploratory objectives
The exploratory objectives are to determine each IP reduces the following:

- Number of days spent in an intensive care unit
- Number of days on invasive mechanical ventilation
- Number of days of hospitalization
- Number of days of hospitalization in the ward
- Number of days using oxygen therapy

2.4 Subgroup objectives
The TOGETHER Trial will also explore the possibility of differential treatment effects of each of the repurposed drugs among clinically important subgroups. The subgroups will be defined by:

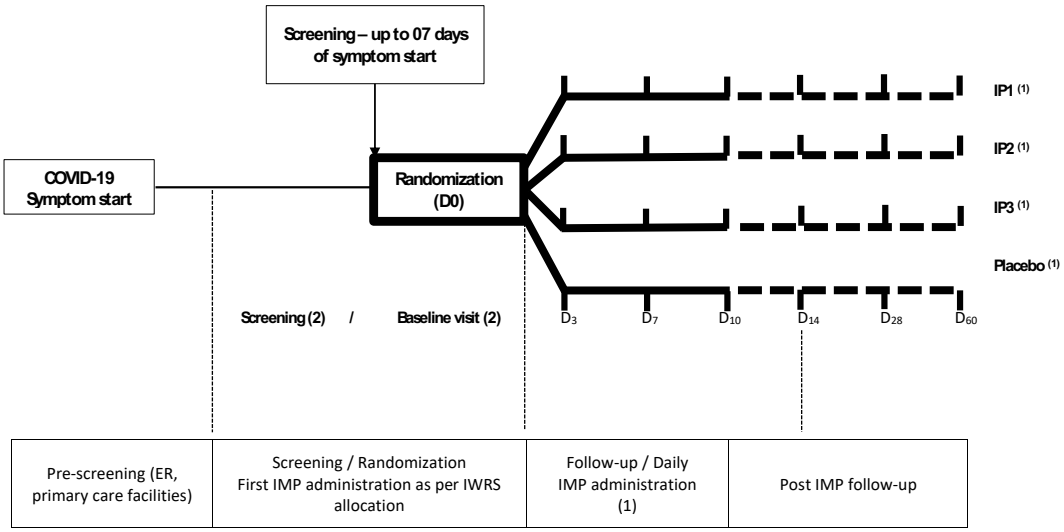
- Age
- Sex
- **Time from onset of symptoms (≥ 120 hours or < 120 hours)**
- Comorbidity at time of screening:
    - Diabetes mellitus
    - Cardiovascular disease
    - Lung disease
    - Immunosuppressed patients / use of corticosteroid therapy
    - Other special categories (solid organ transplantation, end-stage kidney disease)

3.0 TRIAL OVERVIEW
This is a multicenter, adaptive, platform, double-blind, randomized, placebo-controlled clinical study to assess the efficacy and safety of various treatment regimens in reducing hospitalization of patients with mild COVID-19 and high-risk for complications.

This trial represents a master protocol that reflects an adaptive platform trial. This unique design will allow IPs to be discontinued or added as novel data accrues over the course of trial. Based on regular blind interim analyses, the independent Data and Safety Monitoring Committee (DSMC) may make recommendations to the Steering Committee (see Section 11) to end an IP for futility or success. The interim analysis is summarized in the Statistical Analysis Plan. Additional IPs may be added based on potential new drug candidates or treatment combinations identified during the trial. If an intervention is shown to be effective, this design will also allow for the replacement of the placebo group with the effective intervention as the comparator. Treatment arms could be added in some countries but not in others, as per Appendix 2. This protocol can be adapted based on participating countries outlined in this study, as described in this Appendix 2.

Given the urgency of finding effective treatments for COVID-19, this protocol will be shared with other researchers so that they may adapt their protocols to facilitate data sharing. This will allow data from other trials to be included in the analyses of the TOGETHER data (refer to the TOGETHER statistical analysis plan) using Empirical Bayes meta analysis techniques[32].

The trial consists of a face-to-face screening and randomization visits, which will both take place on day 0, and follow-up visits completed primarily through telephone contact and social media applications using video-teleconferencing (Figure 6). The follow-up visits will take place on days 1, 2, 3, 4, 5, 6, 7, 10, 14, and 28. Participants will also be contacted at day 60, to assess long-term outcomes. Participants who prematurely discontinue the product under investigation remain in the trial. Unscheduled visit (during the treatment period) may occur at any time in case of adverse events.



1. Treatment: IP 1, IP 2, IP 3 in parallel groups for the planned period. Discontinue if significant symptoms or adverse reactions.
2. Screening and Randomization (Baseline visit) must be performed on the same visit. Ensure that the patient is randomized when at medical care facility. Patient with confirmed SARS-CoV2 positive test and less than 07 days of symptom onset can be considered for randomization.
3. Subsequent visits: D3, D7, D10, D14, D28, D60 will be carried out primarily by telephone and/or social media App. Extra visits for safety purposes can be made at any time. Visits D14 and D28 are considered outcome visits as per protocol. D60 is considered post-study visit for monitoring late complications related to COVID-19 and eventual evaluation of late adverse reactions to research drugs and will be carried out by telephone. There is no provision for face-to-face visits in this research in view of the regulatory recommendations issued by the public health authority in the context of the pandemic.
4. Daily contact by phone (not marked above) will be made between Days 1 to 7. Phone contact after D7 will be performed as per protocol.

Figure 6 - Research Flowchart

4.0 STUDY PROCEDURES

For a detailed assessment schedule (with all assessments, visits and visit windows required by the protocol) see schedule of events (Table 1).

Table 1. Schedule of Study Activities

	Screening Visit (D-0)	Baseline and Randomization (1) D-0	Day 1	Day 2[4]	Day 3[4] ± 1 day	Day 4 [4]	Day 5[4]	Day 7[4, 11] ± 1 day	Day 10 ± 2 days	Day 14[4] ± 2 days	Day 28[4] ± 3 days	Day 60[4,8,9] or Early Termination ± 5 days
Informed Consent	X											
SARS-CoV2 Rapid Test	X[1]											
Eligibility Criteria Review	X[2]											
Pregnancy Test	X[3]											
Demographics	X[5]											
Co-morbidities and Risk Factors	X											
Medical History	X											
WHO Clinical Worsening Scale	X		X	X	X	X	X	X	X	X	X	X
Exposure to Index Case Information		X										
Substance Abuse		X										
PROMIS Global Health Scale		X[6]								X[6]	X[6]	X[6]
ECG		X										
Height and Weight		X										
Nasopharyngeal Swab		X			X			X				
Randomization		X										
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X
Investigational Treatment Administration			X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]		
Hospitalization / Emergency Room Visits			X	X	X	X	X	X	X	X	X	X
Respiratory Symptoms			X	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X	X
Adverse Drug Reactions			X	X	X	X	X	X	X	X	X	X
Vaccination Status										X	X	X
TICS Scale - Memory Evaluation											X	

Legend

1. Screening and baseline visit: must be carried out at the same time when attending the outpatient setting. Rapid antigen test for COVID-19 at the screening visit. Day 1 visit should also be conducted on the same day as the screening and baseline visit. After completing the screening visit procedures at the baseline visit and present all inclusion / exclusion criteria, participants should be immediately randomized. The first dose of IP must be administered on the same day of randomization (immediately after randomizing). The study medication will be administered as prescribed. Patients must be observed for 30 minutes after the medication administration.
2. Patients can be included in the trial if they have a COVID-19 diagnosis at baseline visit and have less than 7 days of flu-like symptoms.
3. Only women of childbearing potential and / or potential to become pregnant. Women of childbearing potential must necessarily use contraception during the first 15 days of the trial.
4. Visits through telephone contact, video call, telemedicine are calculated from the randomization date.
5. After signing the Informed Consent Form.
6. Questionnaires must be completed BEFORE any procedures of the proposed visit. Only a person not related to the research can help the patient during the questionnaire. In telephone visits, the patient must respond directly, at the time of contact.
7. Maintain the administration of the IP according to schedule. Discontinue it if adverse events prevent the IP from continuing.
8. Assessment of late complications associated with COVID-19.
9. Unscheduled visits may also be conducted as needed. The clinical outcome data collected at the unscheduled visit should be entered at the next scheduled visit.

4.1 Screening and baseline procedures

4.1.1 Screening procedures

The screening visit will be carried out in an outpatient care setting as shown in Figure 6. The identification of eligible patients will occur during the screening or during the clinical consultation. Patients identified with acute flu syndrome in the context of the COVID-19 pandemic will be invited to learn about the trial. If they show interest, they will be sent to a previously designated and trained research member to present the proposed research program and present the free, prior and informed consent which will be presented in accordance with current regulatory standards for clinical research. Within the provisions of the prior, free and informed consent and good clinical judgment regarding participant safety, every effort should be made to ensure that participants complete the treatment phase and visits after the treatment phase. Participants will be informed that they are free to withdraw from the study at any time.

The research procedures will only be initiated after the participant sign the informed consent form. At the screening visit, participants will receive an exclusive participant number. Participants will be screened first to identify those who meet the eligibility criteria. As soon as a participant meets all the eligibility criteria, they will begin the baseline visit phase.

The activities described below will be carried out during the screening visit:

- Review of eligibility criteria
- The participant signs the informed consent form
- Demographics and medical history
- Pregnancy test for women of childbearing age
- WHO clinical worsening scale
- Rapid test for COVID-19 using the nasopharyngeal sample

In this study, patient rescreening is only allowed if it occurs with an interval > 30 days from the first evaluation, in the case of a patient previously defined as selection failure due to the rapid test examination for COVID-19 being negative.

4.2 Eligibility criteria

- The inclusion criteria are:

1. Patients over 18 years old with the ability to provide free, prior and informed consent;
2. Patients presenting to an outpatient care setting with an acute clinical condition compatible with COVID-19 and symptoms beginning within 7 days of the screening date;
3. Patients over 18 and with at least ONE of the following criteria:
    a) Age ≥ 50 years (does not need any other risk criteria)
    b) *Diabetes mellitus* requiring oral medication or insulin

c) Systemic arterial hypertension requiring at least 01 oral medication for treatment
d) Known cardiovascular diseases (heart failure, congenital heart disease, valve disease, coronary artery disease, cardiomyopathies being treated, clinically manifested heart disease and with clinical repercussion)
e) Symptomatic lung disease and / or being treated (emphysema, fibrosing diseases)
f) Symptomatic asthma patients requiring chronic use of agents to control symptoms
g) Obesity, defined as BMI> 30 kg / m2 (weight and height information provided by the patient)
h) Transplant patients
i) Patient with stage IV chronic kidney disease or on dialysis
j) Immunosuppressed patients / using corticosteroid therapy (equivalent to at least 10 mg of prednisone per day) and / or immunosuppressive therapy
k) Patients with a history of cancer in the last 05 years or undergoing current cancer treatment
l) Documented fever (>38C)
m) Patients with at least one of the following symptoms: cough, shortness of breath (SOB), pleuritic chest pain AND/OR myalgias (to a maximum of 25% of enrollment)

4. Patient with positive rapid test for SARS-CoV2 antigen performed at the time of screening or patient with positive SARS-CoV2 diagnostic test within 07 days of symptom onset.
5. Willingness to use the proposed investigational treatment and follow the research procedures.
6. Female patients of childbearing potential and male patients with partners of childbearing potential must agree to use adequate methods of contraception during the study and through 90 days after the last dose of study medication.

Participants who already have a positive RT-PCR test for SARS-CoV2 at the time of screening and meet all the inclusion criteria in the survey will not need a new confirmatory test for COVID-19 and can be considered eligible for the randomization / treatment.

Patients who meet any of the following criteria will be excluded:

1. Diagnostic examination for SARS-CoV2 negative associated with acute flu-like symptoms (patient with negative test taken early and becoming positive a few days later is eligible, if he/she is <07 days after the onset of flu-like symptoms);
2. Patients with acute respiratory condition compatible with COVID-19 treated in the primary care and with hospitalization need;
3. Patients with acute respiratory condition due to other causes;
4. Patients who have received at least one dose of vaccination for SARS-CoV2 > 14 days prior to screening;
5. Dyspnea secondary to other acute and chronic respiratory causes or infections (e.g., decompensated COPD, acute bronchitis, pneumonia, primary pulmonary arterial hypertension);
6. Acute flu showing at least ONE of the criteria below:
    i. Respiratory Rate > 28 / min;
    ii. SaO2 < 90% or < 93% on nasal oxygen therapy at 10 L / min;

iii. PaO2 / FIO2 < 300 mmHg;

7. Use of the following medications in the last 14 days:
    i. Monoamine Oxide Inhibitors (MAOIs): Phenelzine, Tranylcypromine, Selegiline, Isocarboxazide, moclobemide;
    ii. Alpha-1 antagonists, Sotalol, Clonidine, Phosphodiesterase 5 inhibitors, Methyldopa, Prazosin, terasozin, Doxazosin;
    iii. Antiretroviral agents
8. Patients using serotonin reception inhibitors (Donepezil, Sertraline);
9. Pregnant or breastfeeding patients;
10. History of severe ventricular cardiac arrhythmia (ventricular tachycardia, patients with recovered ventricular fibrillation) or long QT syndrome;
11. History of diabetic ketoacidosis or clinical condition that maintains persistent metabolic acidosis;
12. Surgical procedure or use of contrast planned to occur during treatment or up to 05 days after the last dose of the study medication;
13. Current daily and / or uncontrolled alcoholism or drug addiction;
14. History of seizures in the last month or uncontrolled seizure;
15. Clinical history of moderate to severe hepatic deficiency or liver cirrhosis or Child-Pugh C classification;
16. Patients with known severe degenerative neurological diseases and / or severe mental illness;
17. Inability of the patient or representative to give informed consent or adhere to the procedures proposed in the protocol;
18. Known hypersensitivity and / or intolerance to IPs or taking medications contraindicated by IPs;

4.2.1 Baseline visit procedures / randomization

The baseline / randomization visit should be performed immediately after confirming positivity for COVID-19 through the rapid test. Patients who meet all the inclusion criteria and do not present exclusion criteria may be randomized up to 7 full days from the date of onset of symptoms, preferably following the screening visit (both performed at the same time). Clinical site personnel will complete the baseline procedures and collect study data as detailed in Table 1.

Participants will be randomly assigned with equal allocation using a pre-generated randomization list based on block sizes of 10. The block sizes may be increased or decreased depending on the number of active treatment arms.

Different placebos may be used depending on which IPs are included. If IPs are being administered in both pill format and by injection, participants randomized to the placebo group will be randomized again to receive a placebo pill or a placebo injection. If IPs of different duration are being used (e.g. 1 day, 3 days, 10 days, 14 days), participants randomized to the placebo group will be randomized to different placebo durations or regimens.

The randomization will be stratified by clinical site, by age (<50 years vs. >=50 years). The randomization sequence for each clinical site will be prepared by the unblinded statistician and

will be sent to the unblinded pharmacist at each participating clinical site. Allocation of treatment assignment will be concealed from all other study personnel.

The participant will be provided with their medication as per randomization. The first 600 participants enrolled in the study and the first 400 participants enrolled into the subcutaneous treatment arms will be provided with two swab kits (nasopharyngeal swab associated with sputum sample collection / saliva collection to measure viral clearance and viral load). The participant will also receive guidance regarding daily telephone contacts and procedures associated with the next study visits. They will also provide participants with the appropriate COVID-19 guidelines and quarantine recommendations and discuss the details of the telephone contact and follow-up visits.

4.3 Treatment and follow-up phase procedures

The treatment phase will vary depending on the IP (e.g. one day, three days, ten days, 14 days). Considering the transmissibility of COVID-19 and the need to quarantine cases, daily telephone contacts will be made between randomization until day 7.

4.3.1 Daily telephone contacts (Days 1 to 5, Day 7, and Day 10 visits)

- The patient will be contacted daily either by telephone or through social media, and clinical site personnel will complete study assessments as detailed in Table 1.

4.3.2 Day 3 and Day 7 visits

- In addition to the procedures as described in the daily telephone contacts (Table 1), the collection of nasopharyngeal swab or sputum / saliva will be performed by the first 600 participants into the trial and the first 400 enrolled in the subcutaneous treatment arm at days 3 and 7. During the day 3 and day 7 telephone contacts, the participant will be instructed on the collection of the swab samples (will be collected at the participant's home) or at a place to be agreed upon, in the event of the impossibility of accessing the delivery service (place of difficult access, high social vulnerability). In these cases, a designated person will go to a known point at an agreed time to receive the samples.

4.3.3 Day 14 visit

In a telephone / social media contact, clinical site personnel will schedule a face-to-face assessment, which will be carried out the day after the last day of administration of the medication under investigation. Clinical site personnel will complete study assessments as detailed in Table 1. They will also collect the medication kits for drug accountability and treatment compliance.

4.3.4 Day 28, and 60 (End of the Study) visits

These visits will be performed through telephone contact. In visit Day 28, the participant will complete the Telephone Interview for Cognitive Status (TICS) questionnaire. The last visit can be in person, at the discretion of the investigator (in case it is necessary to check any adverse event or if the patient requests it). Clinical site personnel will complete study assessments for each visit

as detailed in Table 1. At the end of the study, they will also advise the participant that their participation in the research study has ended.

-

4.4 Procedures for unscheduled visits

An unscheduled visit may occur at the discretion of the investigator or at the participant's need and can occur during the treatment period until the end of study visit. In an unscheduled visit during any phase of the study, the following activities will be carried out:

- Adverse events evaluation / special situations
- Collection of medications and concomitant procedures
- Evaluation of the reason for the unscheduled visit

Any other study evaluations can be performed at the discretion of the investigator during an unscheduled visit. In the case of expected complications of COVID-19, the related adverse events will be considered as expected for the clinical problem presented. The following activities are optional during an unscheduled visit:

- Physical examination
- Collection of blood sample for hematological evaluation (central laboratory)
- Referral to tertiary care services for continuity of treatment at the hospital level.

Data collected at the unscheduled visit can be entered into the eCRF at the next scheduled visit.

4.5 Early termination procedures

For participants who withdraw prematurely from the study (before the expected end-of-study evaluation date), clinical site personnel should ensure that the participant completes a final termination visit, which must be carried out on the day of withdrawal or as soon as possible after withdrawal. The assessments made during this visit should be the same as the day 28 visit.

However, if a participant withdraws from the study, every effort will be made to determine why the patient withdrew the consent. Although participants are not required to give a reason for withdrawing consent, the investigator will ask for the reason while fully respecting the participant's rights. When provided by the participant, the reasons for withdrawing consent will be recorded on the clinical record and the center should do its utmost to ensure that the participant completes the described early termination procedures. Every effort will be made to contact a participant who fails to attend and / or attend a study visit by phone to ensure that the participant is in a satisfactory state of health.

Participants who wish to withdraw their consent will be offered the opportunity to consent to the following:

- Provide information about their own health status by phone or other means up to the date of the end of the study
- Allow family doctors or the family to be contacted to provide information about the participant's health status
- Allow a final contact at the end of the study (on or after the end of the study)

For any participant who leaves the study early (including participants who withdraw their consent), survival information can be verified by searching public databases at the end of the study.

5.0 STUDY EVALUATIONS AND OUTCOMES

5.1 Laboratory tests

In this clinical research protocol, there is no provision for laboratory tests, except for the rapid test for COVID-19 and RT-PCR tests, both using nasopharyngeal / saliva secretion as biological material to perform the tests. In women of childbearing age, a pregnancy test is planned, and the biological material to be used is urine. Eventual laboratory tests may be performed to elucidate adverse events or alterations for which the investigator deems necessary laboratory evaluations.

5.2 Vital sign data

Considering the extremely transmissible characteristic of SARS-CoV2 and the isolation recommendations of positive individuals, limited vital sign data will be collected. At the randomization visit, arterial oxygen saturation will be measured.

5.3 Physical examination

There is no provision for a complete physical examination in this trial for the same reasons listed in section 5.2.

5.4 ECG assessment

The evaluation of an ECG trace must be carried out to check for any changes resulting from COVID-19 and will be carried out during the baseline visit. We will not monitor the QT interval in this research as the medications in use do not change the QT interval. The participant must rest at least for 5 minutes before the examination and the procedure to be performed according to the guidelines of the Kardiamobile® manufacturer.

Considering the highly transmissible characteristic of COVID-19 and the risks of contamination of the research team and considering the profile of patients participating in the research (patients with mild symptoms, without any complication of the main physiological system at the time of participation), we understand that blood pressure and heart rate data will not contribute to any COVID-19-related risk assessment. In addition, heart rate can be obtained when ECG is performed using the Kardiamobile®. Therefore, it is a procedure that adds transmission risks to the research team without a direct benefit from the data. We will not measure blood pressure or heart rate in the classic way, during this research.

5.5 Vaccination status

Participation in the study will not preclude vaccination against COVID-19. CDC recommendations are to defer receipt of a COVID-19 vaccine until recovery from the acute illness has occurred and criteria for home isolation as outlined by local public health authorities have been met. Participants will be advised to wait at least 2 weeks from study enrollment until receiving vaccination. The date and type of vaccination received will be documented.

5.6 Contraception in participants of childbearing potential

Pregnant and breastfeeding women cannot participate in this research. Pregnancy testing will be performed on all women of childbearing age (the childbearing age being defined in this protocol as at least one menstrual episode occurring in the last 12 months in women between 18 and 55 years of age) at the randomization visit.

Any pregnancy that occurred during the treatment phase of the study will be monitored until birth to assess any complications and adverse events.

Male participants who are sexually active with a woman of childbearing potential, must agree to use a double barrier method of birth control (two different methods of birth control like a condom with a spermicidal) from the time they first take the study drug until they take last dose of study drug (Day 10) to prevent pregnancy. Participants who have had a vasectomy not need to use a double barrier methods of birth control. Participants will also be instructed to tell their study doctor if their partner becomes pregnant. The sponsor may ask collect information about the pregnancy, delivery, and the health of the baby. As the effect of the study drugs on sperm is unknown, male participants will be instructed to not donate sperm while taking the study drug and for three months after they stop taking the study drug.

5.7 Clinical outcomes

Clinical outcomes include:

- Emergency room visits due to the clinical worsening of COVID-19 (defined as participant remaining under observation for > 6 hours)
- Hospitalization due to the progression of COVID-19 (defined as worsening of viral pneumonia) or complications related to COVID
- Viral clearance and viral load (first 150 participants randomized)
- Respiratory symptoms
- Hospitalization for any cause
- Mortality and cause of death
- Adverse events, including serious adverse events (See section 10.0)
- Adverse drug reactions (See section 10.0)

Details regarding each hospital stay will be collected including date of hospital admission and discharge, number of days in the hospital, number of days in an intensive care unit, and if life support was needed.

5.8 Outcomes reported by participants

Participants will complete the PROMIS Global Health Scale before the study team carries out any other evaluations during the telephone contact or in person visit, to avoid influencing the answers from participants. Study coordinators will review the participant's answers immediately after the participant completes the questionnaires to ensure that all questions are answered.

5.8.1 Clinical worsening questionnaire - WHO

We will assess the clinical condition of the participants using the WHO scale: 0-1: ambulatory (no clinical deterioration during the RCT phase), 2: activity limitation, but without hospitalization; 3:

hospitalization, but no need for O_2 therapy; 4: hospitalization, required O_2 therapy; 5: non-invasive ventilation or high flow oxygen; 6: mechanical ventilation required; 7: need for ventilation and additional organ support; 8: death. The scale can be found on page 6 at the following link:https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf.

Since ordinal scales have proven useful in studies of hospitalized patients with respiratory diseases, this measure will be particularly useful as an outcome measure for the subset of study participants who require hospitalization.

5.8.2 PROMIS Global Health Questionnaire (Global-10)

We will assess the global health status of patients on days 0, 14 and 28 using the 10-item PROMIS global health scale (Patient-Reported Outcomes Measurement Information System 10)[33]. The items on this scale assess the general domains of health and functioning, including general physical health, mental health, social health, pain, fatigue and perceived general quality of life. The 10 question from Global-10 have been largely adapted from older measures, such as the SF-36 and EQ-5D, with modifications that have resulted in greater sensitivity and precision than the questions originally formulated.

5.8.3 TICS questionnaire

We will assess cognitive status using the TICS questionnaire[34], which is a validated questionnaire that can be administered over the telephone. The items on this scale assess the general domains of the progressive values and indicate greater memory impairment.

6.0 STUDY TREATMENTS

6.1 Investigational products

See Appendix 1 for information on each IP.

6.2 Packaging and labeling

The products under investigation will be provided to the participants at no cost, along with the orientation of using them only for the purpose of the research. Bottles of identical shape will be provided with the amount of medication sufficient for use. Participants should return with the blister cards to account for the medications delivered. The IP used will come from pharmaceutical factories with commercial authorization for their production.

6.3 Supply, storage and accounting by the study center

6.3.1 Supply by the study center

Once a study center has been approved to receive the study drug, it will receive an initial shipment based on the estimated rate of enrollment. The need for medication replenishment will be assessed regularly, considering the number of enrolled participants, the number of participants screened at the study center and the study's overall participation.

6.3.2 Storage

The pharmacist or the representative will check and acknowledge receipt of each shipment of the study drugs. The study medication will be shipped and stored in a temperature-controlled manner as per the requirements for each IP. All study drugs will be stored in a safe place. No patients,

other than those included in this specific clinical study, should take the drugs provided for this study. The study medication cannot be used in any animal or laboratory research.

6.3.3 Study drug accountability

All products under investigation dispensed to participants must be accurately recorded in the accounting record for the investigated product maintained at the center of the study by the study pharmacist or qualified representative. Participants must be instructed to return all research products dispensed to them (blisters and containers, used or not), which will be collected by the research staff at day 14. All used blisters and containers of the product under investigation will be retained at the center by the study pharmacist / qualified representative for verification of the study monitor. Accounting and verification of adherence to the study medication for all products under investigation will be carried out by the study pharmacist or the qualified representative at each scheduled study visit.

6.4 Blinding of treatment

To minimize the potential for bias during the treatment phase, treatment randomization information will be kept confidential by an unblinded biostatistician and will not be released to third parties until the study database has been locked. Likewise, the sponsor and designees will not have access to randomization data during the course of the trial. The treatment bottles will be dispensed through codes, kept by a non-blinded biostatistician not involved in the research.

6.5 Modification of drug dose

6.5.1 Adverse reactions when using medications

Research participants should contact the research team if they experience any adverse reactions that they believe may be associated with the product under investigation. In the same way, participants will be monitored daily through telephone contacts to assess the presence of undesirable symptoms, adverse reactions and other signs/symptoms that may be present. The participant can be scheduled for extra safety consultation whenever the investigator deems it necessary concerning the information obtained during the telephone contact.

The decision to temporarily suspend medication can be taken at any time by either the participant or the investigator. Whenever possible, the participant should return to use the products under investigation.

6.5.2 Usual care

During the treatment phase, all participants will receive regular treatment following the guidelines. Usual care includes recommendations for all aspects of treatment for patients with acute upper respiratory infections (i.e., recommendations for antipyretics for temperature > 38.0° C, frequent hydration, severe myalgia analgesics and look for medical help if needed). Usual care can also include educating the participants.

6.6 Unblinding of clinical site personnel for emergency medical management

- In the event of a medical emergency that directly affects the health status of the participant, it may become necessary to unblind allocation status to determine the specific treatment the participant has received while enrolled in the study. A medical emergency is defined as an event which necessitates immediate attention regarding the treatment of a participant.

Clinical sites are instructed to contact the lead investigator for each country and provide details of the medical emergency as soon as possible after the event. At no time will the participant's health be compromised, or medical treatment delayed.

The lead investigator for each country is responsible for reviewing and approving all requests for unblinding. Once approved, they will contact the unblinded pharmacist will provide the site with the participant's treatment allocation. This information is to be provided by telephone. No information regarding treatment allocation is to be sent via email or fax. All cases of unblinding must be documented, including clinical site ID, study ID, date of unblinding, parties unblinded, and reason for unblinding.

The unblinded TOGETHER Trial personnel are not to unblind the Principal Investigator or any blinded members of the TOGETHER trial team unless deemed necessary by the Principal Investigator. TOGETHER personnel must keep all information related to the individual unblinding cases confidential. The investigator, clinical site staff, or study pharmacist must do their best not to disclose treatment assignments to other health professionals, external participants in the participant's care, or caregivers.

The clinical research supply management team will have access to the general use of research products at the clinical site level to manage packaging and distribution activities, as well as to oversee stock levels in drug stores and study centers.

6.7 Prohibited therapy, special considerations and concomitant treatment

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

6.7.1 Concomitant medications

Information on concomitant medications (prescription drugs, over-the-counter medications, herbal medicines and naturopathic medicines, etc.) will be collected from screening and throughout the study (including the Early Termination / End of Study visit, follow-up call).

In general, participants should be kept on the same medications and regimens that were in progress at the time of entry into the study. Doses of these concomitant drugs should be kept as stable as possible during the study. Medication the investigator considers suitable for the treatment of any intercurrent illness or a pre-existing condition that are not on the list of prohibited drugs or are not considered an exclusion criterion for participation in this study will generally be allowed.

6.8 Discontinuation of the product under investigation or withdrawal of participants

During the research treatment phase, the participant may suspend the product under investigation at any time. Likewise, the investigator may interrupt the product under investigation whenever necessary, either due to an adverse event or to preserve the participant's safety.

Participants who discontinue treatment under investigation without an apparent reason after randomization and prior to the completion of the study will be encouraged to return with the medication and continue the study as normal. If the treatment is discontinued, the patient will continue in the research for the collection of information regarding events of the composite outcome. These participants will be treated according to the standard of care.

7.0 ADVERSE EVENTS: EVALUATION, REGISTRATION AND REPORTING

7.1 Definition of adverse events

An adverse event (AE) is any unfavourable medical occurrence in a patient or a participant in a clinical study who has received a drug that does not necessarily have a causal relationship to that treatment[35]. An AE can, therefore, be any sign (including an abnormal laboratory finding) or unfavourable and unintended symptom or disease temporally related to the use of a medicinal product (investigational), whether related to the medicinal (investigational) or not. That includes:

1. any new clinical condition, sign or symptom, clinically significant physical examination abnormality or newly diagnosed event that occurs during the reporting period for AEs, including signs or symptoms associated with an underlying condition that was not present prior to the reporting period of AEs;
2. a pre-existing condition that worsened in severity or frequency or changed characteristics after the participant signed the prior and informed consent, during the reporting period for AEs;
3. complications that occur as a result of interventions required by the protocol. An AE can arise from any use of the drug under investigation (e.g. use in combination with another drug) and using any route of administration, formulation or dose, including an overdose. EAs can also be any side effects, damage, toxicity or sensitivity reactions that may be experienced by a participant in this clinical study.

For the purpose of this protocol, events that will not be considered AEs include:

1. Expected signs or symptoms of a pre-existing medical condition (e.g., tremor in a participant with Parkinson's disease; migraine episodes) that did not worsen in severity or frequency or change characteristics during the reporting period for AEs;
2. Surgeries or medical procedures are not AEs; however, the clinical condition (new or worsening) that led to the surgery or medical procedure is the reported AE (e.g., for appendicitis resulting in appendectomy, appendicitis must be reported as the AE);
3. Overdose with no clinical signs or symptoms.

7.2 Adverse event reporting period

AEs, including serious adverse events (SAE), will be collected throughout the study period, from the moment the participant signs the prior and informed consent and until the end of study visit. All AEs still present at the time of completion of the study will be followed up by the investigator through contact with the participant until resolution or stabilization, or until the participant loses follow-up and can no longer be contacted. The result must be documented in the participant's documents. The investigator must report all SAEs that occur after the reporting period specified in the protocol if, according to the investigator's assessment, there is a reasonable possibility that the SAE is related to the product under investigation or any study procedure.

7.3 Obtaining information about adverse events

If the participant reports an AE, it is the investigator's responsibility to obtain sufficient information to assess causality. This may require additional laboratory tests, physical examinations, telephone contacts, etc. To avoid bias in the collection of AEs, participants should

be asked to answer a neutral question, such as "How are you feeling?". It is also important to ask the participant in a non-biased way about changes in their health or use of concomitant medication since their last visit. This information must be collected before evaluations are carried out on all study visits. In addition, any symptoms/conditions reported during the assessments and considered clinically significant by the investigator will be assessed as AEs.

7.4 Assessment of adverse events

7.4.1 Intensity / severity

The medical assessment of intensity will be determined using the following definitions:

- Light: AE is easily tolerated and does not affect usual activities.
- Moderate: AE affects daily activities, but the participant is still able to perform them.
- Severe: The AE is disabling, and the participant is unable to work or perform usual activities.

A new AE will be documented whenever the intensity of an event changes.

It is important to note the distinctions between severe AEs and serious AEs (SAEs). Severity is a classification of the intensity of a specific event (such as mild, moderate, severe); however, the event itself may be of relatively secondary clinical significance (such as severe headache). A SAE, however, is an AE that meets any of the specified regulatory criteria required for designating severity (e.g., a headache can be severe [significantly affects the participant's usual functions], but would not be classified serious, unless it meets any of the criteria for SAEs).

7.4.2 Causality and reporting

The investigator will provide a causality assessment for all AEs using their best clinical judgment based on the medical information available about the event being reported. The causality assessment will be re-evaluated as new information becomes available. If the investigator's assessment of causality is not reported, the event will be considered "related" until such information is received. Each investigator will assess the degree of relationship between the AE and the drugs under investigation using the following definitions:

Not related: There is no reasonable possibility that the product under investigation caused or contributed to AE.

- The event is related to a different etiology from the drug under investigation, such as underlying disease, study or procedures not included in the study, concomitant drugs or clinical status of the participant
- The timing of the occurrence of AE is not reasonably related to the administration of the study drug

Related: There is a reasonable possibility that the product under investigation caused or contributed to the AE.

- There is no compatible temporal association between the event and the administration of the drug under investigation
- There is a biologically plausible mechanism by which study treatment may have caused or contributed to AE

- The event improves or decreases after the study drug is discontinued without the initiation of any specific treatments for the event (withdrawal from exposure) and / or the event recurs or worsens with the reintroduction of study therapy
- The event cannot reasonably be attributed to the concomitant or underlying disease or other medications or procedures

For the purpose of assessing causality, “reasonable possibility” means that, based on the investigator's medical judgment of the available information, there are facts or arguments that suggest a positive causal relationship.

7.4.3 Result categorization

The result can be classified as: recovered/resolved (e.g., no sequelae); recovered/resolved with sequelae; not recovered / not resolved; fatal; or unknown (if tracking is not possible). If the result of an SAE is reported as recovered/resolved with sequelae, the investigator must record the type of sequelae in the SAE form. If the result of an SAE is reported as unknown, the investigator must specify (in the SAE form) the justification for why the unknown was selected.

"Fatal" must be recorded as a result when the AE results in death. The cause of death is necessary when known. If an autopsy was performed, an autopsy report will be provided. If no autopsy has been performed, a death certificate will be provided, if possible. Death will be reported as a result and not as an event. If more than one AE is possibly related to the participant's death, the result of the death should be associated to the AE which, in the investigator's opinion, is the most plausible cause of death. All other AEs / SAEs in progress must be recorded as unrecovered / unresolved at the time of death.

7.5 Registration and reporting

7.5.1 Persistent or recurrent adverse events

AEs that extend continuously, with no resolution, between clinical trial evaluations should be documented. A new adverse event will be documented whenever the intensity of an event changes. AEs resolved that occurred again must have each recurrence documented separately in the clinical record.

7.5.2 Diagnosis versus signs and symptoms

Whenever possible, the investigator should report a diagnosis instead of individual signs and symptoms or abnormal laboratory values. However, if a set of signs and / or symptoms cannot be characterized clinically in as a single diagnosis or syndrome at the time of reporting, each individual event must be documented in the clinical record. If a diagnosis is subsequently established, all AEs previously reported based on signs and symptoms should be canceled and replaced by one AE report based on that single diagnosis, with a start date that corresponds to the date of the appearance of the first symptom of the eventual diagnosis. The researcher should use standard medical terminology / concepts and avoid colloquial terms and abbreviations. Only one term of AE should be documented in each field of events in the clinical record.

7.5.3 Pre-existing clinical conditions

A pre-existing clinical condition is a condition present at the time of the screening visit. Such conditions must be registered in the clinical record. A pre-existing clinical condition should be

registered as an AE only if the frequency, severity or characteristics worsens during the study. When documenting these events in the AE clinical record, it is important to indicate the concept of alteration of the pre-existing condition, including the applicable descriptors (e.g., "most frequent headaches").

7.5.4 Clinical laboratory analyses

Not all laboratory tests with results outside the reference range qualify as an AE. A laboratory investigation result must be reported as an AE if it meets any of the following criteria:

- Be accompanied by clinical symptoms
- Result in changing study treatment (e.g., modifying dose administration, treatment interruption or discontinuing treatment)
- Result in unexpected medical intervention.
- Present the change of a parameter from a normal value to a pathological value or a new aggravation of an already pathological value
- Is considered clinically significant in the investigator's opinion

It is the investigator's responsibility to analyze all laboratory findings. Medical and scientific judgment must be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. When assessing these alterations, the extent of deviation from the reference interval, the duration until returning to the reference interval, either during continuous treatment or after the end of treatment with the experimental product, and the variation range of the respective parameter within your interval should be considered.

The investigator has the responsibility to determine the clinical significance of each abnormality. If, at the end of the treatment phase, there are pathological laboratory values that were not present in the baseline period, additional clinical or laboratory investigations should be carried out, until the values return to the reference range or until a plausible explanation (e.g., concomitant disease) is found for pathological laboratory values. The investigator must decide, based on the above criteria and the participant's clinical condition, whether a change in a laboratory parameter is clinically significant and therefore represents an AE. If the investigator considers it a serious AE, it should be reported as an SAE.

If a laboratory abnormality that meets the above criteria is a sign of a disease or syndrome, only the diagnosis should be recorded in the clinical record. If a laboratory abnormality that meets the above criteria is not a sign of a disease or syndrome, the abnormality itself must be recorded in the clinical record, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "High potassium" instead of "abnormal potassium"). If the laboratory abnormality can be characterized by an accurate clinical term according to standard definitions, the clinical term should be recorded as the AE, for example, hypercalcemia or hypoglycemia. The initial severity of the event must be documented, and the severity or seriousness must be updated at any time, if the event worsens.

All pathological laboratory values/findings diagnosed throughout the treatment period should be analyzed by the investigator to provide a final clinical assessment of the laboratory alterations/abnormalities.

7.5.5 Abnormal vital signs and other abnormalities

Laboratory results, ECGs, vital signs and other non-standard safety assessments will be considered AEs if they meet at least one of the following criteria:

- Are associated with symptoms or result in a diagnosis (in which case, the symptom or diagnosis will be documented as an AE)
- Lead to discontinuation of the product under investigation
- Need treatment or referral of the participant to perform additional tests outside the protocol range (repetition of tests or titration are within the protocol procedures)

It is the investigator's responsibility to analyze all vital signs, ECG and other safety findings. Medical and scientific judgment must be exercised in deciding whether an isolated abnormality should be classified as an AE. If a clinically significant abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be documented in the medical record.

Observations about the same clinically significant laboratory abnormality between visits should not be documented repeatedly unless there are changes in the etiology. The initial severity of the event must be documented, and the severity or seriousness must be updated at any time, if the event worsens.

7.6 Adverse drug reaction and reference safety information

An adverse drug reaction (ADR) is an undesirable and unintended response to a pharmacological product related to any dose administered. This definition implies a reasonable possibility of a causal relationship between the event and the drug under investigation. This means that there are facts (evidence) or arguments to suggest a causal relationship.

Considering that investigational medications have been commercially approved for decades, this study will only consider ADR as an adverse reaction not yet described in the product monographs and assessed by the investigator as a reasonable causal relationship with a medicinal product (investigational). Thus, a report of ADR in relation to the drugs used in this research is not expected.

Reference safety information (RSI) provides the basis for assessing the predictability of a ADR for accelerated reporting and annual safety reports, as well as for monitoring the safety of the participant in a clinical study by regulatory agencies (or ethics committees).

In the context of this study, the report of ADR is not expected, as it is anticipated that the potential adverse reactions are already described in the product monographs.

7.7 Serious adverse event

7.7.1 Definition of a serious adverse event

An SAE is defined as any unfavourable medical occurrence that, at any dose:

- Results in death

- Is life-threatening (the term life-threatening in the definition of seriousness refers to an event during which the participant was at risk of death; it does not refer to an event that hypothetically could have caused death if it was more severe)
- Demands hospitalization or extension of existing hospitalization. Hospitalizations for elective surgery (i.e., a planned, non-emergency medical procedure), social hospitalizations, and hospitalizations of less than 24 hours are not considered SAEs
- Results in persistent or significant disability
- Is a congenital anomaly/birth defect
- Is an important medical event (i.e. clinically significant)

Medical and scientific judgment should be exercised to decide whether an accelerated report is appropriate in other situations, such as in the event of major medical events that may not be an immediate risk to life or result in death or hospitalization but may put the participant at risk or may require intervention to prevent one of the other outcomes listed in the definition above. These events must also be considered serious.

Any worsening of a pre-existing clinical condition or any new clinical condition that meets the above SAE criteria should be considered an SAE and the investigator is encouraged to discuss with the research coordination any AE for which the severity assessment is uncertain or questionable.

7.7.2 Situations that are not considered serious adverse events

The following situations are not considered SAEs:

- Elective or pre-planned surgery for a pre-existing condition that has not worsened
- Routine health assessments requiring hospitalization not associated with a deterioration of the clinical condition
- Social hospitalization (homelessness, family circumstances, etc.)
- Expected adverse reactions associated with the drugs under investigation, according to the product monographs
- Research outcomes (Hospitalization, worsening of COVID-19)

7.7.3 Reporting of a serious adverse event

The reporting period for SAEs begins the moment the participant signs the informed consent. The SAE reporting period continues until the end of the study.

The occurrence of an SAE must be reported immediately to the electronic data capture system within 24 hours after its notification by fax, e-mail or telephone. This includes all SAEs (regardless of their relationship with the study treatment).

A death that occurs during the study period, whether considered treatment-related or not, must be reported using the adverse event form.

Any SAE considered to have a causal relationship (e.g. related) to the product under investigation and discovered by the investigator at any time after the study must be reported. The investigator must provide a justification for the assessment of a causal relationship. All safety information that

is obtained after the clinical database closes will be documented in the safety database and the implications for handling the data in the clinical database assessed on a case-by-case basis.

The SAE start date is defined as the date when the signs and symptoms/diagnosis became serious (that is, they meet at least one of the seriousness criteria). If the participant presents an AE and the participant progresses to an SAE, a new SAE must be registered. The resolution date of the original AE must be the same as the start date of the SAE. However, when the SAE is resolved and the pre-existing AE is still in progress, it must be registered as a new AE. The date of resolution of an SAE is defined as the time when the symptoms resolve or when the event is considered chronic (e.g., sequelae) or stable and/or if the seriousness criteria are no longer applicable. Follow-up information should be handled in the same way and reported in the same time frame as the initial SAE report.

Death must be considered a result and not a separate event. In the case of a fatal outcome, the investigator must provide a working diagnosis (event that caused the outcome, e.g., death due to fatal myocardial infarction) instead of reporting only death; and a necropsy report should be provided, when possible. If the cause of death is found later (e.g. after necropsy), this working diagnosis should be replaced by the established cause of death.

All registered SAEs, regardless of the relationship with the experimental product, will be followed until their resolution or stabilization, or until the participant is a loss of follow-up and can no longer be contacted. At the end of study visit, updates must be documented and sent.

Site investigators are also responsible for reporting SAEs to their institutional ethics committee and any applicable regulatory agencies in accordance with their requirements.

7.7.4 Study events

Based on the design of the specific study and the advanced state of the underlying disease in the population of recruited participants, events suggestive of the study results would automatically qualify to meet the severity criteria in this study. These events include known consequences of the underlying disease and are expected to occur in the study population, regardless of exposure to the drug (see items above). These events should be reported, collected and monitored during the study, as well as all other SAEs, but they will not be reported individually immediately. While these SAEs must meet the definition of unexpected, these events do not require a safety report, accelerated as in individual cases, as it is not possible, based on a single case, determine that there is a reasonable possibility that the study drug caused the event. As a result, they would not meet the definition of suspected adverse reaction. The DSMC will monitor the events identified during the study and alert if there is evidence of a causal relationship between the product under investigation and the event after analysis.

7.7.5 SUSARs

The definition of a suspected unexpected serious adverse reaction (SUSAR) is any ADR (Adverse Drug Reaction) that is serious, and unexpected. For the purposes of this protocol, the occurrence of SUSAR's is not expected since the medications have been widely approved for other indications and used in hundreds of thousands of patients. The adverse reactions of / or idiosyncratic are already well known by the regulatory authorities.

7.8 Special situations

7.8.1 Definition of special situations

The following situations are defined as special:

- Drug abuse: intentional and excessive, persistent or sporadic use of study medication by the participant (not for therapeutic purposes)
- Medication error: an unintended error in the prescription, delivery or administration of an IP during the study. (Medication error is any preventable event that can cause or lead to inappropriate use of medication or harm to the patient while the medication is under the control of the healthcare professional or the patient)
- Misuse of medication: intentional and inappropriate use of an IP by the participant for therapeutic purposes that is not in accordance with the dose, route of administration and / or protocol indication (e.g.: participant deliberately took the medication twice a day instead of once a day)
- Medication overdose: administration of an amount of study medication equivalent to three times the maximum dose allowed by the protocol per administration or per day.
- Drug interaction involving study medication
- Unexpected therapeutic or clinical benefit from using study medication

Suspected AEs associated with medication errors or use outside of the protocol (e.g., overdose) should be reported and documented in medical records.

7.8.2 Recording and reporting of special situations

All special situations must be documented in the participant's source documents. If any special situation leads to an SAE, the event must be reported immediately within 24 hours of notification, by fax, email or phone.

7.8.3 Exposure during pregnancy and birth events

7.8.3.1 Definition of exposure during pregnancy and birth events

IPs should not be prescribed in pregnant patients without a careful assessment of the risks and benefits of using them during this phase. Thus, pregnancy should not occur during the treatment phase (14 days) and women should use contraceptive methods to avoid possible pregnancy (if necessary, we will provide an effective method of contraception to use during the medication period).

If a female participant becomes pregnant during the study and the study treatment has been administered to the participant, the outcome of the pregnancy needs to be monitored and the safety of the mother and unborn child be monitored. Therefore, the outcome of all these pregnancies (including normal births) must be monitored and documented, even if the participant has been withdrawn from the study or if the study has been completed.

A female participant should immediately inform the investigator if she becomes pregnant during the study. The investigator should advise the participant and discuss the risks and benefits of continuing the research medication and guide the patient on follow-up until the child's birth.

The investigator is responsible for monitoring the participant and the pregnancy outcome and for reporting this information to the sponsor. Every effort should be made to collect information on the outcome of pregnancy within 90 days of delivery (or, if not, as appropriate).

7.8.3.2 Exposure during pregnancy and registration and reporting of birth events

Although pregnancy is not considered an SAE, it must be reported within 24 hours of notification by the participant. Pregnancy complications are reported as AEs or SAEs (if applicable). Any pregnancy will be monitored until delivery for the observation of any SAEs. Deaths, spontaneous or elective abortion, congenital abnormalities / birth defects and AEs / SAEs that occur in newborns should be reported as SAEs. Newborns potentially exposed to the study medication through maternal or paternal sources who present an SAE before, during or after delivery (including those who have breastfed from the participating mother) will be followed up until the event is resolved (or for a period of 1 year).

8.0 STUDY COMMITTEES

8.1 Data and Safety Monitoring Committee (DSMC)

An independent DSMC will be established, composed of scientists of unrivalled reputation and expertise, without involvement with this research protocol. The DSMC will monitor the safety of participants in this study. The DSMC follows a charter that explains the work procedures and its responsibilities. The charter will be previously agreed by the DSMC and will follow good research practices.

9.0 STATISTICAL CONSIDERATIONS

Statistical considerations for the trial are comprehensively described in the TOGETHER trial Statistical Analysis Plan.

10.0 ETHICAL CONSIDERATIONS OF THE STUDY

10.1 Ethical conduct of the study

- The study will be conducted in accordance with the principles of the Declaration of Helsinki of the World Medical Association, and the International Council for Harmonization (ICH) guidelines for Good Clinical Practice (GCP)[36], as amended.

-

- The investigator must guarantee the anonymity of all participants who are participating in the study. Each participant will receive a unique participant number, which must be used in all forms associated with the participant's documents or samples that will be provided to the sponsor or any party who performs tests on behalf of the sponsor (e.g. blood for central laboratory evaluations).

-
- All anonymous data are the property of the Research Steering Committee
-

10.2 Free, prior and informed consent (FPIC)

- Participants' individual medical information obtained from this study is considered confidential, and disclosure to unauthorized persons is prohibited. The confidentiality of the participant will be guaranteed through the use of unique participant numbers instead of names. If the results of this study are reported in medical journals or at meetings or are sent to the relevant regulatory authorities in connection with regulatory procedures, such as requests to authorize the marketing of pharmaceutical products, the identity of the participants will not be revealed.
-
- With the participant's authorization, medical information may be provided to the participant's personal physician or other health professional responsible for the participant's well-being.
-
- In accordance with GCP guidelines, all participants will be informed about the purpose of the research, the possible risks, and their right to withdraw at any time from the study, without prejudice and risk for their future medical care at the center. Each participant must agree to cooperate in all aspects of the study and provide written confirmation (signed informed consent form) to the investigator prior to participating in the study. If the FPIC is modified during the study, active participants must sign the new version to continue participating in the study. For any updated or revised FPIC, if applicable, the participant's record must declare that informed consent was obtained to use the updated/revised consent form for continued participation in the clinical study. The FPIC must be revised whenever there are changes in the procedures in the amendment to the protocol associated with the IC's procedures, or when new information is available, that may affect the participant's willingness to participate. Each participant will receive a copy of each version of the form they sign before and during the study.
-

- No participant should participate in study activities until the informed consent form has been obtained. The documentation of the process of obtaining free, prior and informed consent and the discussion of the information provided to the participant must appear in the participant's medical record and include a statement that the informed consent form was obtained before participating in the study. The signed FPIC must remain in the participants' files and must be available for verification by auditors and/or inspectors of the regulatory agency at any time.

-

10.3 Research Ethics Committee approval

- All researchers participating in this study must be governed by an appropriate Ethics Committee (EC). The EC must review and approve this protocol, the FPIC, study documents and any information to be given to the participant before a center can begin to conduct any activities related to the study.

-

- Subsequently, the investigator is responsible for obtaining a new approval by the EC annually, or more frequently, according to the regulatory requirements and policies and procedures established by the EC. The investigator must also inform the EC of any changes or amendments to the protocol, accelerated reports submitted to regulatory authorities, and other significant security concerns in accordance with EC's policy. Written documentation of the EC's approval of the amendment to the protocol must be received prior to its implementation. Upon completion or termination of the study, investigators must notify their EC. The investigator will comply with EC policies for the duration of the study.

-

11.0 QUALITY CONTROL AND QUALITY ASSURANCE

The integrity and quality of the participant's data will be ensured through the training process and instructions for completing clinical records, quality control checks, conducting ongoing clinical data analysis (including medical history and safety analyzes) and conducting verification of data source and data reconciliation.

The investigator will also allow the research steering committee or its representative auditor, EC representatives, or other inspectors from the regulatory authority to examine and inspect the facilities, procedures and all records relevant to this study. These records include, among other documents: the informed consent form signed by the participant, the source documentation, regulatory and essential documents, clinical records and drug accounting records.

The following measures may be taken to ensure that the study is conducted by the research center in accordance with the study protocol, GCP and other applicable regulatory requirements:

- Meeting with the researcher and / or

- Research center initiation
- Routine monitoring of the center, if applicable
- Documented GCP and protocol training
- Review of clinical records and questionnaires compared to source documents
- Collection of normal intervals from the local laboratory

11.1 Quality management: processes and critical data

The following processes and data were identified during the risk management activities for this study as essential to ensure the protection of the patient and the reliability of the study results.

Throughout the study, the clinical study team will work to ensure that the clinical study is operationally possible, with a focus on the study and essential activities for the protection of human participants and the reliability of the study results, including, but not limited to the following:

- Study protocol design and implementation
- Tool and procedures of supporting data collection and processing
- Tools and procedures to guarantee the rights and protection of participants
- Essential activities for study decision making and adherence

12.0 DATA REPORTING AND RECORDING

Source documents are original documents, data and records (e.g., case histories, doctor's progress notes, nurse's notes, medical records, hospital records, clinical and office charts, lab notes, memos or checklists of evaluation, pharmacy dispensing records, automated instrument data records, certified copies or transcripts, records kept at the pharmacy or laboratories and participants' records). The source data is contained in source documents and must be adequate to reconstruct all data transcribed for clinical records and to evaluate the study. Examples of the source data include clinical findings, observations, summary of information about inclusion and informed consent procedures, evaluation of clinical significance for laboratory results, severity and seriousness of AE and the investigator's opinion on the relationship of AE with the drugs under study.

The investigator must prepare and maintain adequate and accurate case histories that document all observations and other data relevant to the investigation for all participants. The source documentation must be available at the monitoring visit to verify data entered in eCRFs, as needed. The source documentation must also be available for verification by auditors and/or inspectors, as needed.

12.1 Source documentation

The investigator must maintain adequate and accurate source documents on which the case reports for each participant are based. They must be separated and differentiated. These records should include detailed notes on:

- Medical history, before participating in the study;
- Basic identification information, such as demographic data, that links the participant's source documents;
- The results of all diagnostic tests performed, diagnoses made, the therapy provided, and any other data on the clinical condition of the participant;

- The exposure of the participant to the treatment of the study;
- All AEs and pregnancies;
- All special situations;
- The participant's exposure to any concomitant therapy;
- All observations and relevant data about the clinical condition of the participant throughout the study;
- Verbal and written communication with the participant about the treatment of the study (including the risks and benefits of the study); the date of free and informed consent must be recorded in the source documentation.

All data for the study must be available in the source documentation.

12.2 Clinical records

A clinical form is designed to record all the information required by the protocol to be reported on each participant in the clinical study. The investigator is responsible for ensuring the accuracy, integrity, legibility, clarity and punctuality of the data reported in the clinical records of the participants. Reported data transcribed from source documents must be consistent with source documents or discrepancies must be explained. An explanation must be provided for all missing data.

All data from the clinical record and resolutions of the visit should be recorded only by the clinical study team designated by the investigator. The center staff will be properly trained before accessing the EDC system.

Any changes or corrections to a clinical record will be tracked by an audit trail within the EDC system. The audit trail will contain the original data value, new data value, the date it was changed, the user who made the change, and the reason (s) for the change. Clinical records must be completed in a timely manner for the respective visit (e.g., the center should not wait for a monitoring visit before entering data). The data from the medical records and consultations will be tracked and inserted into a clinical database. The database system will be a password-protected secure system with the full audit trail utility.

Participant data will be reviewed through scheduled quality checks, and manually through review of data listings. Data that appears inconsistent, incomplete, or inaccurate will be questioned for clarification by the center. Corrections to the data will be updated in the database and tracked on the audit trail. Concurrent AEs and medications will be encoded using standard health care dictionaries (e.g. MedDRA and WHO Drug Dictionary).

The investigator is responsible for analyzing, verifying and approving all the participant's data (e.g., clinical record and answered questions).

12.3 Retention of records

The investigator must maintain adequate records for the study, including completed medical records, laboratory reports, signed informed consent forms, drug distribution records, reports of adverse events, information on participants who discontinued the study, correspondence with the CEP and research steering committee and other pertinent data. The investigator must retain all

records at the health facilities. The investigator will notify in writing if any study records are transferred outside the research institution after the study is closed.

12.4 Center documentation

The investigator must maintain adequate and accurate records to allow the conduct of the study to be fully documented and the study data to be subsequently ascertained.

13.0 PROCEDURE FOR MODIFYING THE PROTOCOL OR PREMATURE CLOSURE OF THE STUDY

13.1 Deviation from the protocol

- The investigator must not deviate from the protocol without prior written approval, except in medical emergencies. In the event of a medical emergency, the investigator should notify the medical monitor as soon as possible. Any other changes to the protocol should be implemented as an amendment. The criteria for describing protocol deviation(s) and how they will be treated will be documented in the Study Manual.

-

13.2 Amendments to the protocol

- Amendments to the protocol, except when necessary, to eliminate an immediate danger to participants, should be made only with the prior approval of the steering committee. Each applicable regulatory authority and EC must review and approve the amendments before they are implemented. Regulatory authority and EC approvals do not need to be obtained before removing an immediate risk to participants.

-

13.3 Study closure

- The Steering Committee reserves the right to terminate the study in its entirety or at a center at any time. The reasons for termination may include (among others) unsatisfactory registration of participants with respect to quality and / or quantity, the center cannot meet the requirements of the protocol or the GCP or the recording of data is inaccurate and / or incomplete.

- If the study is closed, the steering committee and the investigator must ensure the protection of the participant's interests. Both parties will organize the procedures individually after the analysis and the visit, and according to the study contract.

-

- Based on the data analysis, the DSMC may provide recommendations to suspend the study as directed in the DSMC statute. The steering committee will determine whether the study should be terminated early.

-
- The study may be terminated or suspended at the request of regulatory authorities.
-

14.0 DATA PUBLICATION AND PRESENTATION POLICY

- The data generated from this research protocol belong to the steering committee. No data may be disclosed, published, without the prior consent of the Steering Committee. The confidentiality agreement to be established with the participating clinical sites will determine the publication policy. In compliance with applicable laws and regulations, the sponsor will publicly register and provide all mandatory information regarding this study, including, to the extent and within the required timeframes, a summary of the clinical study data and results.

REFERENCES

1. WHO. Novel Coronavirus–China. 2020a.Disponível em: https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/. Acessado em: 21 de março de 2020.

2. ZHOU P, YANG XL, WANG, XG, HU B, ZHANG L, ZHANG W, et al. Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin. bioRxiv. 2020; doi: https://doi.org/10. 1101/2020.01.22.914952

3. WHO. Novel Coronavirus (2019-nCoV) Situation Report – 11. 2020b. Disponível em: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200131-sitrep-11-ncov.pdf?sfvrsn=de7c0f7_4 . Acessado em: 21 de março de 2020.

4. WHO. Novel Coronavirus(2019-nCoV) Situation Report – 22. 2020. Disponível em: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200211-sitrep-22-ncov.pdf?sfvrsn=fb6d49b1_2 . Acessado em: 21 de março de 2020.

5. GORBALENYA, Alexander E.; BAKER, Susan C.; BARIC, Ralph S.; GROOT, Raoul J. de; DROSTEN, Christian; GULYAEVA, Anastasia A.; HAAGMANS, Bart L.; LAUBER, Chris; LEONTOVICH, Andrey M; NEUMAN, Benjamin W.; PENZAR, Dmitry; PERLMAN, Stanley; POON, Leo L.M.; SAMBORSKIY, Dmitry; SIDOROV, Igor A.; SOLA, Isabel; ZIEBUHR, John. Severe acute respiratory syndrome-related coronavirus: The species and its viruses – a statement of the Coronavirus Study Group. Disponível em: bioRxiv 2020.02.07.937862; doi: https://doi.org/10.1101/2020.02.07.937862 .

6. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [Internet]. World Health Organization. World Health Organization; 2020 [cited 2020Mar19]. Disponível em: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks -at-the-media-briefing-on-covid-19---11-march-2020 Acessado em 21 de Março de 2020.

7. WHO Coronavirus disease 2019 (COVID- 19) Situation report – 62. Pesquisado em 23 de Março de 2020 e disponível em https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200322-sitrep-62-covid-19.pdf?sfvrsn=f7764c46_2

8. LI Q, GUAN X, WU P, WANG X, ZHOU L, TONG Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020. https://doi.org/10.1056/NEJMoa2001316

9. LI R, PEI S, CHEN B, et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2) [published online ahead of print, 2020 Mar 16]. Science. 2020;eabb3221. doi:10.1126/science.abb3221

10. LIU T, HU J, KANG M, LIN L, ZHONG H, XIAO J, et al. Transmission dynamics of 2019 novel coronavirus (2019-nCoV). 2020; doi: https://doi.org/10.1101/2020. 01.25.919787.

11. HUANG C, WANG Y, LI X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [published correction appears in Lancet. 2020 Jan 30;:]. Lancet. 2020;395(10223):497–506. doi:10.1016/S0140-6736(20)30183-5

12. ADHIKARI SP, MENG S, WU YJ, et al. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. Infect Dis Poverty. 2020;9(1):29. Published 2020 Mar 17. doi:10.1186/s40249-020-00646-x.

13. Wu, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA https://doi.org/*10.1001/jama.2020.2648*

14. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. https://doi.org/10.1038/s41586-020-2012-7

15. Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, Zhong W, Hao P (2020) Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its Spike protein for risk of human transmission. Sci China Life Sci. https://doi.org/10.1007/s11427-020-1637-5

16. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Medicine. 2020 Mar 3:1-5. https://doi.org/10.1007/s00134-020-05985-9 .

17. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. Nature medicine. 2005 Aug;11(8):875-9.

18. Drosten C. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N. Engl. J. Med. 2003;348(20):1967–1976. [PubMed] [Google Scholar]

19. Peiris J., Guan Y., Yuen K. Severe acute respiratory syndrome. Nat. Med. 2004;10(12):S88–S97.[PubMed] [Google Scholar]

20. Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, Dawood F.S., Jain S., Finelli L., Shaw M.W., Lindstrom S., Garten R.J., Gubareva L.V., Xu X., Bridges C.B., Uyeki T.M. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N. Engl. J. Med. 2009;360(25):2605–2615.[PubMed] [Google Scholar]

21. Zaki A.M. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N. Engl. J. Med. 2012;367(19):1814–1820. [PubMed] [Google Scholar]

22. US CDC Confirmed 2019-nCoV Cases Globally. https://www.cdc.gov/coronavirus/2019-ncov/locations-confirmed-cases.html#map Availabe at. Acessado em 21 de Março de 2020.

23. Geographical Distribution of 2019-nCov Cases Globally. European Centre for Disease Prevention and Control; 2020. https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases Acessado em 23 de Março de 2020.

24. Zhu N., Zhang D., Wang W. A novel coronavirus from patients with pneumonia in China, 2019. N. Engl. J. Med. 2020;382(8):727–733. [PubMed] [Google Scholar]

25. Zhu N., Zhang D., Wang W. A novel coronavirus from patients with pneumonia in China, 2019. N. Engl. J. Med. 2020;382(8):727–733. [PubMed] [Google Scholar]

26. Hui D.S., Zumla A. Severe acute respiratory syndrome: historical, epidemiologic, and clinical features. Infect. Dis. Clin. 2019;33(4):869–889. [PubMed] [Google Scholar]

27. Abdirizak F., Lewis R., Chowell G. Evaluating the potential impact of targeted vaccination strategies against severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) outbreaks in the healthcare setting. Theor. Biol. Med. Model. 2019;16(1):16.[PMC free article] [PubMed] [Google Scholar]

28. WHO. Novel Coronavirus (2019-nCoV) Situation Report – 63. Disponível em https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200323-sitrep-63-covid-19.pdf?sfvrsn=d97cb6dd_2 Acessado em 23 de Março de 2020.

29. National Institutes of Health, US National Library of Medicine. ClinicalTRials.gov. Disponível em https://clinicaltrials.gov/ct2/results?cond=Covid+19 Acessado em 23 de Março de 2.020.

30. World Health Organization. Statement on the second meeting of the International health regulations (2005) emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV), 2005.

31. COVID-19 clinical trials listed as of Dec 15, 2020. https://www.clinicaltrials.gov/ct2/results?cond=COVID-19. Acessado em 15 de Dezembro de 2020.

32. Raudenbush SW, Bryk AS: Empirical Bayes Meta-Analysis. *Journal of Educational Statistics* 1985, 10(2).

33. Hays RD, Bjorner JB, Revicki DA. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. Qual Life Res. 2009 Sep; 18(7):873-80.

34. Fong, Tamara G et al. “Telephone interview for cognitive status: Creating a crosswalk with the Mini-Mental State Examination.” *Alzheimer's & dementia : the journal of the Alzheimer's Association* vol. 5,6 (2009): 492-7.
35. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Harmonised Guideline. E6(R2): Integrated addendum to ICH E6(R1): guideline for good clinical practice. 2016 Nov 9.
36. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. 2013 Oct.

APPENDICES

Appendix 1. Investigational Products

Depending on the treatment arms, IPs relabelling may be completed at the country level in accordance with local and/or national regulatory requirements.

-

Appendix 1.1 Fluvoxamine

- **Date IP (fluxoxamine) arm added**: December 17, 2020

- **Date IP (fluxoxamine) arm closed:** July 26, 2021

-

- **Fluvoxamine administration:**

  - Dose of 100 mg twice daily for a period of 10 days

- **Placebo administration:**

  - Twice daily for 10 days

- **Rationale for evaluating fluvoxamine**

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) and an S1R receptor agonist[1]. The rationale for considering using fluvoxamine in patients with COVID-19 is that S1R receptor agonists can mitigate excessive inflammation in patients with COVID-19. This and other potential mechanisms by which fluvoxamine can act on COVID-19 are summarized below.

- <u>Anti-inflammatory effects via the S1R – IRE1 route</u>

- Sigma-1 receptor (S1R) is an endoplasmic reticulum (ER) chaperone protein involved in many cellular functions, including regulation of ER stress response / unfolded proteins (UPR) response and inflammation[2]. The S1R protein has been shown to inhibit the ER stress sensor 1α enzyme that requires inositol (IRE1) splicing mediated by XBP1, a key regulator of cytokine production[3]. These anti-inflammatory effects may be the most likely explanation for the beneficial effects of fluvoxamine. In COVID-19, an excessive inflammatory process known as a "cytokine storm" can contribute to the worsening of cardiopulmonary symptoms and complications, which can sometimes occur around the second week of the disease. Fluvoxamine can mitigate this excessive inflammatory response.

In a 2019 study by Rosen, fluvoxamine showed benefit in preclinical models of inflammation and sepsis[4]. In one model, mice were exposed to the Toll-like ligand receptor 4 (TLR4), lipopolysaccharide (LPS), which can trigger an inflammatory response. In another model, a fecal concentrate was injected, which triggers infection and inflammatory response that is usually sub-lethal. Transgenic mice ablated for S1R receptors showed excessive increases in cytokine levels and significantly reduced survival in any of these conditions, suggesting that these receptors inhibit the exacerbated inflammatory response. Wild-type mice not genetically manipulated and exposed to the same inflammatory triggers showed reduced levels of cytokines and increased survival when treated with fluvoxamine (an S1R agonist). In investigating the mechanism underlying this effect, the authors demonstrated that S1R receptors inhibit IRE1 activity, which in turn prevents excessive production of cytokines. In an experiment using human peripheral blood, they also showed that fluvoxamine can reduce LPS-induced cytokine production by human cells. In the case of COVID-19, the S1R agonist action of fluvoxamine may have a similar ability to reduce the excessive inflammatory response induced by viral infection, thus reducing inflammation-mediated organ damage.

- Antiviral action through effects on lysosomes, autophagy and / or endocytosis

Coronaviruses use cathepsin-like proteases, present in the late endosome to facilitate entry into the cell and remodel phagosomes and endoplasmic reticulum membranes, transforming them into "viral replication" sites[5,6]. Both processes require stimulation of endocytosis and mediated autophagy-phagosome pathways and then terminate autophagy before lysosomal fusion. The SARS-CoV-2 Nsp6, Nsp2, Orf7b and Orf9b proteins have been shown to locate and modulate components of the autophagy pathway[7,8]. Additional Nsp6 has been shown to physically associate with S1R[9]. Critically, S1R not only conducts an early stage of autophagy via the IRE1 / UPR pathway but is also essential for lysosomal fusion and to complete autophagy, probably accompanying components of the SNARE complex[10]. It is possible that S1R activation with fluvoxamine may overcome Nsp6 inhibition of S1R to allow autophagy to eliminate SARS-CoV2. Others also recognized targeting the autophagy pathway as a promising strategy for treating SARS-CoV2[11,12].

Chemically, fluvoxamine is a cationic amphiphilic drug (CAD) with log P 3.1 and pKa 9.4 and, together with a variety of antipsychotic and antihistamine drugs, accumulates preferentially in the lysosome. Perhaps because of this, fluvoxamine reaches higher concentrations in the lungs (which are rich in lysosomes) than in the brain[13]. In COVID-19, this may increase the effects of treatment on the airway epithelium[14]. In high doses (10 μM), CADs including fluvoxamine, have been shown to inhibit lysosomal acid sphingomyelinase and cause drug-induced phospholipidosis. This non-specific activity can globally deregulate lipid homeostasis, modulating autophagy via the mTOR nutrient detection pathway[15,16].

- Antiviral effects and prevention of organ damage by regulating the ER stress / UPR response pathway

Some viruses hijack the ER / UPR stress response to achieve viral functions and several studies have suggested that drugs targeting the ER / UPR stress response may be beneficial in the treatment of COVID-19[17,18,19]. S1R agonists (such as fluvoxamine) regulate ER-associated stress. The effects

of the S1R ligand during mediated ER stress and other ER functions can reduce organ dysfunction / damage[20,21].

- Antiplatelet effects (common to all SSRIs)

Platelet hyperactivity can contribute to pathophysiological processes that lead to thrombotic complications in COVID-19. SSRIs can inhibit platelet activation, which can reduce the risk of thrombosis, and these antiplatelet effects can be cardioprotective[22,23].

- Elevation of melatonin levels in the body

The SARS-CoV2 virus can activate the NLRP343 inflammasome, which can contribute to the cytokine storm[24,25]. Melatonin can act on this NLRP3 pathway to reduce inflammation[26,27]. Fluvoxamine inhibits melatonin metabolism, so it can increase the level of melatonin in the body, which can be beneficial in COVID-19[28].

- **Justification of dose / regimen, route of administration and duration of treatment**

The STOP COVID 2 study evaluated fluvoxamine in patients with COVID-19 and showed a potential benefit in reducing complications associated with the disease, suggesting the need for conducting randomized, placebo-controlled studies, since the purpose of the study was to explore this possible therapeutic and therefore with a small number of patients involved[29]. Considering contacts made with the researchers of the STOP COVID study, we chose to adopt the dosage of (100 mg twice a day), different from the initial study, which adopted the dose of 100 mg three times a day, considering the dose maximum allowed by the American drug regulatory agency (FDA). According to the authors, 96% of the participants who used fluvoxamine reached a dose of 200 mg/day (86 out of 90), but only 50% of patients raised the dose to 300 mg/day and this occurred only after 5-6 days of treatment, which may already be out of the risk period for complications. In other words, the study's result suggests that it is not necessary to reach 300 mg/day of fluvoxamine. Reviewing the pharmacokinetics and activity of fluvoxamine to S1R receptors, apparently 200 mg/day is enough to the expected S1R agonist effect. Thus, we chose to consider treatment with fluvoxamine at a dose of 100 mg twice a day and for 10 days, which will cover the period of the most significant risk of COVID-19 worsening.

Risks and precautions related to fluvoxamine
The investigator must be attentive to the administration of investigational drugs in the following situations:

- Participants with depression or psychiatric conditions must be carefully evaluated, and their participation may be allowed if there is no evidence of an uncontrolled condition, worsening or major depression. Patients with severe psychiatric conditions should not participate in this study.
- Participants should eat after using medications. It is not advisable to take the drugs while fasting.
- Patients with a history of seizures can participate if they have no manifestation in the last 60 days and if it is a stable condition, under pharmacological control.

Most of the adverse reactions reported in clinical studies conducted with fluvoxamine are gastrointestinal symptoms, usually mild (nausea, dyspepsia, mild diarrhea, abdominal pain). Other adverse reactions: agitation, anxiety, insomnia, headache, anorexia, palpitations, hyperhidrosis and malaise. Aside from gastrointestinal symptoms, the other symptoms during treatments for less than 30 days are not common.

Fluvoxamine is considered a C risk medication and there are reports of primary pulmonary hypertension, especially when used in the third trimester of pregnancy. These drugs can cause neurological withdrawal symptoms in newborns of mothers using fluvoxamine. It is excreted in breast milk in small amounts and therefore should not be used by breastfeeding mothers.

Prohibited Medications
Throughout the study, the following drugs will be prohibited while the participant is being treated with the study medications: Monoamine Oxide Inhibitors: phenelzine, tranylcypromine, selegiline, isocarboxazid, moclobemide.

Protocol modifications
None
References
1. Narita N, Hashimoto K, Tomitaka S, Minabe Y. Interactions of selective serotonin reuptake inhibitors with subtypes of sigma receptors in rat brain. *Eur J Pharmacol.* 1996;307(1):117-119.

2. Delprat B, Crouzier L, Su TP, Maurice T. At the Crossing of ER Stress and MAMs: A Key Role of Sigma-1 Receptor? *Adv Exp Med Biol.* 2020;1131:699-718.

3. Mori T, Hayashi T, Hayashi E, Su TP. Sigma-1 receptor chaperone at the ER-mitochondrion interface mediates the mitochondrion-ER-nucleus signaling for cellular survival. *PLoS One.* 2013;8(10):e76941

4. Rosen DA, Seki SM, Fernandez-Castaneda A, et al. Modulation of the sigma-1 receptor-IRE1 pathway is beneficial in preclinical models of inflammation and sepsis. *Sci Transl Med.* 2019;11(478).

5. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell.* 2020;181(2):271-280 e278

6. Knoops K, Kikkert M, Worm SH, et al. SARS-coronavirus replication is supported by a reticulovesicular network of modified endoplasmic reticulum. *PLoS Biol.* 2008;6(9):e226.

7. Gassen NC, Papies J, Bajaj T, et al. Analysis of SARS-CoV-2-controlled autophagy reveals spermidine, MK-2206, and niclosamide as putative antiviral therapeutics. *bioRxiv.* 2020:2020.2004.2015.997254.

8. Laurent EMN, Sofianatos Y, Komarova A, et al. Global BioID-based SARS-CoV-2 proteins proximal interactome unveils novel ties between viral polypeptides and host factors involved in multiple COVID19-associated mechanisms. *bioRxiv.* 2020:2020.2008.2028.272955

9. Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature.* 2020;583(7816):459-468.

10. Yang H, Shen H, Li J, Guo LW. SIGMAR1/Sigma-1 receptor ablation impairs autophagosome clearance. *Autophagy.* 2019;15(9):1539-1557.

11. Gorshkov K, Chen CZ, Bostwick R, et al. The SARS-CoV-2 cytopathic effect is blocked with autophagy modulators. *bioRxiv : the preprint server for biology.* 2020:2020.2005.2016.091520.

12. Homolak J, Kodvanj I. Widely available lysosome targeting agents should be considered as potential therapy for COVID-19. *Int J Antimicrob Agents.* 2020;56(2):106044.

13. Daniel WA, Wojcikowski J. Contribution of lysosomal trapping to the total tissue uptake of psychotropic drugs. *Pharmacol Toxicol.* 1997;80(2):62-68.

14. Fung TS, Liu DX. The ER stress sensor IRE1 and MAP kinase ERK modulate autophagy induction in cells infected with coronavirus infectious bronchitis virus. *Virology.* 2019;533:34-44.

15. Kornhuber J, Tripal P, Gulbins E, Muehlbacher M. Functional inhibitors of acid sphingomyelinase (FIASMAs). *Handb Exp Pharmacol.* 2013(215):169-186.

16. Breiden B, Sandhoff K. Emerging mechanisms of drug-induced phospholipidosis. *Biol Chem.* 2019;401(1):31-46.

17. Chan SW. The unfolded protein response in virus infections. *Front Microbiol.* 2014;5:518.

18. Jheng JR, Ho JY, Horng JT. ER stress, autophagy, and RNA viruses. *Front Microbiol.* 2014;5:388.

19. Nabirotchkin S, Peluffo AE, Bouaziz J, Cohen D. Focusing on the Unfolded Protein Response and Autophagy Related Pathways to Reposition Common Approved Drugs against COVID-19. *Preprints.* 2020.

20. Hosszu A, Antal Z, Lenart L, et al. sigma1-Receptor Agonism Protects against Renal Ischemia-Reperfusion Injury. *J Am Soc Nephrol.* 2017;28(1):152-165.

21. Tagashira H, Bhuiyan MS, Fukunaga K. Diverse regulation of IP3 and ryanodine receptors by pentazocine through sigma1-receptor in cardiomyocytes. *Am J Physiol Heart Circ Physiol.* 2013;305(8):H1201-1212.

22. Manne BK, Denorme F, Middleton EA, et al. Platelet gene expression and function in patients with COVID-19. *Blood.* 2020;136(11):1317-1329.

23. Schlienger RG, Meier CR. Effect of selective serotonin reuptake inhibitors on platelet activation: can they prevent acute myocardial infarction? *Am J Cardiovasc Drugs.* 2003;3(3):149-162.

24. Van den Berg DF, Te Velde AA. Severe COVID-19: NLRP3 Inflammasome Dysregulated. *Front Immunol.* 2020;11:1580.

25. Ratajczak MZ, Kucia M. SARS-CoV-2 infection and overactivation of Nlrp3 inflammasome as a trigger of cytokine "storm" and risk factor for damage of hematopoietic stem cells. *Leukemia.* 2020;34(7):1726-1729.

26. Garcia JA, Volt H, Venegas C, et al. Disruption of the NF-kappaB/NLRP3 connection by melatonin requires retinoid-related orphan receptor-alpha and blocks the septic response in mice. *FASEB J.* 2015;29(9):3863-3875.

27. Volt H, Garcia JA, Doerrier C, et al. Same molecule but different expression: aging and sepsis trigger NLRP3 inflammasome activation, a target of melatonin. *J Pineal Res.* 2016;60(2):193-205.

28. Hartter S, Wang X, Weigmann H, et al. Differential effects of fluvoxamine and other antidepressants on the biotransformation of melatonin. *J Clin Psychopharmacol.* 2001;21(2):167-174.

29. Lenze EJ, Mattar C, Zorumski CF. Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19: A Randomized Clinical Trial. JAMA. 2020 Dec 8;324(22):2292-2300. doi: 10.1001/jama.2020.22760.

Appendix 1.2 Ivermectin

- **Date IP (ivermectin) arm added:** December 17, 2020

- **Date IP (ivermectin) arm closed:** July 26, 2021

-

- **Ivermectin administration:**

    - Dose based on weight (Table 1), once daily for 3 consecutive days:

Table 1: Dosing for Ivermectin 6mg Oral PO Tablets

Weight (Kg)	Number of 6 mg Pills	Total Dose (mg)	Dose (mcg/kg)
40-45	3	18	400-450
46-50	3	18	360-391
51-55	4	24	436-470
56-60	4	24	400-428
61-65	4	24	369-393
66-70	5	30	428-450
71-80	5	30	422-375
80-90	6	36	400-450
>91	6	36	Up to 400

Placebo administration:

- Once daily for 3 days

- **Rationale for evaluating ivermectin**

In vitro studies have shown that ivermectin inhibits the replication of many viruses, including influenza, zika, dengue and others. It was also seen that it inhibits the replication of SARS-CoV2 in cultures of infected cells, leading to the absence of almost all viral material within 48 hours. In addition to these, in several animal models, when infected with SARS-CoV2 or similar coronaviruses, the use of ivermectin in several preclinical and clinical studies resulted in a significant drop in viral load and blocked several inflammatory pathways associated with proteolysis, cell lysis and consequent reduction of organ damage[1-9].

Likewise, several in vivo studies with animal models using ivermectin resulted in the activation of several anti-inflammatory pathways, potentiating these mechanisms through the inhibition of several cytokines associated with inflammatory activation as well as the transcription of the nuclear factor-κB (NF- κB), a factor involved in an uncontrolled inflammatory response[10-12].

Some observational studies and open randomized studies with a small number of COVID-19 patients using ivermectin suggest that (1) ivermectin prevents the transmission and development of COVID-19 disease in healthy people exposed to infected patients[13-16]; (2) accelerates clinical recovery, minimizing the evolution to complications in patients with mild and moderate clinical condition if treated soon after symptoms[17-19]; (3) accelerates recovery and prevents admission to

the ICU and death of hospitalized patients[20-23] and, in regions where its use was widespread, (4) it indicates a possible reduction in mortality, however, such studies did not adjust the covariates, nor did they perform a sample calculation that demonstrates supporting the conclusions obtained[24,25]. Such evidence shows the need to study this drug using an adaptive design model and using a robust methodology to verify the real role of this drug in the context of the treatment of COVID-19.

-

- **Justification of dose / regimen, route of administration and duration of treatment**

Several studies using ivermectin for either prophylaxis or treatment purposes have used the drug in a single dose, which ranges from 150-250 μg / kg. We initially proposed to use the same dose of ivermectin that is used to treat ectoparasites, intestinal parasites, parasitic infections. Similar to the studies that used ivermectin as an antiparasitic, we chose to use the fixed dose scheme by weight range. Thus, patients weighing less than 60 kg will receive 12 mg of ivermectin, between 60 to 80 kg will receive the dose of 18 mg and patients weighing over 80 kg will receive the dose of 24 mg of ivermectin. This dose has been shown to be safe in these studies and in studies in patients with COVID-19. The literature data regarding an extra dose are conflicting, and therefore in this study, we will choose to use the single dose.

We recently published articles on the use of ivermectin and found that doses up to 600 mcg/kg/ day are being used to treat some diseases, including lice infestations. In addition, doses of up to 800 mcg/kg/day in patients with onchocerciasis, in countries where this disease has high prevalence[26].

We also conducted an extensive review[27] of the effects of ivermectin as an antiviral agent and regulator of the inflammatory process in various diseases. We also reviewed the pharmacokinetic data of the medication in commonly used doses and in high doses, to assess the safety of the use of these doses. Considering the available evidence, including in patients with COVID-19, this protocol will administer ivermectin at an average dose of 400 mcg/kg/day, not exceeding the dose of 470 mcg/kg/day in a single dose for three consecutive days.

Risks and precautions related to ivermectin
The investigator must be attentive to the administration of investigational drugs in the following situations:

- Participants with depression or psychiatric conditions must be carefully evaluated, and their participation may be allowed if there is no evidence of an uncontrolled condition, worsening or major depression. Patients with severe psychiatric conditions should not participate in this study.
- Participants should eat after using medications. It is not advisable to take the drugs while fasting.
- Patients with a history of seizures can participate if they have no manifestation in the last 60 days and if it is a stable condition, under pharmacological control.

Most adverse reactions reported in clinical studies conducted with ivermectin are related to the digestive system, usually mild gastrointestinal symptoms (nausea, dyspepsia, mild diarrhea,

abdominal pain). Other adverse reactions: dizziness, drowsiness, vertigo and skin allergic reactions can occur in less than 1% of patients.

Ivermectin is considered a C risk medication in pregnancy, and there are no studies evaluating its effect on this population. It is excreted in small amounts through breast milk. The recommendation for the use is only under medical guidance and after the risk / benefit assessment.

Prohibited medications

Throughout the study, the following drugs will be prohibited while the participant is being treated with the study medications:

- Use of iodinated contrasts during treatment until 05 days after the end;
- Use of antiretroviral agents (Treatment of Acquired Immunodeficiency Syndrome-AIDS)
- Sertraline, donepezil.

Protocol modifications

None

References

1. S. C. Atkinson, M. D. Audsley, K. G. Lieu, G. A. Marsh, D. R. Thomas, S. M. Heaton, J. J. Paxman, K. M. Wagstaff, A. M. Buckle, G. W. Moseley, D. A. Jans and N. A. Borg. Recognition by host nuclear transport proteins drives disorder-to-order transition in Hendra virus V. Scientific Reports. 8, 358 (2018).

2. S. N. Y Yang, S. C. Atkinson, C. Wang, A. Lee, M. A. Bogoyevitch, N. A. Borg and D. A. Jans. The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. Antiviral Research. 177, 104760 (2020).

3. V. G.tz, L. Magar, D. Dornfeld, S. Giese, A. Pohlmann, D. H.per, B.-W. Kong, D. A. Jans, M. Beer, O. Haller and M. Schwemmle. Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import. Scientific Reports. 6, 23138 (2016).

4. C. Lv, W. Liu, B. Wang, R. Dang, L. Qiu, J. Ren, C. Yan, Z. Yang and X. Wang. Ivermectin inhibits DNA polymerase UL42 of pseudorabies virus entrance into the nucleus and proliferation of the virus in vitro and vivo. Antiviral Research. 177, 104760 (2020).

5. E. Mastrangelo, M. Pezzullo, T. De Burghgraeve, S. Kaptein, B. Pastorino, K. Dallmeier, X. de Lamballerie, J. Neyts, A. M. Hanson, D. N. Frick, M. Bolognesi and M. Milani. Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. Journal of Antimicrobial Chemotherapy. 67, 1884-1894 (2012).

6. M. Y. F. Tay, J. E. Fraser, W. K. K. Chan, N. J. Moreland, A. P. Rathore, C. Wang, S. G. Vasudevan and D. A. Jans. Nuclear localization of dengue virus (DENV) 1–4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin. Antiviral Research. 99, 301-306 (2013).

7. F. S. Varghese, P. Kaukinen, S. Gl.sker, M. Bespalov, L. Hanski, K. Wennerberg, B. M. Kümmerer and T. Ahola. Discovery of berberine, abamectin and ivermectin as antivirals against chikungunya and other alphaviruses. Antiviral Research. 126, 117-124 (2016).

8. K. M. Wagstaff, H. Sivakumaran, S. M. Heaton, D. Harrich, D. A. Jans. Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Biochemical Journal. 443, 851-856 (2012).

9. C. R. King, T. M. Tessier, M. J. Dodge, J. B. Weinberg, J. S. Mymryk, Inhibition of Human Adenovirus Replication by the Importin α/β1 Nuclear Import Inhibitor Ivermectin. Journal of Virology. 94, e00710-20 (2020).

10. X. Zhang et al., Inhibitory effects of ivermectin on nitric oxide and prostaglandin E2 production in LPS-stimulated RAW 264.7 macrophages. Int Immunopharmacol. 9, 354-359 (2009).

11. X. Ci et al., Avermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen-activated protein kinase activation pathway. Fundam Clin Pharmacol. 23, 449-455 (2009).

12. X. Zhang, Y. Song, X. Ci, N. An, Y. Ju, H. Li, X. Wang, C. Han, J. Cui and X. Deng. Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice. Inflamm Res. 57, 524-529 (2008).

13. Carvallo H. https://clinicaltrials.gov/ct2/show/NCT04425850 (2020).

14. Shouman W. https://clinicaltrials.gov/ct2/show/NCT04422561 (2020).

15. P. Behera et al., https://www.medrxiv.org/content/10.1101/2020.10.29.20222661v1.full (2020).

16. A. Elgazzar et al., https://www.researchsquare.com/article/rs-100956/v2 (2020).

17. Robin RC, Alam RF, Saber S, Bhiuyan E, Murshed R, Alam MT. A case series of 100 COVID-19 positive patients treated with combination of ivermectin and doxycycline. Journal of Bangladesh College of Physicians and Surgeons. 38, Supp 10-15 (2020).

18. Mahmud R. https://clinicaltrials.gov/ct2/show/NCT04523831 (2020).

19. M. S. I. Khan, C. R. Debnath, P. N. Nath, M. A. Mahtab, H. Nabeka, S. Matsuda and S. M. F. Akbar. Ivermectin treatment may improve the prognosis of patients with COVID-19. Archivos de Bronconeumología. 10.1016/j.arbres.2020.08.007 (2020).

20. J. C. Rajter, M. S. Sherman, N. Fatteh, F. Vogel, J. Sacks, J. J. Rajter. Use of ivermectin is associated with lower mortality in hospitalized patients with COVID-19 (ICON study). Chest. 10.1016/j.chest.2020.10.009 (2020).

21. Hashim HA et al.,
https://www.medrxiv.org/content/10.1101/2020.10.26.20219345v1 (2020).

22. M. S. Niaee et al., https://www.researchsquare.com/article/rs-109670/v1 (2020).

23. A. Portmann-Baracco, M. Bryce-Alberti, R. A. Accinelli. Antiviral and anti-inflammatory properties of ivermectin and its potential use in Covid-19. Arch Broncopneumol. July 7, doi: 10.1016/j.arbres.2020.06.011 (2020)

24. A. Portmann-Baracco, M. Bryce-Alberti, R. A. Accinelli. Antiviral and anti-inflammatory properties of ivermectin and its potential use in Covid-19. Arch Broncopneumol. July 7, doi: 10.1016/j.arbres.2020.06.011 (2020)

25. J. J. Chamie. https://www.researchgate.net/publication/344469305 (2020).

26. Smit MR, Ochomo EO, Aljayyoussi G et al. Safety and mosquitocidal efficacy of high-dose ivermectin when co-administered with dihydroartemisinin-piperaquine in Kenyan adults with uncomplicated malaria (IVERMAL): a randomised, double-blind, placebo-controlled trial. Lancet Inf Dis 2018, 18(6): 615-626. DOI:https://doi.org/10.1016/S1473-3099(18)30163-4

27. Hill A, Abdulamir A, Ahmed A et Al. Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection. Research Square, 2020, doi: 10.21203/rs.3.rs-148845/v1. Disponível em https://www.researchsquare.com/article/rs-148845/v1 , Acessado em 07 de Fevereiro de 2021.

Appendix 1.3 Metformin

-
- Date IP (metformin) arm added: December 17, 2020
-
- **Date IP (metformin) arm closed**: April 3, 2021
-
- **Metformin administration:**
  - 750 mg dose twice daily for a period of 10 days

Placebo administration:

- Twice daily for 10 days
-
- **Rationale for choice of metformin**
- Since the emergence of the first cases of viral pneumonia associated with SARS-CoV2 to date, several clinical conditions are associated with the complications that occurred, progression of lower respiratory tract infection, respiratory failure and death. It is believed that such conditions provide the virus with the development of an exacerbated inflammatory response. These clinical conditions are now considered to be risk factors for the worsening of COVID-19. Among these, advanced age is one of the most important and is associated with hypertension, diabetes, coronary artery disease, smoking, obesity.

In this context, obesity stands out, since after adjusted for the other risk factors, obesity appears as an important factor associated with worsening ventilation and the need for artificial ventilation assistance[1]. Patients with body mass index > 25 kg / m^2 or men with excess visceral adipose tissue are at higher risk of needing invasive ventilatory support in the case of COVID-19[2].

Visceral adipocytes secrete several inflammatory pro-mediators and pro-coagulant molecules, including interleukin-6, tumor necrosis factor α (TNF-α) adipokines and D-dimer, with a high production of chemokines being observed in patients with COVID-19 inflammatory and procoagulant agents, which were identified and associated with the pulmonary inflammatory condition of these patients[3,4]. In patients with type 2 diabetes mellitus TNF-α and IL-6 are elevated and IL-10 levels are reduced, there is a direct relationship between these changes and the intensity of insulin resistance observed in these patients[5].

Metformin, a type 2 diabetes medication, decreases levels of TNFα, adipokines and IL-6, and increases levels of IL-10, being these changes observed both in experimental studies and in studies

carried out in patients with type 2 diabetes mellitus and are more evident in women[6-8]. These effects associated with the reduction in circulating adipokines may contribute to minimize the degree of inflammatory response and thus reduce the severity of the disease[9].

Clinical studies have suggested that the clinical complications and mortality in patients with COVID-19 may be lower in patients using metformin, however their observational and retrospective design (analysis of medical records) as well as other studies that do not confirm this association makes it difficult to adopt metformin as part of the treatment of inpatients[10-13]. Recently, an observational study identified metformin as a potential mortality reducer in women[14].

Considering these conflicting findings in the literature and the safety of metformin, there is a need for randomized and prospective studies using this drug in patients with COVID-19.

- **Justification of dose / regimen, route of administration and duration of treatment**

At the time of designing this protocol, there are no registered clinical studies (randomized and double-blind) for the treatment of COVID-19 in its initial phase containing metformin. We chose to use the dose of 750 mg in two daily doses of metformin since most clinical studies in which anti-inflammatory effects are clinically relevant, they used the dose of 500 mg in two doses or 750 mg in two daily doses. We chose to use the extended-release formulation since it causes less adverse gastrointestinal effect and bioavailability is more consistent and stable, which becomes an advantage when offering a uniform serum dose.

-

Risks and precautions related to metformin

The investigator must be attentive to the administration of investigational drugs in the following situations:

- Participants with depression or psychiatric conditions must be carefully evaluated, and their participation may be allowed if there is no evidence of an uncontrolled condition, worsening or major depression. Patients with severe psychiatric conditions should not participate in this study.
- Participants using verapamil should be observed carefully as there may be an increase in serum metformin bioavailability.
- Participants should eat after using medications. It is not advisable to take the drugs while fasting.
- Patients with a history of seizures can participate if they have no manifestation in the last 60 days and if it is a stable condition, under pharmacological control.

The major adverse reactions reported in clinical studies conducted with metformin are gastrointestinal symptoms, usually of mild intensity (dysgeusia, nausea, dyspepsia, mild diarrhea, abdominal pain, lack of appetite). Other adverse reactions: reduced absorption of vitamin B_{12} and lactic acidosis are very rare (incidence less than 1: 10,000).

Metformin is considered a risk B medication in pregnancy and is excreted in minimal amounts through breast milk. Considering the data above, pregnant and breastfeeding women cannot participate in this research.

Prohibited medications
Throughout the study, the following drugs will be prohibited while the participant is being treated with the study medications: use of iodinated contrast agent during treatment and for 5 days following the end of treatment.

Protocol modifications
None

References
1. Simonnet A, Chetboun M, Poissy J, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obesity 2020; 28: 1195–99.

2. Bosch TA, Steinberger J, Sinaiko AR, et al. Identification of sex-specific thresholds for accumulation of visceral adipose tissuein adults. Obesity 2015; 23: 375–82.

3. Bray GA. Medical consequences of obesity. J Clin Endocrinol Metab 2004; 89: 2583–89.

4. Tufan A, Avanoğlu Güler A, Matucci-Cerinic M. COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. Turk J Med Sci 2020; 50: 620–32.

5. Blüher M, Fasshauer M, T.njes A, Kratzsch J, Sch.n MR, Paschke R. Association of interleukin-6, C-reactive protein, interleukin-10 and adiponectin plasma concentrations with measures of obesity, insulin sensitivity and glucose metabolism. Exp Clin Endocrinol Diabetes 2005; 113: 534–37.

6. Matsiukevich D, Piraino G, Lahni P, et al. Metformin ameliorates gender-and age-dependent hemodynamic instability and myocardial injury in murine hemorrhagic shock. Biochim Biophys Acta Mol Basis Dis 2017; 1863: 2680–91.

7. Quan H, Zhang H, Wei W, Fang T. Gender-related different effects of a combined therapy of exenatide and metformin on overweight or obesity patients with type 2 diabetes mellitus. J Diabetes Complications 2016; 30: 686–92.

8. Park JW, Lee JH, Park YH, et al. Sex-dependent difference in the effect of metformin on colorectal cancer-specific mortality of diabetic colorectal cancer patients. World J Gastroenterol 2017; 23: 5196–205.

9. Chen X, Guo H, Qiu L, Zhang C, Deng Q, Leng Q. Immunomodulatory and Antiviral Activity of Metformin and Its Potential Implications in Treating Coronavirus Disease 2019 and Lung Injury. Front Immunol. 2020 Aug 18;11:2056. doi: 10.3389/fimmu.2020.02056.

10. Scheen AJ. Metformin and COVID-19: From cellular mechanisms to reduced mortality. Diabetes Metab. 2020 Nov;46(6):423-426. doi: 10.1016/j.diabet.2020.07.006.

11. Luo P, Qiu L, Liu Y, et al. Metformin treatment was associated with decreased mortality in COVID-19 patients with diabetes in a retrospective analysis. Am J Trop Med Hyg 2020; 103: 69–72.

12. Cariou B, Hadjadj S, Wargny M, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia 2020; 63: 1500–15.

13. Pérez-Belmonte LM, Torres-Peña JD, López-Carmona MD. Mortality and other adverse outcomes in patients with type 2 diabetes mellitus admitted for COVID-19 in association with glucose-lowering drugs: a nationwide cohort study. BMC Med. 2020 Nov 16;18(1):359. doi: 10.1186/s12916-020-01832-2.

14. Bramante CT, Ingraham NE, Murray TA. Metformin and risk of mortality in patients hospitalised with COVID-19: a retrospective cohort analysis. Lancet Health Longevity 2020 Dec 3, S2666-7568 (20) 30033-7. doi: https://doi.org/10.1016/S2666-7568(20)30033-7

Appendix 1.4 Doxazosin

-
- **Date IP (doxazosin) arm added:** 26-Jun-2021
-
- **Date IP (doxazosin) arm closed:** TBD
-
- **Doxazosin administration:**
  - Progressive dosing based on blood pressure, administered once per day for 14 days in form of 2mg tablets as detailed below.

Placebo administration:

  - Progressive dosing based on blood pressure, administered once per day for 14 days in form of placebo tablets as detailed below.

Overview of dosing schedule for active drug and placebo in study arms for <u>patients with initial SBP <120 mmHg:</u>

Doxazosin	Drug	Dose	Total daily dose
Day 1-2	Doxazosin 2 mg	0.5 tablet	1 mg
Day 3-4	Doxazosin 2 mg	1 tablet	2 mg
Day 5-7	Doxazosin 2 mg	2 tablets	4 mg
Day 8-10	Doxazosin 2 mg	3 tablets	6 mg
Day 11-14	Doxazosin 2 mg	4 tablets	8 mg
Placebo			
Day 1-2	Placebo	0.5 tablet	NA
Day 3-4	Placebo	1 tablet	NA
Day 5-7	Placebo	2 tablets	NA
Day 8-10	Placebo	3 tablets	NA
Day 11-14	Placebo	4 tablets	NA

Overview of dosing schedule for active drug and placebo in study arms for <u>participants with initial SBP ≥120 mmHg:</u>

Doxazosin	Drug	Dose	Total daily dose
Day 1-2	Doxazosin 2 mg	1 tablet	2 mg
Day 3-4	Doxazosin 2 mg	2 tablets	4 mg
Day 5-7	Doxazosin 2 mg	3 tablets	6 mg

Day 8-14	Doxazosin 2 mg	4 tablets	8 mg
Placebo			
Day 1-2	Placebo	1 tablet	NA
Day 3-4	Placebo	2 tablets	NA
Day 5-7	Placebo	3 tablets	NA
Day 8-14	Placebo	4 tablets	NA

Specific dosing and dose escalation considerations for doxazosin

First dose (day 1) for participants with SBP <120 mmHg at time of enrollment:

1. The participant will be started on doxazosin 1 mg by mouth daily on the first day of therapy to see whether the medication is tolerated or whether signs or symptoms of hypotension develop (e.g., dizziness, lightheadedness).
    - At the time of enrollment, the participant will be mailed an automated blood pressure cuff and instructions provided on how to monitor and record blood pressure at home at least once daily. The participant will be instructed to on how complete the Blood Pressure Patient Diary.
    - Prior to the first dose, a baseline blood pressure measurement at rest (sitting for at least 5 minutes prior to measurement) should be recorded.
    - The participant should be counseled about possible adverse effects of doxazosin and advised what measures to take should symptoms of hypotension, namely, dizziness and lightheadedness develop. The participant should be counseled that mild lightheadedness with rapid change of position is not uncommon. Accordingly, they should be instructed to slowly change position and take 30 seconds to move from supine to a sitting position, from a sitting to standing position, and from standing to ambulation (until they completed the dose escalation protocol and know that their current dose is tolerated). Participants should be counseled that caution should be taken when getting up and walking to the bathroom at night since they are at increased risk of syncope, falling, and injury. Participants should be counseled to sit down to urinate until they have completed the dose escalation protocol and they have tolerated stable doses for several days.
2. Blood pressure should be measured and recorded prior to the first dose on day 2 (24 hours after the first dose): if the participant remains asymptomatic (e.g., no intolerable lightheadedness or dizziness after standing up, no [near-]fainting, no confusion), the participant will be continued on 1 mg by mouth daily.
3. Blood pressure measurement on day 3 (prior to the first dose): if the participant remains asymptomatic, the dose will be increased to 2 mg by mouth daily.
4. Blood pressure measurement on day 5 (prior to the first dose): if the participant remains asymptomatic, the dose will be increased to 4 mg by mouth daily.
5. Blood pressure measurement on day 8 (prior to the first dose): if the participant remains asymptomatic, the dose will be increased to 6 mg by mouth daily.
6. Blood pressure measurement on day 11 (prior to the first dose): if the participant remains asymptomatic, the dose will be increased to 8 mg by mouth daily.
7. Participants will continue on this dose (or the highest tolerated dose) for the rest of the study unless they develop signs or symptoms of hypotension that warrants dose reduction.
8. The maximum dose of doxazosin in this study is 8 mg by mouth daily.

- If the SBP is <90 mmHg on repeat spot measurement ***and*** the participant is symptomatic of hypotension (e.g., intolerable lightheadedness or dizziness when standing up, [near-]fainting, confusion, new blurred vision), the next dose of doxazosin should be postponed ***until symptoms resolve***, and the participant instructed to continue with the highest previously tolerated dose (not dose escalated). For participants with low baseline blood pressure of ≤90/50 mmHg who are not symptomatic (prior to starting first dose of drug or placebo), a drop of 10 mmHg or more of systolic blood pressure should trigger dose adjustment to the highest previously tolerated dose (i.e., dose on which the systolic blood pressure was not 10 mmHg below the baseline measurement and on which the participant had no symptoms of hypotension).
- An attempt to introduce the higher dose can be made if the participant remains asymptomatic on the highest previously tolerated dose for 24 hours.
- Repeated occurrences of postural dizziness should trigger drug dose reduction of doxazosin.
- Treatment is discontinued after 14 days of treatment.

First dose (day 1) for participants with SBP ≥120 mmHg at time of enrollment:

1. The participant will be started on doxazosin 2 mg by mouth daily on the first day of therapy to see whether the medication is tolerated or whether signs or symptoms of hypotension develop (e.g., dizziness, lightheadedness).
    - At the time of enrollment, the participant will be mailed an automated blood pressure cuff and instructions provided on how to monitor and record blood pressure at home at least once daily. The participant will be instructed to on how complete the Blood Pressure Patient Diary.
    - Prior to the first dose, a baseline blood pressure measurement at rest (sitting for at least 5 minutes prior to measurement) should be recorded.
    - The participant should be counseled about possible adverse effects of doxazosin and advised what measures to take should symptoms of hypotension, namely, dizziness and lightheadedness develop. The participant should be counseled that mild lightheadedness with rapid change of position is not uncommon. Accordingly, they should be instructed to slowly change position and take 30 seconds to move from supine to a sitting position, from a sitting to standing position, and from standing to ambulation (until they completed the dose escalation protocol and know that their current dose is tolerated). Participants should be counseled that caution should be taken when getting up and walking to the bathroom at night since they are at increased risk of syncope, falling, and injury. Participants should be counseled to sit down to urinate until they have completed the dose escalation protocol and they have tolerated stable doses for several days.

2. The blood pressure should be measured and recorded prior to the first dose on day 2 (24 hours after the first dose): if the participant remains asymptomatic (e.g. no intolerable lightheadedness or dizziness after standing up, no [near-]fainting, no confusion), the participant will be continued on 2 mg by mouth daily.
3. Blood pressure measurement on day 3 (prior to the first dose): if the participant remains asymptomatic, the dose will be increased to 4 mg by mouth daily.
4. Blood pressure measurement on day 5 (prior to the first dose): if the participant remains asymptomatic, the dose will be increased to 6 mg by mouth daily.

5. Blood pressure measurement on day 8 (prior to the first dose): if the participant remains asymptomatic, the dose will be increased to 8 mg by mouth daily.
6. Participants will continue on this dose (or the highest tolerated dose) for the rest of the study unless they develop signs or symptoms of hypotension that warrants dose reduction.
7. The maximum dose of doxazosin in this study is 8 mg by mouth daily.
    - If the SBP is <90 mmHg on repeat spot measurement *and* the participant is symptomatic of hypotension (e.g., intolerable lightheadedness or dizziness when standing up, [near-]fainting, confusion, new blurred vision), the next dose of doxazosin should be postponed *until symptoms resolve*, and the participant instructed to continue with the highest previously tolerated dose (not dose escalated). For participants with low baseline blood pressure of ≤90/50 mmHg who are not symptomatic (prior to starting first dose of drug or placebo), a drop of 10 mmHg or more of systolic blood pressure should trigger dose adjustment to the highest previously tolerated dose (i.e., dose on which the systolic blood pressure was not 10 mmHg below the baseline measurement and on which the participant had no symptoms of hypotension).
    - An attempt to introduce the higher dose can be made if the participant remains asymptomatic on the highest previously tolerated dose for 24 hours.
    - Repeated occurrences of postural dizziness should trigger drug dose reduction of doxazosin.
    - Treatment is discontinued after 14 days of treatment.

Rational for the use of doxazosin for the treatment of COVID-19

In early stages of infection with SARS-CoV-2, an appropriate immune response is initiated against the virus, as occurs against similar coronavirus infections SARS-CoV-1 and MERS-CoV[22,23]. In a subset of patients, the disease course can progress to a dysregulated immune state characterized by systemic hyperinflammation ("cytokine storm syndrome")[20,22,24,25]. This state can manifest clinically as ARDS, shock, and multi-organ failure. Resulting mortality equals or exceeds 50% in this population[26,27]. Furthermore, the profile of immune dysregulation of COVID-19 shares similarities with Cytokine Release Syndrome (CRS) seen as an adverse effect of cellular immunotherapies, including CAR-T cell therapy[46–49]. Interventions that address this subset of patients are critically needed. Current approaches are limited to still experimental immunosuppressive therapies in patients who already developed advanced disease[15,17,28]. Disease-modifying therapies that address the underlying pathophysiology and *prevent* progression to the hyperinflammatory state will be essential for mitigating morbidity and mortality due to COVID-19 on a population level[20].

Some recent studies showed that CRS observed with bacterial infections, CAR-T cells, and other T cell-activating therapies is accompanied by a surge in catecholamines[63]. Catecholamines enhance inflammatory injury by augmenting the production of IL-6 and other cytokines through a self-amplifying feed-forward loop in immune cells (macrophages and T cells) that requires alpha-1 adrenergic receptor signaling[19,63]. Other studies have demonstrated in animal models that production of catecholamines from immune cells increases downstream cytokine production and enhances inflammatory lung injury whereas blockade of catecholamine signaling decreases lung inflammation[64,65]. Prophylactic inhibition of catecholamine synthesis by treatment with metyrosine, a tyrosine hydroxylase antagonist, reduced levels of catecholamines and cytokine responses and resulted in markedly increased survival following various inflammatory stimuli in

mice[63]. Similar protection against a hyper-inflammatory stimulus was observed after prazosin administration[63], demonstrating that alpha-1 adrenergic receptor antagonism can also prevent cytokine storm in mice.

Additional studies have explored the effects of alpha-adrenergic blockade in prevention or protection of inflammatory cascades and cytokine-induced injuries. In models of pulmonary edema that are characterized by inflammation and neutrophil accumulation, adrenergic blockade with phentolamine or prazosin attenuated the increase of proinflammatory cytokines in the lung and peripheral blood, and resulted in restoration of normal fluid transport capacity of alveolar epithelium after hemorrhagic shock[66,67]. In a model of brainstem encephalitis, early alpha-1 adrenergic receptor blockade allowed for preservation of cardiac output, reversed neutrophil infiltration in lungs, and prevented hemorrhagic pulmonary edema[68,69]. Prazosin was also found to suppress the clinical and histological expression of experimental autoimmune encephalomyelitis in preclinical models[70–72]. In a mouse model of ischemia-reperfusion injury, prazosin administration led to a decrease in the expression levels of IL-6, TNF-α, IL-10, and IL-1, and prevented mortality[73]. In humans, prazosin is a first-line treatment in scorpion envenomation, a process that involves dysregulated inflammatory responses that can progress to ARDS[74]. Expression of alpha-1 adrenergic receptors are increased during sepsis[75], and catecholamine levels are elevated in septic shock[76]. Finally, alpha-1 adrenergic receptor antagonism has been shown to block cytokine production in human peripheral blood mononuclear cells from patients with juvenile polyarticular arthritis, and treatment with doxazosin abrogated any catecholamine-augmented secretion of IL-6[19].

Together, these findings offer a rationale for studying alpha-1 adrenergic receptor antagonists such as doxazosin or prazosin in the prophylaxis of patients with COVID-19. Prospective, randomized clinical trials of alpha-1 adrenergic receptor antagonists administered prior to the onset of severe symptoms, as proposed herein, are needed to assess their utility in preventing CSS and reducing morbidity and mortality in patients with COVID-19[20]. Prazosin has a significant shorter half-life than doxazosin mesylate (2-3 hours versus 22 hours, respectively)[77,78]. As such, doxazosin mesylate may facilitate dosing in the outpatient setting, increase compliance, and thereby reduce subtherapeutic episodes[79]. While we have used prazosin in preclinical models of cytokine storm, doxazosin – like prazosin – inhibits all three alpha-1 adrenergic receptor subtypes[80]. Since doxazosin does not inhibit alpha-2 adrenergic receptors (which do not mediate the desired immune-modulatory effects) and binds all three alpha-1 adrenergic receptors as a pure antagonist (and not as an inverse agonist)[63,81,82], use of doxazosin may have an even more favorable safety profile. This is supported by clinical trials with cross-over design comparing doxazosin to the prostate-selective alpha-1 adrenergic receptor antagonist tamsulosin, which did not show significant differences in blood pressure-related adverse events.

- <u>Benefit on mortality in patients with COVID-19</u>

In a cohort of patients with COVID-19, use of any α1-AR antagonist, compared to non-users, was associated with a 18% lower incidence of death compared to non-users (OR=0.73, p≤0.001, n=22,847). Strikingly, use of doxazosin, a non-selective α1-AR antagonist like prazosin used in preclinical studies of cytokine storm, resulted in a 74% lower incidence of death (OR=0.23, p=0.028) (Figure 2). The findings in the VA cohort are moreover consistent with preliminary data

from high-risk patients with kidney transplants in the United Kingdom who developed COVID-19. In these patients, baseline use of doxazosin was associated with a reduced risk of requiring hospitalization (use in patients requiring hospitalization 18% vs 55% in patients not requiring hospitalization, p=0.019) (data not shown). In unpublished data from New York City, baseline use of any α1-AR antagonist was associated with significantly reduced mortality, showing a OR for death of 0.26 (p=0.002) for patients age 45-65 with confirmed α1-AR antagonist use as an inpatient and OR of 0.451 (p=0.003) in patients age 55-75. A similar trend was observed in older patients. Mirroring findings from pre-clinical models, these data suggest a strong clinical rationale to study alpha-1 adrenergic receptor antagonists for the prevention of states of local and systemic immune dysregulation. In patients with COVID-19, Bettegowda *et al.* expect that pre-emptive treatment with doxazosin will decrease the risk of developing severe complications of disease (e.g. ARDS, cytokine storm, and death) and reduce morbidity should they develop.

- Justification of dose / regimen, route of administration and duration of treatment

Doxazosin is approved for the treatment of benign prostatic hyperplasia and arterial hypertension, either alone or in combination with other drugs. The initial dose of doxazosin is 1 mg daily to establish tolerability, with therapeutic target dosages most commonly employed ranging from 1 mg to 16 mg by mouth daily[77]. Clinical trial data suggest a significant increase in adverse events (orthostasis) at doses >8 mg PO daily[77].

The minimal effective dose of doxazosin to prevent hyperinflammation has not been established. In pre-clinical models of preventing hyperinflammation in mice, a total daily dose equivalent to ~10 mg of prazosin in humans was used (equivalent to ~10 mg of doxazosin)[63].

Real-world retrospective data from patients using doxazosin for blood pressure control and/or benign prostatic hyperplasia provide best evidence of required doses to observe clinical meaningful benefit in preventing mechanical ventilation or death with lower respiratory tract infection. In preliminary data from high-risk patients with kidney transplants who developed COVID-19, baseline use of doxazosin was associated with a reduced risk of requiring hospitalization (use in patients requiring hospitalization 18% vs 55% in patients not requiring hospitalization, p=0.019, unpublished data). Doses of doxazosin used for blood pressure control in this high-risk cohort of patients with COVID-19 ranged from 2 mg to 8 mg by mouth daily. These data suggest that doxazosin doses of 8 mg or less daily can be sufficient to show substantial clinical benefit in humans.

Since some of the blood pressure-related side effects of doxazosin are thought to be dose-dependent, with significant increase in frequency at doses >8 mg daily[77], this trial uses dose escalation of doxazosin over a period of 8 days to achieve a target treatment dose of 8 mg daily. Given that lower doses are likely to also provide benefit, this trial allows for individualized dosing based on the highest tolerated daily dose of doxazosin identified following the prescribed dose escalation protocol.

-

Risks and precautions related to doxazocin

As with all alpha-1 adrenergic receptor antagonists, doxazosin may cause hypotension and rarely syncope. In most cases, this is believed to be due to an excessive postural hypotensive effect. Postural hypotension with or without symptoms (e.g., dizziness) may develop within a few hours following administration of doxazosin. However, infrequently, symptomatic postural hypotension has also been reported later than a few hours after dosing. As with other alpha-blockers, there is a potential for syncope, especially after the initial dose or after an increase in dosage strength.

Concomitant administration of doxazosin with a PDE-5 inhibitor can result in additive blood pressure lowering effects and symptomatic hypotension.

If syncope occurs, the participant should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and, in most cases, does not recur after the initial period of therapy or during subsequent dose titration.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and light-headedness. The participant should be cautioned about these possible adverse effects and advised what measures to take should they develop. The participant should also be cautioned to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed.

Men should be advised of the possibility of priapism and to seek immediate medical attention if symptoms occur.

Should overdosage lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the participant in the supine position. If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressors should then be used. Renal function should be monitored and supported as needed. Laboratory data indicate doxazosin is not dialysable because it is protein bound.

If a dose of doxazosin is missed for more than 1 hour or if a participant vomits after the dose, the dose should be skipped, and dosing should resume at the next scheduled dose.

Prohibited medications

Throughout the study, the following drugs will be prohibited while the participant is being treated with the study medications:

1. Systemic or inhaled glucocorticoids at time of enrollment, use of rituximab, use of alpha-1 adrenergic receptor antagonists, combined alpha-1/beta- adrenergic receptor antagonists, sotalol, clonidine, phosphodiesterase type 5 inhibitors, nitrates, asenapine, alpha-methyldopa.
2. Recent history of any exposure to investigational medications targeting COVID-19. If the patient is hospitalized, no investigational drug will be re-initiated during or after hospitalization until the end of the study (day 14).
3. Use of alpha-1 adrenergic receptor antagonists, combined alpha-1 / beta-adrenergic receptor antagonists, sotalol, clonidine, type 5 phosphodiesterase inhibitors, nitrates, asenapine, alpha-methyldopa.

4. Severe side effects: boceprevir- Hepatitis B/Hepatitis C Agents; HCV Protease Inhibitors
5. Serious side effects: sildenafil, tamsulosin, vardenafil, yohimbe
6. Mild interactions: brimonidine, butcher's broom, ethanol, lofexidine, phenylephrine, tizanidine, treprostinil.

Protocol modifications

Participants randomized to a 14-day treatment regimen (i.e. doxazocin or corresponding placebo) will receive an automatic blood pressure measurement device so that they may measure their blood pressure prior to taking the study medication each day. Participants will record their daily blood pressure in a diary and discuss it with the research personnel at each follow-up visit. On visit day 14, the participant will make a copy (photo) of the diary and send it through social media applications to the research personnel.

Additional exclusion criteria:

Known history of orthostatic hypotension, unexplained history of syncope, postural orthostatic tachycardia syndrome (POTS), neutrally-mediated hypotension (last year), heart failure (NYHA III or IV), myocardial infarction (within 3 months of screening), stable or unstable angina, coronary bypass surgery (within 3 months of screening), stroke (within 3 months of screening), symptomatic carotid disease, or moderate to severe mitral or aortic stenosis.

REFERENCES:

1. Zhou, F. *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet* S0140673620305663 (2020) doi:10.1016/S0140-6736(20)30566-3.
2. Baud, D. *et al.* Real estimates of mortality following COVID-19 infection. *Lancet Infect Dis* (2020) doi:10.1016/S1473-3099(20)30195-X.
3. CEBM Global Covid-19 Case Fatality Rates. https://www.cebm.net/global-covid-19-case-fatality-rates (2020).
4. Wu, Z. & McGoogan, J. M. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* (2020) doi:10.1001/jama.2020.2648.
5. Korean Society of Infectious Diseases *et al.* Report on the Epidemiological Features of Coronavirus Disease 2019 (COVID-19) Outbreak in the Republic of Korea from January 19 to March 2, 2020. *J. Korean Med. Sci.* **35**, e112 (2020).
6. Guan, W.-J. *et al.* Clinical Characteristics of Coronavirus Disease 2019 in China. *N. Engl. J. Med.* (2020) doi:10.1056/NEJMoa2002032.
7. Chen, T. *et al.* Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* **368**, m1091 (2020).
8. Ruan, Q., Yang, K., Wang, W., Jiang, L. & Song, J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* (2020) doi:10.1007/s00134-020-05991-x.
9. Qin, C. *et al.* Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clinical Infectious Diseases* ciaa248 (2020) doi:10.1093/cid/ciaa248.
10. Mehta, P. *et al.* COVID-19: consider cytokine storm syndromes and immunosuppression. *The Lancet* (2020) doi:https://doi.org/10.1016/S0140-6736(20)30628-0.

11. Chen, G. *et al.* Clinical and immunologic features in severe and moderate Coronavirus Disease 2019. *J. Clin. Invest.* (2020) doi:10.1172/JCI137244.
12. Huang, C. *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet* **395**, 497–506 (2020).
13. Chen, X. *et al.* Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely associated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. *medRxiv* 2020.02.29.20029520 (2020) doi:10.1101/2020.02.29.20029520.
14. Liu, T. *et al. The potential role of IL-6 in monitoring severe case of coronavirus disease 2019*. http://medrxiv.org/lookup/doi/10.1101/2020.03.01.20029769 (2020) doi:10.1101/2020.03.01.20029769.
15. Xu, X. *et al.* Effective treatment of severe COVID-19 patients with tocilizumab. *PNAS* (2020) doi:10.1073/pnas.2005615117.
16. Luo, P. *et al.* Tocilizumab treatment in COVID-19: a single center experience. *J. Med. Virol.* (2020) doi:10.1002/jmv.25801.
17. Sanofi: Press Releases, Monday, April 27, 2020. *https://www.sanofi.com/en/media-room/press-releases/2020/2020-04-27-12-58-00* https://www.sanofi.com/media-room/press-releases/2020/2020-04-27 12-58-00 2022288.
18. Staedtke, V. *et al.* Disruption of a self-amplifying catecholamine loop reduces cytokine release syndrome. *Nature* **564**, 273–277 (2018).
19. Heijnen, C. J. *et al.* Functional alpha 1-adrenergic receptors on leukocytes of patients with polyarticular juvenile rheumatoid arthritis. *J. Neuroimmunol.* **71**, 223–226 (1996).
20. Konig, M. F. *et al.* Preventing cytokine storm syndrome in COVID-19 using α-1 adrenergic receptor antagonists. *J. Clin. Invest.* (2020) doi:10.1172/JCI139642.
21. Dong, E., Du, H. & Gardner, L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis* (2020) doi:10.1016/S1473-3099(20)30120-1.
22. Siddiqi, H. K. & Mehra, M. R. COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal. *The Journal of Heart and Lung Transplantation* S105324982031473X (2020) doi:10.1016/j.healun.2020.03.012.
23. Li, G. *et al.* Coronavirus infections and immune responses. *J Med Virol* **92**, 424–432 (2020).
24. Mehta, P. *et al.* COVID-19: consider cytokine storm syndromes and immunosuppression. *The Lancet* S0140673620306280 (2020) doi:10.1016/S0140-6736(20)30628-0.
25. McGonagle, D., Sharif, K., O'Regan, A. & Bridgewood, C. The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. *Autoimmunity Reviews* 102537 (2020) doi:10.1016/j.autrev.2020.102537.
26. Arentz, M. *et al.* Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *JAMA* (2020) doi:10.1001/jama.2020.4326.
27. Vital Surveillances: The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020. http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51 (2020).
28. Cavalli, G. *et al.* Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *The Lancet Rheumatology* S2665991320301272 (2020) doi:10.1016/S2665-9913(20)30127-2.
29. Wan, S. *et al.* Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). *medRxiv* 2020.02.10.20021832 (2020) doi:10.1101/2020.02.10.20021832.

30. Wu, C. *et al.* Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* (2020) doi:10.1001/jamainternmed.2020.0994.
31. Liu, J. *et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients*. http://medrxiv.org/lookup/doi/10.1101/2020.02.16.20023671 (2020) doi:10.1101/2020.02.16.20023671.
32. Blanco-Melo, D. *et al.* Imbalanced host response to SARS-CoV-2 drives development of COVID-19. *Cell* 46.
33. He, X. *et al.* Integrative Bioinformatics Analysis Provides Insight into the Molecular Mechanisms of 2019-nCoV. *medRxiv* 2020.02.03.20020206 (2020) doi:10.1101/2020.02.03.20020206.
34. Xu, Y. *et al.* Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nat Med* (2020) doi:10.1038/s41591-020-0817-4.
35. Channappanavar, R. & Perlman, S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol* **39**, 529–539 (2017).
36. Wong, C. K. *et al.* Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin. Exp. Immunol.* **136**, 95–103 (2004).
37. Mahallawi, W. H., Khabour, O. F., Zhang, Q., Makhdoum, H. M. & Suliman, B. A. MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile. *Cytokine* **104**, 8–13 (2018).
38. He, L. *et al.* Expression of elevated levels of pro-inflammatory cytokines in SARS-CoV-infected ACE2+ cells in SARS patients: relation to the acute lung injury and pathogenesis of SARS. *J. Pathol.* **210**, 288–297 (2006).
39. Cai, X. *An Insight of comparison between COVID-19 (2019-nCoV disease) and SARS in pathology and pathogenesis*. https://osf.io/hw34x (2020) doi:10.31219/osf.io/hw34x.
40. Kim, E. S. *et al.* Clinical Progression and Cytokine Profiles of Middle East Respiratory Syndrome Coronavirus Infection. *J Korean Med Sci* **31**, 1717 (2016).
41. Lew, T. W. K. Acute Respiratory Distress Syndrome in Critically Ill Patients With Severe Acute Respiratory Syndrome. *JAMA* **290**, 374 (2003).
42. Ramos-Casals, M., Brito-Zerón, P., López-Guillermo, A., Khamashta, M. A. & Bosch, X. Adult haemophagocytic syndrome. *Lancet* **383**, 1503–1516 (2014).
43. Karakike, E. & Giamarellos-Bourboulis, E. J. Macrophage Activation-Like Syndrome: A Distinct Entity Leading to Early Death in Sepsis. *Front Immunol* **10**, 55 (2019).
44. Seguin, A., Galicier, L., Boutboul, D., Lemiale, V. & Azoulay, E. Pulmonary Involvement in Patients With Hemophagocytic Lymphohistiocytosis. *Chest* **149**, 1294–1301 (2016).
45. Crayne, C. B., Albeituni, S., Nichols, K. E. & Cron, R. Q. The Immunology of Macrophage Activation Syndrome. *Front. Immunol.* **10**, 119 (2019).
46. Brudno, J. N. & Kochenderfer, J. N. Toxicities of chimeric antigen receptor T cells: recognition and management. *Blood* **127**, 3321–3330 (2016).
47. Hay, K. A. *et al.* Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor–modified T-cell therapy. *Blood* **130**, 2295–2306 (2017).
48. Neelapu, S. S. *et al.* Chimeric antigen receptor T-cell therapy — assessment and management of toxicities. *Nat Rev Clin Oncol* **15**, 47–62 (2018).
49. Moore, J. B. & June, C. H. Cytokine release syndrome in severe COVID-19. *Science* **368**, 473–474 (2020).

50. Gritti, G. *et al. Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support*. http://medrxiv.org/lookup/doi/10.1101/2020.04.01.20048561 (2020) doi:10.1101/2020.04.01.20048561.
51. Perricone, C. *et al.* The anti-viral facet of anti-rheumatic drugs: Lessons from COVID-19. *J Autoimmun* (2020) doi:10.1016/j.jaut.2020.102468.
52. Dienz, O. *et al.* Essential role of IL-6 in protection against H1N1 influenza virus by promoting neutrophil survival in the lung. *Mucosal Immunol* **5**, 258–266 (2012).
53. Karnowski, A. *et al.* B and T cells collaborate in antiviral responses via IL-6, IL-21, and transcriptional activator and coactivator, Oct2 and OBF-1. *J Exp Med* **209**, 2049–2064 (2012).
54. Rose-John, S., Winthrop, K. & Calabrese, L. The role of IL-6 in host defence against infections: immunobiology and clinical implications. *Nat Rev Rheumatol* **13**, 399–409 (2017).
55. Ritchie, A. I. & Singanayagam, A. Immunosuppression for hyperinflammation in COVID-19: a double-edged sword? *The Lancet* S0140673620306917 (2020) doi:10.1016/S0140-6736(20)30691-7.
56. Schett, G., Sticherling, M. & Neurath, M. F. COVID-19: risk for cytokine targeting in chronic inflammatory diseases? *Nat Rev Immunol* **20**, 271–272 (2020).
57. Russell, C. D., Millar, J. E. & Baillie, J. K. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *The Lancet* **395**, 473–475 (2020).
58. Arabi, Y. M. *et al.* Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. *Am. J. Respir. Crit. Care Med.* **197**, 757–767 (2018).
59. Lee, N. *et al.* Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. *J. Clin. Virol.* **31**, 304–309 (2004).
60. Emanuel, E. J. *et al.* Fair Allocation of Scarce Medical Resources in the Time of Covid-19. *N Engl J Med* NEJMsb2005114 (2020) doi:10.1056/NEJMsb2005114.
61. Truog, R. D., Mitchell, C. & Daley, G. Q. The Toughest Triage — Allocating Ventilators in a Pandemic. *N Engl J Med* NEJMp2005689 (2020) doi:10.1056/NEJMp2005689.
62. Zumla, A., Hui, D. S., Azhar, E. I., Memish, Z. A. & Maeurer, M. Reducing mortality from 2019-nCoV: host-directed therapies should be an option. *The Lancet* **395**, e35–e36 (2020).
63. Staedtke, V. *et al.* Disruption of a self-amplifying catecholamine loop reduces cytokine release syndrome. *Nature* **564**, 273–277 (2018).
64. Flierl, M. A. *et al.* Phagocyte-derived catecholamines enhance acute inflammatory injury. *Nature* **449**, 721–725 (2007).
65. Flierl, M. A. *et al.* Upregulation of Phagocyte-Derived Catecholamines Augments the Acute Inflammatory Response. *PLoS ONE* **4**, e4414 (2009).
66. Rassler, B. Contribution of α - and β -Adrenergic Mechanisms to the Development of Pulmonary Edema. *Scientifica (Cairo)* **2012**, 829504 (2012).
67. Laffon, M., Lu, L. N., Modelska, K., Matthay, M. A. & Pittet, J. F. alpha-adrenergic blockade restores normal fluid transport capacity of alveolar epithelium after hemorrhagic shock. *Am. J. Physiol.* **277**, L760-768 (1999).
68. Lu, W.-H. *et al.* Different impacts of α- and β-blockers in neurogenic hypertension produced by brainstem lesions in rat. *Anesthesiology* **120**, 1192–1204 (2014).
69. Degos, V. & London, M. J. Timing is everything in protecting the heart and lungs in a 'sympathetic storm': α before β? *Anesthesiology* **120**, 1069–1071 (2014).
70. Brosnan, C. F. *et al.* Prazosin, an alpha 1-adrenergic receptor antagonist, suppresses experimental autoimmune encephalomyelitis in the Lewis rat. *Proc. Natl. Acad. Sci. U.S.A.* **82**, 5915–5919 (1985).

71. Brosnan, C. F., Sacks, H. J., Goldschmidt, R. C., Goldmuntz, E. A. & Norton, W. T. Prazosin treatment during the effector stage of disease suppresses experimental autoimmune encephalomyelitis in the Lewis rat. *J. Immunol.* **137**, 3451–3456 (1986).
72. Goldmuntz, E. A., Brosnan, C. F. & Norton, W. T. Prazosin treatment suppresses increased vascular permeability in both acute and passively transferred experimental autoimmune encephalomyelitis in the Lewis rat. *J. Immunol.* **137**, 3444–3450 (1986).
73. Wang, L. *et al.* Prazosin protects myocardial cells against anoxia-reoxygenation injury via the extracellular signal‑regulated kinase signaling pathway. *Mol Med Rep* **17**, 2145–2152 (2018).
74. Chippaux, J.-P. Emerging options for the management of scorpion stings. *Drug Des Devel Ther* **6**, 165–173 (2012).
75. Hwang, T. L., Lau, Y. T., Huang, S. F., Chen, M. F. & Liu, M. S. Changes of alpha 1-adrenergic receptors in human liver during intraabdominal sepsis. *Hepatology* **20**, 638–642 (1994).
76. Jan, S.-L. *et al.* Urine catecholamines in children with severe Enterovirus A71 infection: comparison with paediatric septic shock. *Biomarkers* **24**, 277–285 (2019).
77. Drug Approval: Cardura (doxazosin mesylate) NDA #019668.
78. Drug Approval: Minipress (prazosin hydrochloride) NDA #017442.
79. Smith, C. & Koola, M. M. Evidence for Using Doxazosin in the Treatment of Posttraumatic Stress Disorder. *Psychiatr Ann* **46**, 553–555 (2016).
80. Schwinn, D. A. & Roehrborn, C. G. α1-Adrenoceptor subtypes and lower urinary tract symptoms. *Int J Urol* **15**, 193–199 (2008).
81. prazosin | Ligand page | IUPHAR/BPS Guide to PHARMACOLOGY. https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?tab=biology&ligandId=503.
82. doxazosin | Ligand page | IUPHAR/BPS Guide to PHARMACOLOGY. https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?tab=biology&ligandId=7170.
83. Product Information: CARDURA(R) oral tablets, doxazosin mesylate oral tablets. Roerig, New York, NY, Revised: 3/2019.

Appendix 1.5 IFN Lambda

-
- **Date IP (IFN lambda) arm added**: June 30, 2021
-
- **Date IP (IFN lambda) arm closed:** TBD
-
- **Lambda administration:**
  - One subcutaneous injection of 180μg peginterferon lambda (0.45ml) in the lower abdomen during the baseline/randomization visit
-
- **Placebo administration:**
  - One subcutaneous injection of normal saline (0.45ml) in the lower abdomen during the baseline/randomization visit

Rational for choice of IFN-lambda (interferon type III) for the treatment of COVID-19
The cornerstone of the innate antiviral immune response is the interferon (IFN) system. Sensing of viral infection leads to production of Type I (alpha, beta) and Type III (lambda) IFNs, which drive a potent antiviral response through the induction of a wide array of genes, collectively known as IFN-stimulated genes (ISGs)[3]. Both Type I and Type III IFNs signal through the JAK-STAT pathway to drive ISG induction with comparable antiviral activity, however their systemic effects differ markedly due to the use of distinct receptors with different tissue distributions[3]. The Type I IFN receptor is highly expressed on all cells in the body, whereas the IFN-lambda receptor is primarily expressed on epithelial cells with high expression in lung, intestine and liver and very limited expression in hematopoietic and central nervous system cells[4]. As a result, production of or treatment with Type I IFNs leads to significant off-target effects, which have limited the safety, tolerability and ultimately clinical use of this class of agents. Interferon-alpha was used with some evidence of clinical efficacy in a pilot trial during the first SARS outbreak[5], however, concerns have been raised of the toxicity of a Type I IFN for COVID. IFN-lambda was developed as a therapeutic to overcome the toxicity seen with IFN alfa and beta. Conjugation of IFN- lambda to polyethylene glycol increases the half-life and allows for once weekly dosing. Peginterferon-lambda has been studied in Phase 1, 2 and 3 clinical trials in over 3000 patients for the treatment of hepatitis C virus[6], hepatitis B virus[7] and most recently hepatitis delta virus[8] infections, showing comparable antiviral activity to IFN- alfa, but with a much better safety and tolerability profile.

IFN- lambda is particularly attractive for acute respiratory disease due to the high expression of the IFN- lambda receptor in lung epithelia. In vitro and mouse studies have shown that IFN-lambda is strongly induced in influenza, SARS-CoV-1 and other respiratory virus infections but induction is limited by SARS-CO-V-2 infection[9]. IFN- lambda treatment has been shown to be

highly effective in a mouse model of severe influenza A infection. In mice challenged with influenza A, pre-treatment with either IFN-alfa or IFN- lambda prevented mortality[10]. However, when the IFNs were given after infection, IFN-alpha worsened outcome, whereas IFN- lambda treatment improved survival[10]. IFN- lambda is particularly attractive as a treatment strategy for SARS-CoV-2 infection because in addition to its anticipated effect in the lung, the IFN- lambda receptor is highly expressed in intestine and liver[11], which would address intestinal and hepatic involvement documented in patients with COVID-19[1, 12]. Furthermore, the lack of the lambda receptor on hematopoietic cells limits concerns about the potential to worsen cytokine storm syndrome[13].

Based on the above rationale, trials of peginterferon-lambda to treat COVID-19 have been undertaken. Feld *et al.* completed a small randomized trial showing that treatment with peginterferon-lambda in outpatients with mild to moderate COVID-19 accelerated viral decline and was very well tolerated[14]. In this placebo-controlled trial, 60 outpatients with COVID-19 were randomized to a single dose of peginterferon lambda 180 µg SC or saline placebo. Treatment with peginterferon-lambda accelerated viral decline compared to placebo. After controlling for baseline viral load, those receiving peginterferon lambda had a 4.12 (95%CI 1.15-16.7, p=0.029) higher odds of viral clearance by Day 7 compared to those who received placebo. The probability of clearance by Day 7 increased with increasing baseline viral load.

A similar study was conducted by Jagannathan *et al.* in 120 outpatients with mild COVID-19[15]. Although the study did not confirm a significant antiviral effect of peginterferon lambda, likely because of recruitment of participants late in the course of their infection (median Ct at baseline of 30), they documented a very similar safety profile with no concerning safety signals. Enriching the population for those with high viral loads and/or at higher risk of severe COVID-19 would be useful to target therapy to those most likely to benefit.

- **Justification of dose / regimen, route of administration and duration of treatment**

In this clinical trial, we are administering 180 µg of peginterferon lambda in a single dose to be administered on the day of randomization. This dose has been used in two clinical studies in COVID-19 phase II and with no evidence of significant adverse reactions. An additional 3 clinical trials are being planned for the use of interferon lambda at the same dose.

<u>Clinical activity in chronic HCV and HBV infection</u>
The antiviral activity of peginterferon lambda against HCV was demonstrated in 2 Phase 2 studies that investigated peginterferon lambda regimens in naive individuals receiving chronic HCV treatment. In these two studies approximately 700 patients used the drug for up to 12 months. The SVR model established the optimal duration of treatment for Phase 3 studies, but did not differentiate between the 120 and 180 mg dose. Hruska et al (2014) described the derivation of regression models for 12 weeks of virologic response in treatment and safety outcomes in 120, 180, and 240 μg peginterferon lambda with ribavirin. In patients with HCV genotypes 1 or 4, there was a significant relationship (P=0.024) between undetectable HCV-RNA at Week 4 and exposure to peginterferon lambda (AUC or Cmax), with the greatest difference between adjacent dose levels between the exposure ranges of 180 and 120 μg. The risk of 3-4 aminotransferase levels or bilirubin elevations relative to a peginterferon alfa-2a/ribavirin control was related to peginterferon

lambda exposure for all patients, and the greatest increase between adjacent dose levels was seen for 240 versus 180 μg. Anemia and neutropenia events were inferior to control at all doses and exposures.

Based on these findings, Phase 3 studies for HCV were designed to evaluate fixed doses of 180 μg peginterferon lambda in combination with ribavirin and a direct acting antiviral for 24-48 weeks in genotypes 1 or 4 or 12-24 weeks in genotypes. genotypes 2 or 3 of HCV.

Taking these clinical trials as a reference, as well as the two clinical trials already carried out and published on the use of this drug in patients with COVID-19, we selected a dose of 180 μg in a single subcutaneous dose at the time of randomization.

Risks and precautions related to peginterferon lambda
Peginterferon lambda has been generally well tolerated in clinical studies. Most adverse reactions reported are self-limiting and resolve with non-pharmacological or anti-inflammatory measures. Mild flu-like symptoms (chills, myalgia, fever) can occur in up to 20% of patients, with the same statistic for gastrointestinal symptoms (nausea, vomiting). Reactions at the injection site (pain, local erythema, edema and itching) can occur in up to 30% of patients. Other common symptoms are headache and nausea, usually within 24 hours of taking the medication. Elevations in liver enzymes (> 3x normal value) and hematological enzymes occur in 1% and 4% of patients with repeated use of peginterferon lambda, respectively. Less than 1% of treated patients have urticaria and angioedema, which are reversed with corticosteroid therapy and antihistamines. Depression and suicidal ideation can occur in up to 2% of patients and arise after repeated and prolonged administration of the drug. Other than transient grade 1-2 aminotransferase elevations, no laboratory AEs were seen more frequently with peginterferon-lambda than placebo in the two outpatient studies of this agent for COVID-19 to date.

Female participants should not be pregnant or lactating at the time of exposure to peginterferon lambda. Female and male subjects should use appropriate measures to avoid pregnancy during the administration of peginterferon lambda and for up to 3 months after the last dose of peginterferon lambda.

- Contraindications

- Hypersensitivity to peginterferon lambda
- Pregnancy
- Lactation
- History of or current decompensated cirrhosis (ascites, hepatic encephalopathy, variceal hemorrhage)

Prohibited medications
Given that only a single dose will be used in this trial, concern about drug interactions is limited compared to other settings in which peginterferon lambda is given weekly for long durations.

Protocol modifications

- Participants allocated to receive subcutaneous injections will remain under observation for 30 minutes following treatment administration for monitoring of immediate adverse events.

-

- Participants allocated to receive subcutaneous injections will have a face-to-face visit with research personnel on Day 7.

REFERENCES:

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 02 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5
2. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med*. Mar 2020;doi:10.1056/NEJMoa2001282
3. Hermant P, Michiels T. Interferon-λ in the context of viral infections: production, response and therapeutic implications. *J Innate Immun*. 2014;6(5):563-74. doi:10.1159/000360084
4. Syedbasha M, Egli A. Interferon Lambda: Modulating Immunity in Infectious Diseases. *Front Immunol*. 2017;8:119. doi:10.3389/fimmu.2017.00119
5. Loutfy MR, Blatt LM, Siminovitch KA, et al. Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: a preliminary study. *JAMA*. Dec 2003;290(24):3222-8. doi:10.1001/jama.290.24.3222
6. Muir AJ, Arora S, Everson G, et al. A randomized phase 2b study of peginterferon lambda-1a for the treatment of chronic HCV infection. *J Hepatol*. Dec 2014;61(6):1238-46. doi:10.1016/j.jhep.2014.07.022
7. Chan HLY, Ahn SH, Chang TT, et al. Peginterferon lambda for the treatment of HBeAg-positive chronic hepatitis B: A randomized phase 2b study (LIRA-B). *J Hepatol*. May 2016;64(5):1011-1019. doi:10.1016/j.jhep.2015.12.018
8. Etzion O, Hamid S, Lurie Y, et al. End of study results from LIMT HDV study: 36% durable virologic response at 24 weeks post-treatment with pegylated interferon lambda monotherapy in patients with chronic hepatitis delta virus infection. presented at: International Liver Congress 2019; 2019; Vienna, Austria.
9. Crotta S, Davidson S, Mahlakoiv T, et al. Type I and type III interferons drive redundant amplification loops to induce a transcriptional signature in influenza-infected airway epithelia. *PLoS Pathog*. 2013;9(11):e1003773. doi:10.1371/journal.ppat.1003773
10. Davidson S, McCabe TM, Crotta S, et al. IFNλ is a potent anti-influenza therapeutic without the inflammatory side effects of IFNα treatment. *EMBO Mol Med*. 09 2016;8(9):1099-112. doi:10.15252/emmm.201606413

11. Mordstein M, Neugebauer E, Ditt V, et al. Lambda interferon renders epithelial cells of the respiratory and gastrointestinal tracts resistant to viral infections. *J Virol*. Jun 2010;84(11):5670-7. doi:10.1128/JVI.00272-10
12. Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut*. Mar 2020;doi:10.1136/gutjnl-2020-320926
13. Zhang W, Du RH, Li B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. *Emerg Microbes Infect*. 2020;9(1):386-389. doi:10.1080/22221751.2020.1729071
14. Feld J, C K, Biondi M, et al. **Peginterferon-lambda for the treatment of COVID-19 in outpatients: A phase 2, placebo-controlled randomized trial**. *Lancet Respiratory Medicine*. 2020;*In Press*
15. P J, Andrews J, Bonilla H, et al. Peginterferon Lambda-1a for treatment of outpatients with uncomplicated COVID-19: a randomized placebo-controlled trial. *MedRxiv*. 2020;
16. Regeneron. Regeneron's REGN-COV2 antibody cocktail reduced viral levels and improved symptoms in non-hospitalized COVID-19 patients Accessed September 29, 2020, 2020. https://investor.regeneron.com/news-releases/news-release-details/regenerons-regn-cov2-antibody-cocktail-reduced-viral-levels-and
17. Guedj J, Dahari H, Pohl RT, Ferenci P, Perelson AS. Understanding silibinin's modes of action against HCV using viral kinetic modeling. *J Hepatol*. May 2012;56(5):1019-24. doi:10.1016/j.jhep.2011.12.012
18. Guedj J, Dahari H, Rong L, et al. Modeling shows that the NS5A inhibitor daclatasvir has two modes of action and yields a shorter estimate of the hepatitis C virus half-life. *Proc Natl Acad Sci U S A*. Mar 2013;110(10):3991-6. doi:10.1073/pnas.1203110110
19. Larios OE, Coleman BL, Drews SJ, et al. Self-collected mid-turbinate swabs for the detection of respiratory viruses in adults with acute respiratory illnesses. *PLoS One*. 2011;6(6):e21335. doi:10.1371/journal.pone.0021335
20. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature*. Sep 2009;461(7262):399-401. doi:10.1038/nature08309
21. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature*. Oct 2009;461(7265):798-801. doi:10.1038/nature08463
22. Prokunina-Olsson L, Muchmore B, Tang W, et al. A variant upstream of IFNL3 (IL28B) creating a new interferon gene IFNL4 is associated with impaired clearance of hepatitis C virus. *Nat Genet*. Feb 2013;45(2):164-71. doi:10.1038/ng.2521

Appendix 2. Country Specific
Appendix 2.1 Brazil
Clinical sites in Brazil will follow the master protocol, with the following exceptions:
1. Clinical sites in Brazil will use the following eligibility criteria:

Inclusion criteria:

1. Patients over 18 years old with the ability to provide free, prior and informed consent;
2. Patients presenting to an outpatient care setting with an acute clinical condition compatible with COVID-19 and symptoms beginning within 07 days from the randomization date;
3. Patients over 18 and with at least ONE of the following criteria:
    a. Age ≥ 50 years (does not need any other risk criteria)
    b. *Diabetes mellitus* requiring oral medication or insulin
    c. Systemic arterial hypertension requiring at least 01 oral medication for treatment
    d. Known cardiovascular diseases (heart failure, congenital heart disease, valve disease, coronary artery disease, cardiomyopathies being treated, clinically manifested heart disease and with clinical repercussion)
    e. Symptomatic lung disease and / or being treated (emphysema, fibrosing diseases)
    f. Symptomatic asthma patients requiring chronic use of agents to control symptoms
    g. Obesity, defined as BMI> 30 kg / m2 (weight and height information provided by the patient)
    h. Transplant patients
    i. Patient with stage IV chronic kidney disease or on dialysis
    j. Patients with documented fever at screening > 38º C
    k. Patients with at least one of the following symptoms: cough, dyspnea, dependent ventilatory chest pain or myalgia with limited daily activities (to a maximum of 25% of enrollment)
    l. Immunosuppressed patients / using corticosteroid therapy (equivalent to a maximum of 10 mg of prednisone per day) and / or immunosuppressive therapy
    m. Patients with a history of cancer in the last 05 years or undergoing current cancer treatment
4. Patient with positive rapid test for SARS-CoV2 antigen performed at the time of screening or patient with positive SARS-CoV2 diagnostic test within 07 days of symptom onset (antigen test or RT-PCR).
5. Willingness to use the proposed investigational treatment and follow the research procedures.

Exclusion criteria:

1. Diagnostic examination for SARS-CoV2 negative associated with acute flu-like symptoms (patient with negative test taken early and becoming positive a few days later is eligible, if he/she is <07 days after the onset of flu-like symptoms).
2. Patients with acute respiratory condition compatible with COVID-19 treated in the primary care and with hospitalization need.
3. Patients with acute respiratory condition due to other causes.
4. Patients who have received at least one dose of vaccination for SARS-CoV2 > 14 days prior to screening.
5. Dyspnea secondary to other acute and chronic respiratory causes or infections (e.g., decompensated COPD, acute bronchitis, pneumonia, primary pulmonary arterial hypertension).
6. Patients in need of hospitalization due to COVID-19.
7. Patients using serotonin receptor inhibitors including donepezil or sertraline.
8. Exclusion criteria valid only for oral medication administration arms:
    i. The continued use of monoamine oxide inhibitors (phenelzine, tranylcypromine, selegiline, isocarboxazide, moclobemide);
    ii. Use of antiretroviral agents (Treatment of Acquired Immunodeficiency Syndrome - AIDS);
    iii. Use of alpha-1 adrenergic receptor antagonists, combined alpha-1 / beta-adrenergic receptor antagonists, sotalol, clonidine, phosphodiesterase type 5 inhibitors, nitrates, asenapine, alpha-methyldopa;
    iv. History of hypersensitivity or serious adverse reactions to the use of quinazolines (Prazosin, Doxazosin or Terazosin).
9. Patients with severe psychiatric disorders including schizophrenia, uncontrolled bipolar disorders, major depression with suicidal ideation.
10. Pregnant or breastfeeding patients.
11. History of severe ventricular cardiac arrhythmia (ventricular tachycardia, patients with recovered ventricular fibrillation) or long QT syndrome.
12. Known history of orthostatic hypotension, unexplained history of syncope, postural orthostatic tachycardia syndrome (POTS), neurally mediated hypotension (last year), heart failure (NYHA III or IV), myocardial infarction (within 3 months of screening), stable or unstable angina, coronary bypass surgery (within 3 months of screening), stroke (within 3 months of screening), symptomatic carotid disease, or moderate to severe mitral or aortic stenosis.
13. Surgical procedure or use of contrast planned to occur during treatment or up to 05 days after the last dose of the study medication.
14. Current daily and / or uncontrolled alcoholism or drug addiction, what, in the investigator's view, could compromise participation in the study.
15. History of seizures in the last month or uncontrolled seizure.
16. Clinical history of moderate to severe hepatic deficiency or liver cirrhosis or Child-Pugh C classification.
17. Patients with known severe degenerative neurological diseases and / or severe mental illness.
18. Inability of the patient or representative to give informed consent or adhere to the procedures proposed in the protocol.

19. Any clinical conditions, including psychiatric conditions, which in the investigator's view could impede the use of the research drugs.
20. Known hypersensitivity and / or intolerance to IPs or taking medications contraindicated by IPs.
21. Inability to take oral medications.

2. Brazilian Version of the Telephone Interview for Cognitive State Assessment – Modified Version (TICS-M)

Summary of Changes to the Protocol

Protocol Version	Protocol Date	Randomization	Treatment Arms
1.0	17-Dec-2021	3:1	• Ivermectin (low dose) • Metformin • Fluvoxamine • Placebo
2.0	15-Feb-2021	3:1 2:1 (Metformin was stopped on 3-Apr-2021)	• Ivermectin (high dose) • Metformin • Fluvoxamine • Placebo
3.0	20-April-2021	4:1	• Ivermectin • Fluvoxamine • Doxazosin • Placebo
4.0	21-May-2021	5:1	• Ivermectin • Fluvoxamine • Doxazosin • Interferon Lambda • Interferon Beta 1A (added to the protocol not activated) • Placebo

All protocol versions can be found at the following link:
togethertrial.com/protocols

Cytel **Statistical Analysis Plan**

Sponsor:	McMaster University		
Protocol:	TOGETHER MP		
Document Version No.:	2.0	**Document Date:**	22-June-2021

Table of Contents

Sponsor:	McMaster University		
Protocol:	TOGETHER MP		
Document Version No.:	2.0	**Document Date:**	22-June-2021

Protocol

Repurposed Approved Therapies for Outpatient Treatment of Patients with Early-Onset COVID-19 and Mild Symptoms

Protocol Number:	TOGETHER Trial Master Protocol V3.0
(Version Date)	June 22, 2021
Name of Test Drug:	Refer to the Master Protocol Appendix 1
Phase:	3
Methodology:	A placebo-controlled adaptive randomized platform trial
Sponsor:	McMaster University, Hamilton, Ontario
Principal Investigators:	Dr. Edward Mills Email: edward.mills@cytel.com Dr. Gilmar Reis Email: administrador@cardresearch.org
Document Date:	June 22, 2021
Document Version:	TOGETHER MP SAP Version 2.0

Sponsor:	McMaster University		
Protocol:	TOGETHER MP		
Document Version No.:	2.0	**Document Date:**	22-June-2021

SIGNATURE PAGE

Protocol Title:	Master Clinical Trial Protocol: Repurposed Approved Therapies for Outpatient Treatment of Patients with Early-Onset COVID-19 and Mild Symptoms
Principal Investigators:	Edward Mills Email: edward.mills@cytel.com Gilmar Reis, CardResearch Email: administrador@cardresearch.org
Protocol Number:	Version 3.0
Document Date/Version:	June 22, 2021
Cytel, Inc. Author: **Ofir Harari** Cytel, Inc.	Signature: DocuSigned by: Ofir Harari 617D6BE49659440... Date: 6/22/2021
Cytel, Inc. Author: **Hinda Ruton** Cytel, Inc.	Signature: DocuSigned by: Hinda Ruton 05965639190F4FC... Date: 6/22/2021

Sponsor:	McMaster University		
Protocol:	TOGETHER MP		
Document Version No.:	2.0	**Document Date:**	22-June-2021

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

Principal Investigator Signatory:
Edward Mills

Email: edward.mills@cytel.com

Signature: DocuSigned by: Ed Mills 5CDFE860A63E45A...
Date: 6/22/2021

Principal Investigator Signatory:
Gilmar Reis

Email: administrador@cardresearch.org

Signature: DocuSigned by: Gilmar Reis 4DEB36C09947460...
Date: 6/22/2021

Sponsor:	McMaster University		
Protocol:	TOGETHER MP		
Document Version No.:	2.0	**Document Date:**	22-June-2021

ABBREVIATIONS

Abbreviation	Definition
ATC	Anatomic Therapeutic Class
BUGS	Bayesian inference using Gibbs Sampling
CER	Control Event Rate
COVID-19	Coronavirus disease 2019
CRF	Case report form
CSR	Clinical Study Report
ICH	International Council Harmonisation
IP	Investigational Product
ITT	Intention-To-Treat
JAGS	Just Another Gibbs Sampler
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per-Protocol
PROMIS	Patient-Reported Outcomes Management Information System
RRR	Relative Risk Reduction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAP	Statistical Analysis Plan
SOC	System/Organ/Class
WHO	World Health Organization

Sponsor:	McMaster University		
Protocol:	TOGETHER MP		
Document Version No.:	2.0	**Document Date:**	22-June-2021

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

The TOGETHER master protocol represents an adaptive platform trial for treating persons with early severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection at high risk of disease progression who do not require hospital admission. The TOGETHER trial will start with a placebo as a control in the clinical evaluation of repurposed investigational products (IPs) to treat SARS-CoV-2. Other affordable candidate drug regimens that can be repurposed for coronavirus disease 2019 (COVID-19) may be considered and incorporated into this trial as an additional arm (s). If an intervention is shown to be effective, this design will allow the replacement of the placebo group with the effective intervention as the comparator. To ensure timely results the master protocol allows for data from trials that follow a similar protocol as TOGETHER to be included in the analyses.

1.2. Objectives of Statistical Analysis

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data to answer the study objective(s). We provided the populations for analysis, data handling rules, statistical methods, and data presentation formats. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

2. STUDY DESIGN

2.1. Synopsis of Study Design

TOGETHER trial is an international multicenter adaptive randomized platform trial for the early treatment of SARS-CoV-2 infection in high-risk adults not requiring hospital admission. The TOGETHER Trial will start with a placebo as a control in the clinical evaluation of three IPs. This

Sponsor:	McMaster University		
Protocol:	TOGETHER MP		
Document Version No.:	2.0	**Document Date:**	22-June-2021

trial is designed as a platform trial design that can add new arms onto the trial under standardized eligibility criteria, outcomes, and measurements, as the other experimental interventions. Other affordable candidate drug regimens that can be repurposed for COVID-19 may also be considered for this trial. The decision to add new therapeutic strategies will be based on external findings with local stakeholders' consultations.

2.2. Randomization Methodology

Please refer to the master protocol for the randomization methodology.

2.3. Stopping Rules and Unblinding

Stopping rules are outlined in section 4.3. In the case of potential recruitment challenges, it is important to reach statistical conclusions about the experimental treatments as fast as possible; therefore, continual Bayesian learning methods have been prepared and simulated to prepare for potential protocol changes. These simulation results are described in section 4.3.

2.4. Study Procedures

Please refer to the study protocol for the study procedures.

2.5 Efficacy and Safety Variables

2.5.1 Efficacy Variables

Primary endpoint:

- Emergency room visit due to the clinical worsening of COVID-19 (defined as participants remaining under observation for > 6 hours) within 28 days of randomization

- Hospitalization due to the progression of COVID-19 (defined as worsening of viral pneumonia) and/or complications within 28 days of randomization

Secondary endpoints:

- All cause mortality, including COVID-19 related mortality
- Reduction of viral load after randomization (D3 and D7)
- Number of days with respiratory symptoms
- Time to hospitalization/urgent care due to the progression of COVID-19
- Time to hospitalization for any cause
- Hospitalization for any cause
- Time to death
- Time to clinical improvement
- Symptoms as assessed by the WHO Clinical Worsening Scale
- Health-related quality of life as assessed by PROMIS global health scale (“Global-10”) scores (day 14 and day 28)
- Cognitive ability at day 28 (Telephone Interview for Cognitive Status)
- Adverse events
- Adverse reactions to the study medications
- Adherence with the IPs

Exploratory endpoints:

- Number of days spent in an intensive care unit
- Number of days on invasive mechanical ventilation
- Number of days of hospitalization
- Number of days of hospitalization in the ward
- Number of days using oxygen therapy

2.5.1 Safety Variables

Safety assessments performed during the study included measurement of vital signs and monitoring of adverse events and adverse IP reactions.

3. SUBJECT POPULATIONS

3.1. Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data:

- Intent-to-treat (ITT) Population: The ITT Population includes all randomized patients.
- Per-protocol (PP) Population: Randomized patients who adhered to more than 80% of the assigned therapy.
- Safety Population: Randomized patients who received at least 1 dose of IP.

The ITT Population is typically the primary population for the analysis of efficacy parameters. A subset of efficacy parameters will be evaluated for the PP population (see Section 4.6).

The Safety Population is typically the primary population for the analysis of safety endpoints.

3.2. Protocol Violations

At the discretion of the sponsor, major protocol violations as determined by a review of the data prior to unblinding of the study results and the conduct of statistical analyses may result in the removal of a subject's data from the per-protocol population.

Sponsor:	McMaster University		
Protocol:	TOGETHER MP		
Document Version No.:	2.0	**Document Date:**	22-June-2021

The sponsor, or designee, will be responsible for producing the final protocol violation file (formatted as a Microsoft Excel file), in collaboration with Cytel and the data monitoring group as applicable; this file will include a description of the protocol violation, and clearly identify whether or not this violation warrants exclusion from the Efficacy Evaluable Population. This file will be finalized prior to hard database lock.

All protocol violations will be presented in the data listings. The major protocol violations will include:

- Failure to obtain informed consent prior to initiation of study-related procedures
- A research subject met withdrawal criteria or wished to withdraw from the study but was not withdrawn
- Inappropriate IP dosage
- Inappropriate randomization
- Inadvertent loss of samples or data
- Other major violation

The minor protocol deviations include:

- Concomitant medication
- Non-compliance to study procedures
- Visit made outside of the visit window

Sponsor:	McMaster University		
Protocol:	TOGETHER MP		
Document Version No.:	2.0	**Document Date:**	22-June-2021

4. STATISTICAL METHODS

4.1. Sample Size Justification

The sample size of 681 patients per arm has been chosen for each experimental group to achieve 80% power with 0.05 two-sided Type 1 error for a pairwise comparison against the control to detect minimum treatment efficacy defined by 37.5% relative risk reduction (RRR) of preventing hospitalization assuming a control event rate (CER) of 15%.

4.1.1. Sample Size Re-Assessment

Sample size re-assessment procedures are described in section 4.3.

4.2. General Statistical Methods and Data Handling

4.2.1. General Methods

All output will be incorporated into Microsoft Excel or Word files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the mean, median, standard deviation, minimum and maximum values will be presented. Time to event data will be summarized using Bayesian Kaplan-Meier estimates.

Bayesian bivariate analysis will be performed on secondary efficacy endpoints outlined in 0. Summary statistics will be presented, as well as their corresponding 95% credible intervals.

4.2.2. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.4), unless otherwise noted. Medical History and adverse events will be coding using MedDRA version 23.0. Concomitant medications will be coded using World Health Organization (WHO) Drug dictionary (version March 1, 2020).

4.2.3. Statistical Analysis Details

4.2.3.1. Bayesian inference for dichotomous outcomes with covariate adjustment

Here we may use the generalized linear model framework for binary outcome with the logistic link function, namely

$$y_i \sim \text{Binom}(1, p_i)$$

with

$$\log \frac{p_i}{1-p_i} = x_i^{\mathrm{T}}\beta + \gamma T_i,$$

using the same notations as before. Assigning a noninformative prior distribution $p(\beta, \gamma) \propto 1$, the logarithm of the posterior distribution (after some simple algebra) is given by

$$\log p(\beta, \gamma|\boldsymbol{y}) = \log p(\beta, \gamma) + \sum_{\mathrm{i}=1}^{\mathrm{n}} \log p(y_i|\beta, \gamma)$$

$$= \sum_{i=1}^{n} \{y_i(x_i^T\beta + \gamma T_i) - log[1 + exp(x_i^T\beta + \gamma T_i)]\}, (1)$$

and a random sample from $p(\beta, \gamma|\boldsymbol{y})$ may then be drawn using Markov Chain Monte Carlo (MCMC) such as the Metropolis-Hastings algorithm[1] using (5**Error! Reference source not found.** o r Gibbs sampling using any software for Hierarchical Bayesian modeling such as BUGS[2] or JAGS[3]. Inference on the treatment effect will then follow the same procedure as in the numeric case. The treatment effects on dichotomous outcomes will be estimated using R.

4.2.3.2. Bayesian inference for time-to-event outcomes with covariate adjustment

We assume here that the data satisfies the Cox proportional hazards assumption, that is –

$$\log h(t; x, T, \beta, \gamma) = \log h_0(t) + x^{\mathrm{T}}\beta + \gamma T,$$

where $h_0(t)$ is the baseline hazard function and $h(t; x, T, \beta, \gamma)$ is the hazard function of an individual with covariate vector x who was assigned to treatment T, evaluated at time t.

We model the baseline hazard as a piecewise constant function

$$h_0(t; \boldsymbol{\lambda}) = \sum_{j=1}^{J} \lambda_j \, \mathbb{I}\big(t \in (a_{j-1}, a_j]\big) \quad (1)$$

as in Ibrahim et al.[4] for $\lambda_1, \ldots \lambda_J \geq 0$ and some partition $a_0 = 0 < a_1 < \cdots < a_J = t_{max}$ of the real line with t_{max} the end of the follow-up period. This induces the baseline survival function

$$S_0(t; \boldsymbol{\lambda}) = -\sum_{j=1}^{J} \lambda_j \, (t - a_{j-1}) \mathbb{I}\big(t \in (a_{j-1}, a_j]\big), \quad (2)$$

and, denoting $\boldsymbol{t} = [t_1, \ldots, t_n]^{\mathrm{T}}$ the vector of event times, the log-likelihood function is given by

$$\ell(\boldsymbol{t}; \beta, \gamma, \boldsymbol{\lambda}) = \sum_{i=1}^{n} [(1 - \delta_i) log \; h_0(t_i; \boldsymbol{\lambda}) + {x_i}^T \beta + \gamma T_i + \log S_0(t_i; \boldsymbol{\lambda}) + \exp({x_i}^T \beta + \gamma T_i)], \quad (3)$$

where δ_i is an indicator assuming the value of 1 if the i^{th} observation was right-censored and 0 otherwise. We may then assign an improper, independent prior $p(\beta, \gamma, \boldsymbol{\lambda}) \propto \prod_{j=1}^{J} \lambda_j^{-1}$, and proceed to generate an MCMC sample from the posterior distribution, using the log-posterior

$$\log p(\beta, \gamma, \boldsymbol{\lambda} | \boldsymbol{t}) = \text{const} + \ell(\boldsymbol{t}; \beta, \gamma, \boldsymbol{\lambda}) - \sum_{j=1}^{J} \log \lambda_j$$

within a Metropolis-Hastings scheme. Inference on treatment efficacy, as always, will be based on the $100(1 - \alpha)\%$ credible interval for γ.

The treatment effects on time-to-event outcomes will be estimated using R.

4.2.3.2.1. Checking for proportional hazards assumption for time-to-event analyses

The proportional hazards assumption will first be checked visually inspecting the Kaplan-Meier plots of the survival function versus the survival time. Plots of log(-log(survival)) versus log(survival) will also be generated to check the proportional hazards assumption.

4.2.4. Multiple Comparisons/Multiplicity

All subgroup analyses are considered exploratory for this stage of the TOGETHER trial and thus do not require adjustment for multiplicity. Treatment comparisons in focus are solely experimental versus placebo comparisons and for each treatment a matching placebo exists. Thus, all placebo comparisons can be considered approximately independent and therefore not requiring multiplicity adjustments. Lastly, multiplicity due to repeated testing is handled with Bayesian stopping rules (see section 4.3).

4.2.5. Subpopulations

The following subpopulations will be considered for subgroup analyses:

- Age:
    - ≥50 years or <50 years
- Sex: Male or female
- Time from onset of symptoms:
    - ≥ 120 hours or < 120 hours
- Comorbidity in screening
    - Diabetes mellitus (yes or no);
    - Cardiovascular disease (yes or no);
    - Lung disease (yes or no);

- Immunosuppressed patients / use of corticosteroid therapy (Yes or No);
- Other special categories (solid organ transplantation, end-stage kidney disease).

4.2.6. Withdrawals, Dropouts, Loss to Follow-up

Subjects who withdrew from the study will not to be replaced.

4.2.7. Missing, Unused, and Spurious Data

All data recorded on the CRF will be included in data listings that will accompany the clinical study report. Due to the design of the study and retention activities, we expect to be able to measure outcomes on all or the vast majority of participants. Multiple imputation will be employed where statistical models require adjustment for baseline covariates with up to 20% missing values. No multiple imputation of outcomes will be performed.

4.2.8.

superiority and futility thresholds were determined based on 200,000 simulation runs in which different values of the RRR were considered (0%, 20%, and 37.5%). A description of this interim analysis in an event-based Bayesian adaptive trial and accompanying illustrating example can be found in the appendix of this document.

4.3.1. Sample Size Re-Assessment for Brazil

Given that intervention arm(s) are neither superior or futile at the time of the first interim analysis for binary outcome analysis, sample size re-assessment will be performed based on COVID-19 related hospitalization or emergency room visit (for patients under observation for 6 hours or more). For binary outcomes, the sample size and the observed number of events in the control and treatment arms at the time of interim analysis will be used to calculate the future sample size required to achieve 90% BPP. The technical details can be found in Harari and colleagues' paper published in the Pharmaceutical Statistics.[5]

4.3.2. Borrowing Strengths from External Studies

Should individual patient data (IPD) from other relevant studies become available, we may use Empirical Bayes IPD meta-analysis[6] to borrow information from the treatment effects emerging from these studies. This is effectively a random effect Bayesian model that results in simultaneous shrinkage of the treatment effect estimates reported in the various studies toward the meta-analysis estimate, while still providing standalone estimates. Schoenfeld et al. have shown[7] that this approach is, in some ways, equivalent to the power prior approach of Ibrahim and Chen[8], whereby historical studies are assigned a fractional weight whose magnitudes correspond to the consistency of their data with that of the study they are thought to inform. Under the Empirical Bayes IPD meta-analysis model, covariates that may explain differences between studies will be retrieved, converted to similar scales and be included in the model for

statistical adjustments. The selection of covariates will be pseudo informal, partially guided by expert advice and partially guided for *forward selection*.

4.4. Subject Disposition

A tabulation of subject disposition will be tabulated, including the number screened, the number dosed with each experimental drug(s) and control, the number in each subject population for analysis, the number that withdrew prior to completing the study, and reasons for withdrawal.

A by-subject listing of study completion information, including the reason for premature study withdrawal, if applicable, will be presented.

4.5. Demographic and Baseline Characteristics

Baseline, demographic and medical history information will be summarized for the *<XX, XX and XX populations>* using descriptive statistics. No formal statistical comparisons will be performed.

Demographic and Baseline data will be provided in data listings.

4.6. Efficacy Evaluation

Efficacy analysis will be conducted using the ITT and PP Populations as outlined below. The two primary endpoints will be analyzed as a composite. Secondary endpoints will be assessed within 28 days of randomization, unless stated differently.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	

Sponsor:	McMaster University		
Protocol:	TOGETHER MP		
Document Version No.:	2.0	**Document Date:**	22-June-2021

• Reduction in the need for emergency room visits due to the clinical worsening of COVID-19 and keeping the participant under observation for > 6 hours within 28 days of randomization in acutely affected patients and with evidence of high-risk for complications	• Proportion of those in need of emergency care under observation for more than 6 hours for COVID-19
• Reduction in the need for hospitalization due to the progression of COVID-19 (worsening of viral pneumonia) or complications within 28 days of randomization in acutely affected patients and with evidence of high-risk for complications	• Proportion of those in need of hospitalization due to progression of COVID-19 and/or complications
Secondary	
• Reduction in all-cause and COVID-19-related mortality up to 28 days after randomization	• Proportion of participants who died due to any cause • Proportion of participants who died due do COVID-19-related complications
• To test the efficacy of experimental interventions to reduce SARS-CoV-2 viral load at day 3 and day 7	• Proportion of persons with clearance of SARS-CoV-2 from nasal swabs or saliva, defined as 1 negative swab • Proportion of days with SARS-CoV-2 detected from mid-nasal swabs by PCR • Change in viral load on day 3 and day 7 compared to baseline
• To test whether any of the IPs decrease time to resolution for symptomatic SARS-CoV-2 infection / COVID-19 disease	• Number of days with respiratory symptoms • Time to clinical improvement (up to 28 days of randomization), defined as the first day on which the participant reports a score of 0 on the WHO Clinical Worsening Scale • Proportion of patients with change in WHO clinical worsening scale over the treatment period and over the follow-up period

Sponsor:	McMaster University		
Protocol:	TOGETHER MP		
Document Version No.:	2.0	**Document Date:**	22-June-2021

• To test whether any of the IPs are associated with decreased time to mortality within 28 days of randomization	• Time to death for any cause, including COVID-19
• To test whether any of the IP are associated with decreased hospitalization for any causes	• Hospitalized for any cause, including COVID-19
• To test whether any of the IPs are associated with the time of hospitalization/urgent care due to COVID-19	• Time to hospitalization/urgent care due to COVID-19 progression
• To test the whether any of the IPs are associated with quality-of-life (QoL)	• Change in quality of life measured by PROMIS Global-10 from baseline to Day 14 and Day 28
• To test whether any of the IPS are associated with improved cognitive ability at day 28	• Telephone Interview for Cognitive Status (TICS) questionnaire score at day 28
Exploratory	
• To test whether any of the IPS are associated with the number of days spent in the intensive care unit	• Number of days spent in an intensive care unit
• To test whether any of the IPS are associated with the number of days on invasive mechanical ventilation	• Number of days on invasive mechanical ventilation
• To test whether any of the IPS are associated with the number of days in hospital	• Number of days of hospitalization
• To test whether any of the IPS are associated with the number of days on the hospital ward	• Number of days of hospitalization in the ward
• To test whether any of the IPS are associated with the number of days using oxygen therapy	• Number of days using oxygen therapy

Sponsor:	McMaster University		
Protocol:	TOGETHER MP		
Document Version No.:	2.0	**Document Date:**	22-June-2021

4.7. Safety Analyses

Safety analyses will be conducted using the Safety Population.

4.7.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and displayed in tables and listings using System/Organ/Class (SOC) and Preferred Term.

Analyses of adverse events will be performed for those events that are considered treatment emergent, where treatment emergent is defined as any adverse event with onset after the administration of study medication or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the investigator through the end of the study.

Adverse events are summarized by subject incidence rates, therefore, in any tabulation, a subject contributes only once to the count for a given adverse event (SOC or preferred term).

The number and percentage of subjects with any treatment-emergent adverse events assessed by the Investigator as related to treatment (definite, probable, or possible relationship), and with any serious adverse event will be summarized by treatment group and overall. In these tabulations, each subject will contribute only once (i.e., the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes.

No formal hypothesis-testing analysis of adverse events incidence rates will be performed.

All adverse events occurring on study will be listed in subject data listings.

By-subject listings also will be provided for the following: subject deaths; serious adverse events; and adverse events leading to withdrawal.

Sponsor:	McMaster University		
Protocol:	TOGETHER MP		
Document Version No.:	2.0	**Document Date:**	22-June-2021

4.7.2. Temperature and Arterial Oxygen Saturation

Temperature and arterial oxygen saturation will be summarized descriptively, including the number and percent of subjects with normal, abnormal, and clinically significant results at Baseline. All temperature and arterial oxygen saturation data for each subject will be provided in data listings.

4.7.3. Electrocardiogram

ECG results will be summarized descriptively, including the number and percent of subjects with normal, abnormal and clinically significant abnormal results at Baseline. All ECG data for each subject will be provided in data listings.

4.7.4. Concomitant Medications

Concomitant medications will be coded using the WHO Drug dictionary. Results will be tabulated by Anatomic Therapeutic Class (ATC) and preferred term. The use of concomitant medications will be included in by-subject data listing.

4.7.5. Vaccination Status

Vaccination status will be tabulated and will be included in by-subject data listing. It may also be used in a sensitivity analysis.

Sponsor:	McMaster University		
Protocol:	TOGETHER MP		
Document Version No.:	2.0	**Document Date:**	22-June-2021

4.8. CHANGES TO PLANNED ANALYSES

As of this date, there have been no changes between the protocol-defined statistical analyses and those presented in this statistical plan. Post-protocol analyses may be added later due to the rapid evolvement of discoveries for COVID-19, but these will be considered exploratory.

Sponsor:	McMaster University		
Protocol:	TOGETHER MP		
Document Version No.:	2.0	**Document Date:**	22-June-2021

REFERENCES

1. Gelman A, Carlin JB, Stern HS, Dunson DB, Vehtari A, Rubin DB. Bayesian data analysis: CRC press; 2013.
2. Sturtz S, Ligges U, Gelman AE. R2WinBUGS: a package for running WinBUGS from R. 2005.
3. Plummer M. JAGS: Just another Gibbs sampler. 2004.
4. Ibrahim JG, Chen MH, Sinha D. B ayesian Survival Analysis. Wiley StatsRef: Statistics Reference Online. 2014.
5. Harari O, Hsu G, Dron L, Park JJH, Thorlund K, Mills EJ. Utilizing Bayesian predictive power in clinical trial design. Pharm Stat. 2020.
6. Raudenbush SW, Bryk AS. Empirical Bayes Meta-Analysis. Journal of Educational Statistics. 1985;10(2).
7. Schoenfeld DA, Hui Z, Finkelstein DM. Bayesian design using adult data to augment pediatric trials. Clin Trials. 2009;6(4):297-304.
8. Chen M-H, Ibrahim JG. Power prior distributions for regression models. Statistical Science. 2000;15(1):46-60.

Sponsor:	McMaster University		
Protocol:	TOGETHER MP		
Document Version No.:	2.0	**Document Date:**	22-June-2021

APPENDIX

1. Interim analysis in an even-based Bayesian adaptive clinical trial

Suppose that we have I active treatments, such that

$$y_{ij}|p_i \sim \text{Binom}(n_{ij}, p_i), \qquad i = 1, \dots, I,$$

where $j = 1, \dots, J$ denotes the number of interim analysis, n_{ij} is the number of patients randomized to the i^{th} arm, and p_i is the corresponding event rate. If we then assign a prior distribution

$$p_i \sim \text{Beta}(a, b),$$

Then by conjugation we obtain

$$p_i|y_{ij} \sim \text{Beta}(a + y_{ij}, b + n_{ij} - y_{ij}). \quad (1)$$

Control comparisons will then be based on *posterior efficacy*, namely

$$\Pr(p_i < p_{\text{ctrl}}|y_{ij}, y_{\text{ctrl}}),$$

which can be handily calculated by drawing independent Monte Carlo samples from the posterior distributions of the two arms using (1). Posterior inference on the relative risk reduction (RRR) can then be derived using the relationship

$$R_i = 1 - \frac{p_i}{p_{\text{ctrl}}}. \quad (2)$$

Proposed design for a 4-arm trial

- Perform interim analysis when 171, 342, and 513 patient outcomes have been recorded for each of the trial arms – corresponding to 25%, 50% and 75% of the maximum enrollment - and a final analysis when all 681 patient outcomes have been registered.
- Use $a = b = 1$ for beta prior distribution of all arms, corresponding to a uniform distribution.
- Stop early for efficacy if the posterior probability of efficacy exceeds 97.6%. The same test is conducted at the end of the trial if no early stopping rules are triggered.

- Stop early for futility if the posterior probability of efficacy is smaller than 20% in the first analysis; 40% in the second analysis; 60% in the third analysis.

The operating characteristics of this design, as determined by 200,000 simulation runs, are as follows.

Table *2*: Operating Characteristics for the Proposed Bayesian Design

Arm	RRR	Power	Mean % of patients (SD)	Pr(Stop at 1)	Pr(Stop at <=2)	Pr(Stop at <=3)
1	37.50%	84.80%	64.1 (29.6)	25.20%	53.50%	73.80%
2	20%	30.70%	84.2 (26.0)	10.40%	23.90%	39.20%
3	0%	2.50%	71.1 (28.4)	16.80%	42.50%	67.00%

From Table 2 it is evident that the type I error rate of this trial design is 2.5% (one-sided). Note that a treatment with a relative risk reduction of 37.5% will – on average – require only two-thirds of the maximum sample size of 681.

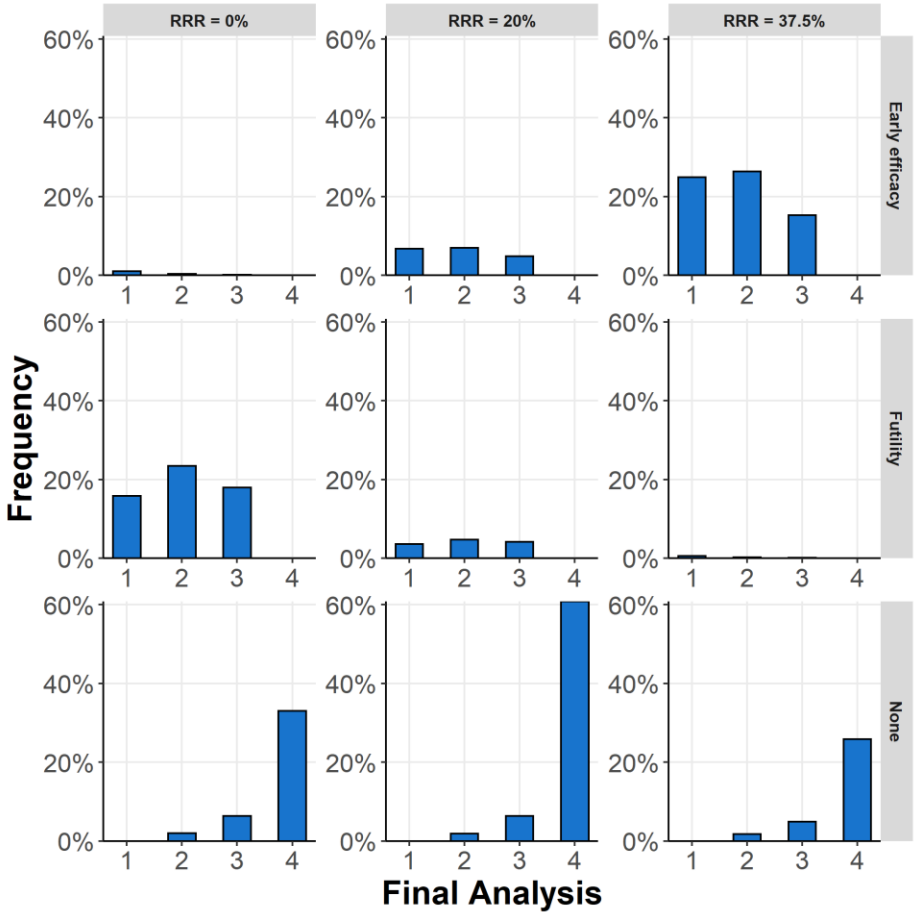
The simulation run also allows us to evaluate the frequency of the reasons for early stopping under each scenario. The details are given in Table 3 and Figure 2.

Table *3*: Distribution of the Causes for Early Stopping Under Various Scenarios

RRR	Stopping Reason	Analysis 1	Analysis 2	Analysis 3	Analysis 4
0%	Early efficacy	1.00%	0.30%	0.20%	0.00%
	Futility	15.80%	23.50%	18.00%	0.00%
	None	0.00%	1.90%	6.40%	32.90%
20%	Early efficacy	6.70%	6.90%	4.90%	0.00%
	Futility	3.60%	4.70%	4.10%	0.00%
	None	0.00%	1.80%	6.30%	60.90%
37.5%	Early efficacy	24.70%	26.40%	15.30%	0.00%
	Futility	0.50%	0.20%	0.20%	0.00%
	None	0.00%	1.70%	4.90%	26.20%

Figure 2: a graphical illustration of Table 2.

Sponsor:	McMaster University		
Protocol:	TOGETHER MP		
Document Version No.:	2.0	**Document Date:**	22-June-2021



Example: a simulated 4-arm trial

To illustrate the application of the decision rules in the proposed design, we drew one instance of the data according to the 15% control event rate and the specified effect sizes. The resultant trial consisted of 4 analyses: three interim analyses and one final analysis. Table 4 monitors the cumulative number of events over time for each arm. Note that already at the first interim look, arm 3 was dropped due to hitting a futility rule after 171 patient outcomes were observed. Two analyses and 342 patients later, arm 1 crossed the efficacy threshold, following which no more patients were randomized to it. Arm 2 continued until all 681 patient outcomes were recorded and did not hit either decision boundary. This is illustrated in Figure 3.

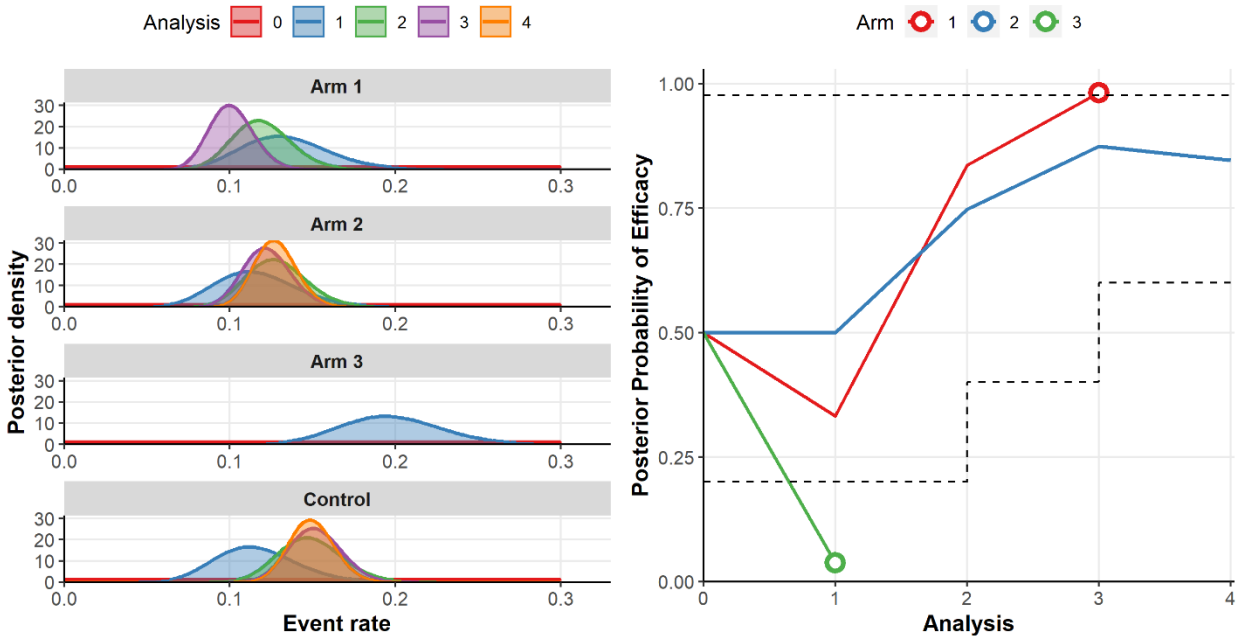
An alternative form of Bayesian data monitoring is an examination of the posterior densities of the different p_i parameters ($i \in \{\text{Control}, 1,2,3\}$) over time as in Figure 3, starting from a uniform prior reflecting ignorance, and with centers that change over time and with reduced uncertainty, as more evidence is gathered.

Table 4 also records the proportion of patient outcomes out of the maximum number of 681 that were recorded in the trial, as well as the final decision (efficacious/non-efficacious) and a 95% interval estimate of the relative risk reduction, based on the relationship (2).

Table *4*: Data and Bayesian Analysis of a Single Simulated Trial

Arm	Analysis 1 events	Analysis 2 events	Analysis 3 events	Analysis 4 events	Stopping Reason	% patients	Pr(Efficacy|Data)	Efficacy	RRR
1	15	28	45		Early efficacy	75.3	98.60%	Yes	36.3% [9.3%; 55.9%]
2	21	44	67	90	Enrolled all	100	52.60%	No	1.0% [-30.6%; 24.2%]
3	28	56			Futility	50.2	15.90%	No	-23.5% [-78.2%; 11.7%]
Control	22	45	71	91		100			

*Figure 3: the evolution of the posterior density of the event rate of each arm by interim analysis for the simulated example and posterior efficacy of all active arms by interim analysis**



**The dashed lines mark the decision boundaries.*

Cytel

Statistical Analysis Plan

Sponsor:	McMaster University		
Protocol:	TOGETHER trial		
Document Version No.:	1.0	**Document Date:**	27-March-2021

Table of Contents

Sponsor:	McMaster University		
Protocol:	TOGETHER trial		
Document Version No.:	1.0	**Document Date:**	27-March-2021

Protocol

Repurposed Approved Therapies for Outpatient Treatment of Patients with Early-Onset COVID-19 and Mild Symptoms

Protocol Number:	TOGETHER trial V2.0
(Version Date)	March 25, 2021
Name of Test Drug:	• Fluvoxamine • Ivermectin • Metformin • Placebo
Phase:	3
Methodology:	A placebo-controlled adaptive randomized platform trial
Sponsor:	McMaster University, Hamilton, Ontario
Principal Investigators:	Edward Mills Email: edward.mills@cytel.com Gilmar Reis Email: administrador@cardresearch.org
Document Date:	March 27, 2021
Document Version:	TOGETHER SAP Version 1.0

Sponsor:	McMaster University		
Protocol:	TOGETHER trial		
Document Version No.:	1.0	**Document Date:**	27-March-2021

SIGNATURE PAGE

Protocol Title:	A multicenter, adaptive, double-blind, randomized, placebo-controlled study to evaluate the effect of fluvoxamine, ivermectin and metformin, in reducing hospitalization in patients with mild COVID-19 and high-risk for complications
Principal Investigators:	Edward Mills Email: edward.mills@cytel.com Gilmar Reis, CardResearch Email: administrador@cardresearch.org
Protocol Number:	Version 2.0
Document Date/Version:	March 25, 2021
Cytel, Inc. Author: **Ofir Harari** Cytel, Inc.	Signature: DocuSigned by: Ofir Harari 617D6BE49659440... Date: 4/8/2021
Cytel, Inc. Author: **Hinda Ruton** Cytel, Inc.	Signature: DocuSigned by: Hinda Ruton 05965639190F4FC... Date: 4/8/2021

Sponsor:	McMaster University		
Protocol:	TOGETHER trial		
Document Version No.:	1.0	**Document Date:**	27-March-2021

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

Principal Investigator Signatory:
Edward Mills

Email: edward.mills@cytel.com

Signature: DocuSigned by: 5CDEE860A63E45A...

Date: 3/29/2021

Principal Investigator Signatory:
Gilmar Reis

Email: administrador@cardresearch.org

Signature: DocuSigned by: Gilmar Reis 6165DB6742E14C5...

Date: 3/29/2021

Sponsor:	McMaster University		
Protocol:	TOGETHER trial		
Document Version No.:	1.0	**Document Date:**	27-March-2021

LIST OF IN-TEXT TABLES

Sponsor:	McMaster University		
Protocol:	TOGETHER trial		
Document Version No.:	1.0	**Document Date:**	27-March-2021

ABBREVIATIONS

Abbreviation	Definition
ATC	Anatomic Therapeutic Class
BUGS	Bayesian inference using Gibbs Sampling
CER	Control Event Rate
COVID-19	Coronavirus disease 2019
CRF	Case report form
CSR	Clinical Study Report
ICH	International Council Harmonisation
ITT	Intention-To-Treat
JAGS	Just Another Gibbs Sampler
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per-Protocol
PROMIS	Patient-Reported Outcomes Management Information System
RRR	Relative Risk Reduction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAP	Statistical Analysis Plan
SOC	System/Organ/Class
WHO	World Health Organization

Sponsor:	McMaster University		
Protocol:	TOGETHER trial		
Document Version No.:	1.0	**Document Date:**	27-March-2021

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

TOGETHER trial is an adaptive platform trial for treating persons with early severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection at high risk of disease progression who do not require hospital admission. The TOGETHER trial will start with a placebo as a control in the clinical evaluation of fluvoxamine, ivermectin, and metformin. Other affordable candidate drug regimens that can be repurposed for coronavirus disease 2019 (COVID-19) may be considered and incorporated into this trial as an additional arm (s). If an intervention is shown to be effective, this design will allow the replacement of the placebo group with the effective intervention as the comparator.

1.2. Objectives of Statistical Analysis

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data to answer the study objective(s). We provided the populations for analysis, data handling rules, statistical methods, and data presentation formats. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

2. STUDY DESIGN

2.1. Synopsis of Study Design

TOGETHER trial is an international multicenter adaptive randomized platform trial for the early treatment of SARS-CoV-2 infection in high-risk adults not requiring hospital admission. Initially, TOGETHER Trial will start with a placebo as a control in the clinical evaluation of fluvoxamine, ivermectin, and metformin. This trial is designed as a platform trial design that can add new arms

onto the trial under standardized eligibility criteria, outcomes, and measurements, as the other experimental interventions. Other affordable candidate drug regimens that can be repurposed for COVID-19 may also be considered for this trial. The decision to add new therapeutic strategies will be based on external findings with local stakeholders' consultations.

2.2. Randomization Methodology

Eligible participants will be randomized at an equal allocation ratio to study experimental intervention(s) or placebo. Individual randomization will be stratified by clinical site, by age (<50 years vs. >=50 years), and time from onset of symptoms (<120 hours vs. >=120 hours). Clinical sites in South Africa will also be stratified by HIV status. The randomization sequence for each clinical site will be prepared by the unblinded statistician and will be sent to the unblinded pharmacist at each participating clinical site. Allocation of treatment assignment will be concealed from all other study personnel.

2.3. Stopping Rules and Unblinding

Stopping rules are outlined in section 4.3. In the case of potential recruitment challenges, it is important to reach statistical conclusions about the experimental treatments as fast as possible; therefore, continual Bayesian learning methods have been prepared and simulated to prepare for potential protocol changes. These simulation results are described in section 4.3.

2.4. Study Procedures

As outlined in the study protocol, the schedule of assessment is provided in **Error! Reference source not found.**.

Sponsor:	McMaster University		
Protocol:	TOGETHER trial		
Document Version No.:	1.0	**Document Date:**	27-March-2021

Table 1. Schedule of Study Activities

	Screening and Treatment Period[9]								Post-treatment Period[9]			
	Screening Visit (D-0)	Baseline and Randomization (1) D-0	Day 1	Day 2[(4)]	Day 3[(4)] ± 1 day	Day 4 [(4)]	Day 5[(4)]	Day 7[(4)] ± 1 day	Day 10 ± 2 days	Day 14[(4)] ± 2 days	Day 28[(4)] ± 3 days	Day 60[(4,8)] or Early Termination ± 5 days
Informed Consent	X											
SARS-CoV2 Rapid Test	X[(1)]											
Eligibility Criteria Review	X[(2)]											
Pregnancy Test	X[(3)]											
Demographics	X[(5)]											
Co-morbidities and Risk Factors	X											
Medical History	X											
WHO Clinical Worsening Scale	X		X	X	X	X	X	X	X	X	X	X
Temperature, Arterial O_2 Saturation		X										
Exposure to Index Case Information		X										
Substance Abuse		X										
PROMIS Global Health Scale		X[(6)]								X[(6)]	X[(6)]	X[(6)]
ECG		X										
Height and Weight		X										
Nasopharyngeal Swab		X			X			X				
Randomization		X										
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X
Investigational Treatment Administration			X[(7)]	X[(7)]	X[(7)]	X[(7)]	X[(7)]	X[(7)]	X[(7)]			

Sponsor:	McMaster University		
Protocol:	TOGETHER trial		
Document Version No.:	1.0	**Document Date:**	27-March-2021

Hospitalization / Emergency Room Visits			X	X	X	X	X	X	X	X	X	X
Respiratory Symptoms			X	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X	X
Adverse Drug Reactions			X	X	X	X	X	X	X	X	X	X

Legend

1. Screening and baseline visit: must be carried out at the same time when attending the outpatient setting. Rapid antigen test for COVID-19 at the screening visit. Day 1 visit should also be conducted on the same day as the screening and baseline visit. After completing the screening visit procedures at the baseline visit and present all inclusion / exclusion criteria, participants should be immediately randomized. The first dose of treatment under investigation must be administered on the same day of randomization (immediately after randomizing). The study medication will be administered as prescribed. Patients must be observed for 30 minutes after the medication administration.
2. Patients can be included in the trial if they have a COVID-19 diagnosis at baseline visit and have less than 7 days of flu-like symptoms.
3. Only women of childbearing potential and / or potential to become pregnant. Women of childbearing potential must necessarily use contraception during the first 15 days of the trial.
4. Visits through telephone contact, video call, telemedicine are calculated from the randomization date.
5. After signing the Informed Consent Form.
6. Questionnaires must be completed BEFORE any procedures of the proposed visit. Only a person not related to the research can help the patient during the questionnaire. In telephone visits, the patient must respond directly, at the time of contact.
7. Maintain the administration of the product under investigation according to schedule. Discontinue it if adverse events prevent the medication from continuing.
8. Assessment of late complications associated with COVID-19.
9. Unscheduled visits may also be conducted as needed. The clinical outcome data collected at the unscheduled visit should be entered at the next scheduled visit. The treatment period is up to 10 days.

Sponsor:	McMaster University		
Protocol:	TOGETHER trial		
Document Version No.:	1.0	**Document Date:**	27-March-2021

2.5. Efficacy and Safety Variables

2.5.1. Efficacy Variables

Primary endpoint:

- Emergency room visit due to the clinical worsening of COVID-19 (defined as participants remaining under observation for > 6 hours) within 28 days of randomization
- Hospitalization due to the progression of COVID-19 (defined as worsening of viral pneumonia) and/or complications within 28 days of randomization

Secondary endpoints:

- Viral clearance and viral load on D3 and D7 after randomization;
- Time (in days) to clinical improvement (up to 28 days of randomization), defined as the first day on which the participants report a score of 0 on the World Health Organization (WHO) Clinical Worsening Scale;
- Time (in days) to clinical failure;
- Number of days with respiratory symptoms since randomization;
- Hospitalization for any causes;
- Time to hospitalization due to COVID-19 progression;
- Mortality due to pulmonary complications;
- Mortality due to cardiovascular complications;
- Mortality from any causes;
- Adverse events that occurred (up to 28 days);
- Adverse drug reactions;
- WHO clinical worsening scale over the follow-up period;
- WHO clinical worsening scale during the treatment phase;
- PROMIS global health scale scores (days 14 and 28).

2.5.2. Safety Variables

Safety assessments performed during the study included measurement of vital signs and monitoring of adverse events and adverse drug reactions.

3. SUBJECT POPULATIONS

3.1. Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data:

- Intent-to-treat (ITT) Population: The ITT Population includes all randomized patients.
- Per-protocol (PP) Population: Randomized patients who adhered to more than 80% of the assigned therapy.
- Safety Population: Randomized patients who received at least 1 dose of study medication.

The ITT Population is typically the primary population for the analysis of efficacy parameters. A subset of efficacy parameters will be evaluated for the PP population (see Section 4.6).

The Safety Population is typically the primary population for the analysis of safety endpoints.

3.2. Protocol Violations

At the discretion of the sponsor, major protocol violations as determined by a review of the data prior to unblinding of the study results and the conduct of statistical analyses may result in the removal of a subject's data from the per-protocol population.

The sponsor, or designee, will be responsible for producing the final protocol violation file (formatted as a Microsoft Excel file), in collaboration with Cytel and the data monitoring group as applicable; this file will include a description of the protocol violation, and clearly identify

whether or not this violation warrants exclusion from the Efficacy Evaluable Population. This file will be finalized prior to hard database lock.

All protocol violations will be presented in the data listings. The major protocol violations will include:

- Failure to obtain informed consent prior to initiation of study-related procedures
- A research subject met withdrawal criteria or wished to withdraw from the study but was not withdrawn
- Inappropriate study drug dosage
- Inappropriate randomization
- Inadvertent loss of samples or data
- Other major violation

The minor protocol deviations include:

- Concomitant medication
- Non-compliance to study procedures
- Visit made outside of the visit window

4. STATISTICAL METHODS

4.1. Sample Size Justification

The sample size of 681 patients per arm has been chosen for each experimental group to achieve 80% power with 0.05 two-sided Type 1 error for a pairwise comparison against the control to detect minimum treatment efficacy defined by 37.5% relative risk reduction (RRR) of preventing hospitalization assuming a control event rate (CER) of 15%.

4.1.1. Sample Size Re-Assessment

Sample size re-assessment procedures are described in section 4.3.

4.2. General Statistical Methods and Data Handling

4.2.1. General Methods

All output will be incorporated into Microsoft Excel or Word files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the mean, median, standard deviation, minimum and maximum values will be presented. Time to event data will be summarized using Bayesian Kaplan-Meier estimates.

Bayesian bivariate analysis will be performed on secondary efficacy endpoints outlined in 2.5.1. Summary statistics will be presented, as well as their corresponding 95% credible intervals.

4.2.2. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.4), unless otherwise noted. Medical History and adverse events will be coding using MedDRA version 23.0. Concomitant medications will be coded using World Health Organization (WHO) Drug dictionary (version March 1, 2020).

4.2.3. Statistical Analysis Details

4.2.3.1. Bayesian inference for dichotomous outcomes with covariate adjustment

Here we may use the generalized linear model framework for binary outcome with the logistic link function, namely

$$y_i \sim \text{Binom}(1, p_i)$$

with

$$\log \frac{p_i}{1-p_i} = x_i^{\mathrm{T}}\beta + \gamma T_i,$$

using the same notations as before. Assigning a noninformative prior distribution $p(\beta, \gamma) \propto 1$, the logarithm of the posterior distribution (after some simple algebra) is given by

$$\log p(\beta, \gamma|\boldsymbol{y}) = \log p(\beta, \gamma) + \sum_{\mathrm{i}=1}^{\mathrm{n}} \log p(y_i|\beta, \gamma)$$

$$= \sum_{i=1}^{n} \{y_i(x_i^T\beta + \gamma T_i) - log[1 + exp(x_i^T\beta + \gamma T_i)]\}, (1)$$

and a random sample from $p(\beta, \gamma|\boldsymbol{y})$ may then be drawn using Markov Chain Monte Carlo (MCMC) such as the Metropolis-Hastings algorithm[1] using (5**Error! Reference source not found.** or Gibbs sampling using any software for Hierarchical Bayesian modeling such as BUGS[2] or JAGS[3]. Inference on the treatment effect will then follow the same procedure as in the numeric case. The treatment effects on dichotomous outcomes will be estimated using R.

4.2.3.2. Bayesian inference for time-to-event outcomes with covariate adjustment

We assume here that the data satisfies the Cox proportional hazards assumption, that is –

$$\log h(t; x, T, \beta, \gamma) = \log h_0(t) + x^{\mathrm{T}}\beta + \gamma T,$$

where $h_0(t)$ is the baseline hazard function and $h(t; x, T, \beta, \gamma)$ is the hazard function of an individual with covariate vector x who was assigned to treatment T, evaluated at time t.

We model the baseline hazard as a piecewise constant function

$$h_0(t;\boldsymbol{\lambda}) = \sum_{j=1}^{J} \lambda_j \, \mathbb{I}\left(t \in \left(a_{j-1}, a_j\right]\right) \quad (1)$$

as in Ibrahim et al.[4] for $\lambda_1, \ldots \lambda_J \geq 0$ and some partition $a_0 = 0 < a_1 < \cdots < a_J = t_{max}$ of the real line with t_{max} the end of the follow-up period. This induces the baseline survival function

$$S_0(t;\boldsymbol{\lambda}) = -\sum_{j=1}^{J} \lambda_j \left(t - a_{j-1}\right) \mathbb{I}\left(t \in \left(a_{j-1}, a_j\right]\right), \quad (2)$$

and, denoting $\boldsymbol{t} = [t_1, \ldots, t_n]^{\mathrm{T}}$ the vector of event times, the log-likelihood function is given by

$$\ell(\boldsymbol{t};\beta,\gamma,\boldsymbol{\lambda}) = \sum_{i=1}^{n} [(1-\delta_i) log\, h_0(t_i;\boldsymbol{\lambda}) + x_i{}^T\beta + \gamma T_i + \log S_0(t_i;\boldsymbol{\lambda}) + \exp(x_i{}^T\beta + \gamma T_i)], \quad (3)$$

where δ_i is an indicator assuming the value of 1 if the i^{th} observation was right-censored and 0 otherwise. We may then assign an improper, independent prior $p(\beta,\gamma,\boldsymbol{\lambda}) \propto \prod_{j=1}^{J} \lambda_j^{-1}$, and proceed to generate an MCMC sample from the posterior distribution, using the log-posterior

$$\log p(\beta,\gamma,\boldsymbol{\lambda}|\boldsymbol{t}) = \text{const} + \ell(\boldsymbol{t};\beta,\gamma,\boldsymbol{\lambda}) - \sum_{j=1}^{J} \log \lambda_j$$

within a Metropolis-Hastings scheme. Inference on treatment efficacy, as always, will be based on the $100(1-\alpha)\%$ credible interval for γ.

The treatment effects on time-to-event outcomes will be estimated using R.

4.2.3.2.1. Checking for proportional hazards assumption for time-to-event analyses

The proportional hazards assumption will first be checked visually inspecting the Kaplan-Meier plots of the survival function versus the survival time. Plots of log(-log(survival)) versus log(survival) will also be generated to check the proportional hazards assumption.

4.2.4. Multiple Comparisons/Multiplicity

All subgroup analyses are considered exploratory for this stage of the TOGETHER trial and thus do not require adjustment for multiplicity. Treatment comparisons in focus are solely experimental versus placebo comparisons and for each treatment a matching placebo exists. Thus, all placebo comparisons can be considered approximately independent and therefore not requiring multiplicity adjustments. Lastly, multiplicity due to repeated testing is handled with Bayesian stopping rules (see section 4.3).

4.2.5. Subpopulations

The following subpopulations will be considered for subgroup analyses:

- Age:
    - ≥50 years or <50 years
- Sex: Male or female
- Time from onset of symptoms:
    - ≥ 120 hours or < 120 hours
- Comorbidity in screening
    - Diabetes mellitus (yes or no);
    - Cardiovascular disease (yes or no);
    - Lung disease (yes or no);
    - Immunosuppressed patients / use of corticosteroid therapy (Yes or No);
    - Other special categories (solid organ transplantation, end-stage kidney disease);
    - HIV status (clinical sites in South Africa).

4.2.6. Withdrawals, Dropouts, Loss to Follow-up

Subjects who withdrew from the study will not to be replaced.

4.2.7. Missing, Unused, and Spurious Data

All data recorded on the CRF will be included in data listings that will accompany the clinical study report. Due to the design of the study and retention activities, we expect to be able to measure outcomes on all or the vast majority of participants. Multiple imputation will be employed where statistical models require adjustment for baseline covariates with up to 20% missing values. No multiple imputation of outcomes will be performed.

4.2.8. Visit Windows

Table 1 Evaluation Intervals for Efficacy Analysis

Evaluation	Protocol-Specified Interval	Interval for Analysis
Baseline	Day 0	Day 0 to Day 1
Treatment period	Day 1 to 3 or Day 1 to Day 10	Day 0 to Day 10 (Day 3 and Day 7 ±1 day)
End-of-Therapy	Day 3 or Day 10	Day 10 (±2 days)
Post-Treatment	Day 11 to Day 60	Day 14 (±2 days); Day 28 (±3 days); Day 60 (±5 days)

Actual dates and times will be used for pharmacokinetic analyses rather than nominal days and times.

4.3. Interim Analyses

Three interim efficacy analyses are planned. Assuming a uniform prior assigned to the different event rates, a total sample size of 681 patients per arm, a CER of 15%, and a RRR equals to 37.5%, we will do an interim analysis after observing 25%, 50% and 75% of the maximum number of patient outcomes, as well as at the trial completion. The posterior efficacy threshold will be 97.6% and the futility threshold will be 20%, 40% and 60%. Intervention arms(s) showing a posterior probability of efficacy crossing either boundary, will be stopped for either reason. These superiority and futility thresholds were determined based on 200,000 simulation runs in which different values of the RRR were considered (0%, 20%, and 37.5%). A description of this interim analysis in an event-based Bayesian adaptive trial and accompanying illustrating example can be found in the appendix of this document.

4.3.1. Sample Size Re-Assessment for Brazil

Given that intervention arm(s) are neither superior or futile at the time of the first interim analysis for binary outcome analysis, sample size re-assessment will be performed based on COVID-19 related hospitalization or emergency room visit (for patients under observation for 6 hours or more). For binary outcomes, the sample size and the observed number of events in the control and treatment arms at the time of interim analysis will be used to calculate the future sample size required to achieve 90% BPP. The technical details can be found in Harari and colleagues' paper published in the Pharmaceutical Statistics.[5]

4.3.2. Borrowing Strengths from External Studies

Should individual patient data (IPD) from other relevant studies become available, we may use Empirical Bayes IPD meta-analysis[6] to borrow information from the treatment effects emerging from these studies. This is effectively a random effect Bayesian model that results in simultaneous shrinkage of the treatment effect estimates reported in the various studies toward

the meta-analysis estimate, while still providing standalone estimates. Schoenfeld et al. have shown[7] that this approach is, in some ways, equivalent to the power prior approach of Ibrahim and Chen[8], whereby historical studies are assigned a fractional weight whose magnitudes correspond to the consistency of their data with that of the study they are thought to inform. Under the Empirical Bayes IPD meta-analysis model, covariates that may explain differences between studies will be retrieved, converted to similar scales and be included in the model for statistical adjustments. The selection of covariates will be pseudo informal, partially guided by expert advice and partially guided for *forward selection*.

4.4. Subject Disposition

A tabulation of subject disposition will be tabulated, including the number screened, the number dosed with each experimental drug(s) and control, the number in each subject population for analysis, the number that withdrew prior to completing the study, and reasons for withdrawal.

A by-subject listing of study completion information, including the reason for premature study withdrawal, if applicable, will be presented.

4.5. Demographic and Baseline Characteristics

Baseline, demographic and medical history information will be summarized for the *<XX, XX and XX populations>* using descriptive statistics. No formal statistical comparisons will be performed.

Demographic and Baseline data will be provided in data listings.

4.6. Efficacy Evaluation

Efficacy analysis will be conducted using the ITT and PP Populations as outlined below. The two primary endpoints will be analyzed as a composite. Secondary endpoints will be assessed within 28 days of randomization, unless stated differently.

Table 3: Objectives and Endpoints

Objectives	Endpoints
Primary	
• Reduction in the need for emergency room visits due to the clinical worsening of COVID-19 and keeping the participant under observation for > 6 hours within 28 days of randomization in acutely affected patients and with evidence of high-risk for complications	• Proportion of those in need of emergency care under observation for more than 6 hours for COVID-19
• Reduction in the need for hospitalization due to the progression of COVID-19 (worsening of viral pneumonia) or complications within 28 days of randomization in acutely affected patients and with evidence of high-risk for complications	• Proportion of those in need of hospitalization due to progression of COVID-19 and/or complications
Secondary	
• To test the efficacy of experimental interventions to reduce SARS-CoV-2 viral shedding at day 3 and day 7	• Proportion of persons with clearance of SARS-CoV-2 from nasal swabs or saliva, defined as 1 negative swab • Proportion of days with SARS-CoV-2 detected from mid-nasal swabs by PCR • Change in viral load on day 3 and day 7 compared to baseline
• To test whether any of the experimental interventions decrease time to resolution for symptomatic SARS-CoV-2 infection / COVID-19 disease	• Time to clinical improvement (up to 28 days of randomization), defined as the first day on which the participant reports a score of 0 on the WHO Clinical Worsening Scale

	• Time to clinical failure • Number of days with respiratory symptoms after randomization • Proportion of patients on each scale of the WHO clinical worsening scale over the treatment period and over the follow-up period
• To test whether any of the experimental interventions is associated with decreased mortality within 28 days of randomization	• Proportion of participants who died due to any cause • Proportion of participants who died due do pulmonary complications • Proportion of participants who died due do cardiovascular complications
• To test whether any of the experimental interventions is associated with decreased hospitalization for any causes	• Proportion of participants hospitalized due to any cause
• To test whether any of the experimental interventions is associated with the time of hospitalization due to COVID-19	• Time to hospitalization due to COVID-19 progression
• To test the quality-of-life (QoL) of experimental interventions for treatment of high-risk outpatients with SARS-CoV-2 infection	• Change in quality of life measured by PROMIS Global-10 from baseline to Day 14 and Day 28

4.7. Safety Analyses

Safety analyses will be conducted using the Safety Population.

4.7.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and displayed in tables and listings using System/Organ/Class (SOC) and Preferred Term.

Sponsor:	McMaster University		
Protocol:	TOGETHER trial		
Document Version No.:	1.0	**Document Date:**	27-March-2021

Analyses of adverse events will be performed for those events that are considered treatment emergent, where treatment emergent is defined as any adverse event with onset after the administration of study medication or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the investigator through the end of the study.

Adverse events are summarized by subject incidence rates, therefore, in any tabulation, a subject contributes only once to the count for a given adverse event (SOC or preferred term).

The number and percentage of subjects with any treatment-emergent adverse events assessed by the Investigator as related to treatment (definite, probable, or possible relationship), and with any serious adverse event will be summarized by treatment group and overall. In these tabulations, each subject will contribute only once (i.e., the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes.

No formal hypothesis-testing analysis of adverse events incidence rates will be performed.

All adverse events occurring on study will be listed in subject data listings.

By-subject listings also will be provided for the following: subject deaths; serious adverse events; and adverse events leading to withdrawal.

4.7.2. Temperature and Arterial Oxygen Saturation

Temperature and arterial oxygen saturation will be summarized descriptively, including the number and percent of subjects with normal, abnormal, and clinically significant results at Baseline. All temperature and arterial oxygen saturation data for each subject will be provided in data listings.

4.7.3. Electrocardiogram

ECG results will be summarized descriptively, including the number and percent of subjects with normal, abnormal and clinically significant abnormal results at Baseline. All ECG data for each subject will be provided in data listings.

4.7.4. Concomitant Medications

Concomitant medications will be coded using the WHO Drug dictionary. Results will be tabulated by Anatomic Therapeutic Class (ATC) and preferred term. The use of concomitant medications will be included in by-subject data listing.

4.8. CHANGES TO PLANNED ANALYSES

As of this date, there have been no changes between the protocol-defined statistical analyses and those presented in this statistical plan. Post-protocol analyses may be added later due to the rapid evolvement of discoveries for COVID-19, but these will be considered exploratory.

REFERENCES

1. Gelman A, Carlin JB, Stern HS, Dunson DB, Vehtari A, Rubin DB. Bayesian data analysis: CRC press; 2013.
2. Sturtz S, Ligges U, Gelman AE. R2WinBUGS: a package for running WinBUGS from R. 2005.
3. Plummer M. JAGS: Just another Gibbs sampler. 2004.
4. Ibrahim JG, Chen MH, Sinha D. B ayesian Survival Analysis. Wiley StatsRef: Statistics Reference Online. 2014.
5. Harari O, Hsu G, Dron L, Park JJH, Thorlund K, Mills EJ. Utilizing Bayesian predictive power in clinical trial design. Pharm Stat. 2020.
6. Raudenbush SW, Bryk AS. Empirical Bayes Meta-Analysis. Journal of Educational Statistics. 1985;10(2).
7. Schoenfeld DA, Hui Z, Finkelstein DM. Bayesian design using adult data to augment pediatric trials. Clin Trials. 2009;6(4):297-304.
8. Chen M-H, Ibrahim JG. Power prior distributions for regression models. Statistical Science. 2000;15(1):46-60.

Sponsor:	McMaster University		
Protocol:	TOGETHER trial		
Document Version No.:	1.0	**Document Date:**	27-March-2021

APPENDIX

1. Interim analysis in an even-based Bayesian adaptive clinical trial

Suppose that we have I active treatments, such that

$$y_{ij}|p_i \sim \text{Binom}(n_{ij}, p_i), \qquad i = 1, \dots, I,$$

where $j = 1, \dots, J$ denotes the number of interim analysis, n_{ij} is the number of patients randomized to the i^{th} arm, and p_i is the corresponding event rate. If we then assign a prior distribution

$$p_i \sim \text{Beta}(a, b),$$

Then by conjugation we obtain

$$p_i|y_{ij} \sim \text{Beta}(a + y_{ij}, b + n_{ij} - y_{ij}). \quad (1)$$

Control comparisons will then be based on *posterior efficacy*, namely

$$\Pr(p_i < p_{\text{ctrl}}|y_{ij}, y_{\text{ctrl}}),$$

which can be handily calculated by drawing independent Monte Carlo samples from the posterior distributions of the two arms using (1). Posterior inference on the relative risk reduction (RRR) can then be derived using the relationship

$$R_i = 1 - \frac{p_i}{p_{\text{ctrl}}}. \quad (2)$$

Proposed design for a 4-arm trial

- Perform interim analysis when 171, 342, and 513 patient outcomes have been recorded for each of the trial arms – corresponding to 25%, 50% and 75% of the maximum enrollment - and a final analysis when all 681 patient outcomes have been registered.
- Use $a = b = 1$ for beta prior distribution of all arms, corresponding to a uniform distribution.
- Stop early for efficacy if the posterior probability of efficacy exceeds 97.6%. The same test is conducted at the end of the trial if no early stopping rules are triggered.

- Stop early for futility if the posterior probability of efficacy is smaller than 20% in the first analysis; 40% in the second analysis; 60% in the third analysis.

The operating characteristics of this design, as determined by 200,000 simulation runs, are as follows

Table 4: Operating Characteristics for the Proposed Bayesian Design

Arm	RRR	Power	Mean % of patients (SD)	Pr(Stop at 1)	Pr(Stop at <=2)	Pr(Stop at <=3)
1	37.50%	84.80%	64.1 (29.6)	25.20%	53.50%	73.80%
2	20%	30.70%	84.2 (26.0)	10.40%	23.90%	39.20%
3	0%	2.50%	71.1 (28.4)	16.80%	42.50%	67.00%

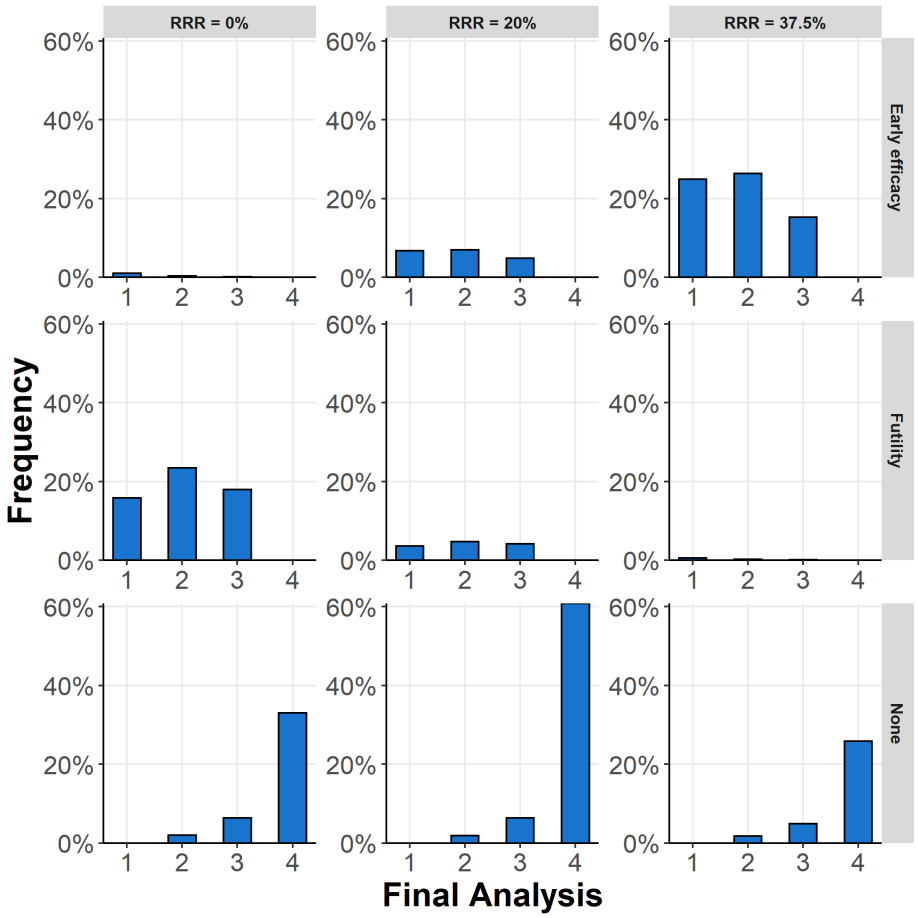
From Table 4 it is evident that the type I error rate of this trial design is 2.5% (one-sided). Note that a treatment with a relative risk reduction of 37.5% will – on average – require only two-thirds of the maximum sample size of 681.

The simulation run also allows us to evaluate the frequency of the reasons for early stopping under each scenario. The details are given in Table 2 and Figure 2.

Table 5: Distribution of the Causes for Early Stopping Under Various Scenarios

RRR	Stopping Reason	Analysis 1	Analysis 2	Analysis 3	Analysis 4
0%	Early efficacy	1.00%	0.30%	0.20%	0.00%
	Futility	15.80%	23.50%	18.00%	0.00%
	None	0.00%	1.90%	6.40%	32.90%
20%	Early efficacy	6.70%	6.90%	4.90%	0.00%
	Futility	3.60%	4.70%	4.10%	0.00%
	None	0.00%	1.80%	6.30%	60.90%
37.5%	Early efficacy	24.70%	26.40%	15.30%	0.00%
	Futility	0.50%	0.20%	0.20%	0.00%
	None	0.00%	1.70%	4.90%	26.20%

Figure 2: a graphical illustration of Table 2.



Example: a simulated 4-arm trial

To illustrate the application of the decision rules in the proposed design, we drew one instance of the data according to the 15% control event rate and the specified effect sizes. The resultant trial consisted of 4 analyses: three interim analyses and one final analysis. Table 3 monitors the cumulative number of events over time for each arm. Note that already at the first interim look, arm 3 was dropped due to hitting a futility rule after 171 patient outcomes were observed. Two analyses and 342 patients later, arm 1 crossed the efficacy threshold, following which no more

patients were randomized to it. Arm 2 continued until all 681 patient outcomes were recorded and did not hit either decision boundary. This is illustrated in Figure 3.

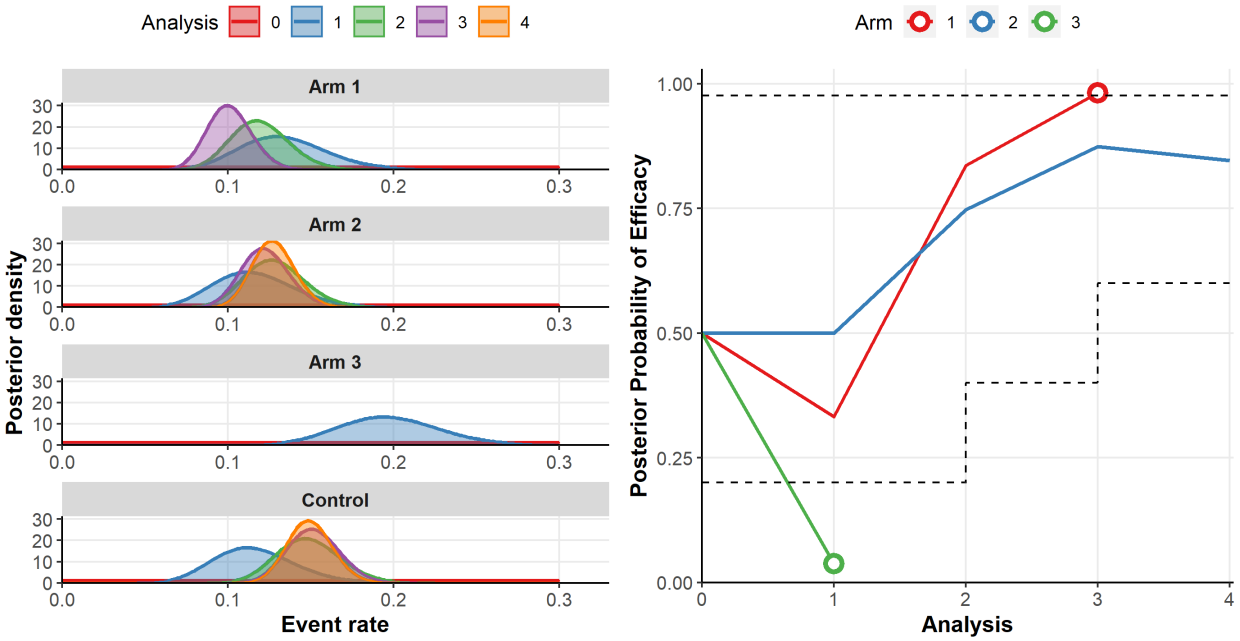
An alternative form of Bayesian data monitoring is an examination of the posterior densities of the different p_i parameters ($i \in \{\text{Control}, 1,2,3\}$) over time as in Figure 3, starting from a uniform prior reflecting ignorance, and with centers that change over time and with reduced uncertainty, as more evidence is gathered.

Table 3 also records the proportion of patient outcomes out of the maximum number of 681 that were recorded in the trial, as well as the final decision (efficacious/non-efficacious) and a 95% interval estimate of the relative risk reduction, based on the relationship (2).

Table 6: Data and Bayesian Analysis of a Single Simulated Trial

Arm	Analysis 1 events	Analysis 2 events	Analysis 3 events	Analysis 4 events	Stopping Reason	% patients	Pr(Efficacy|Data)	Efficacy	RRR
1	15	28	45		Early efficacy	75.3	98.60%	Yes	36.3% [9.3%; 55.9%]
2	21	44	67	90	Enrolled all	100	52.60%	No	1.0% [-30.6%; 24.2%]
3	28	56			Futility	50.2	15.90%	No	-23.5% [-78.2%; 11.7%]
Control	22	45	71	91		100			

*Figure 3: the evolution of the posterior density of the event rate of each arm by interim analysis for the simulated example and posterior efficacy of all active arms by interim analysis**



**The dashed lines mark the decision boundaries.*

Summary of Changes to the Statistical Analysis Plan

SAP Version	SAP Date	Changes
1.0	27 March 2021	Original
1.1	5 May 2021	• Updated schedule of events to include the vaccination status • Added section 4.7.5 to include the vaccination status
2.0	22 June 2021	• Updated to correspond with a master protocol format • Removed drug names and referenced investigational products • Provided introduction and rationale for the master protocol • Updated visit window section to reference the master protocol as windows may • change across investigational products • Updated secondary and exploratory endpoints to correspond with the master protocol • Revised the efficacy evaluation to correspond with the secondary and exploratory • endpoints and provided clarification on the definitions of each endpoint

All SAP versions can be found at the following link:
togethertrial.com/protocols