Protocol

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

EFFECT OF EARLY TREATMENT WITH PEGYLATED INTERFERON LAMBDA AMONG PATIENTS WITH COVID-19

TOGETHER Trial Protocols

SUPPLEMENTARY APPENDIX PROTOCOL AND STATISTICAL ANALYSIS PLAN

Contents:

TOGETHER TRIAL PROTOCOLS

Statistical Analysis Plans

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: 4.0; dated 8-Feb-2022

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

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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 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 and Wisconsin Upper Respiratory Symptom Survey (WURSS-21) • 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 • Oxygen saturation ≤ 93% after randomization 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 a placebo. IP treatment arms may be discontinued or added during the course of the trial.
Duration of Treatment	It 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 • Oxygen saturation • Hospitalization for any cause • WHO clinical worsening scale • PROMIS global health scale • WURSS-21 • 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, 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 a global pandemic[6,7].

1.2   Transmission

Initially, the vast majority of cases resulted from 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 higher mortality than individuals with COVID-19 without these comorbidities (Figure 2 and Figure 3)[13].
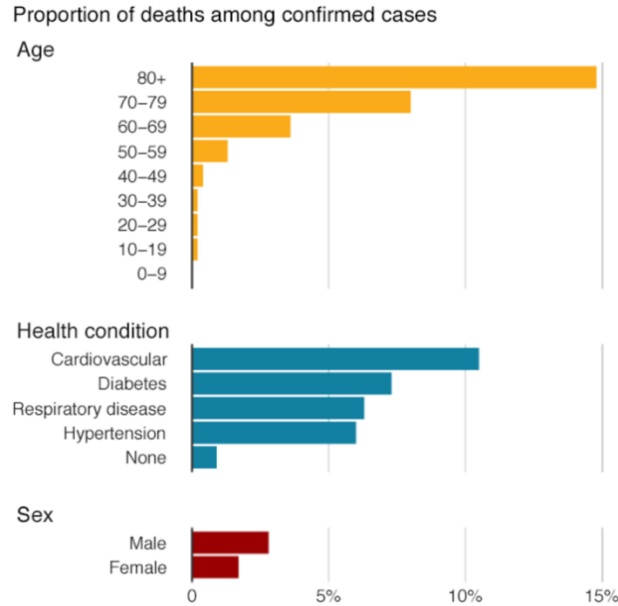
Figure 2 – Global Mortality by Age group – COVID-19
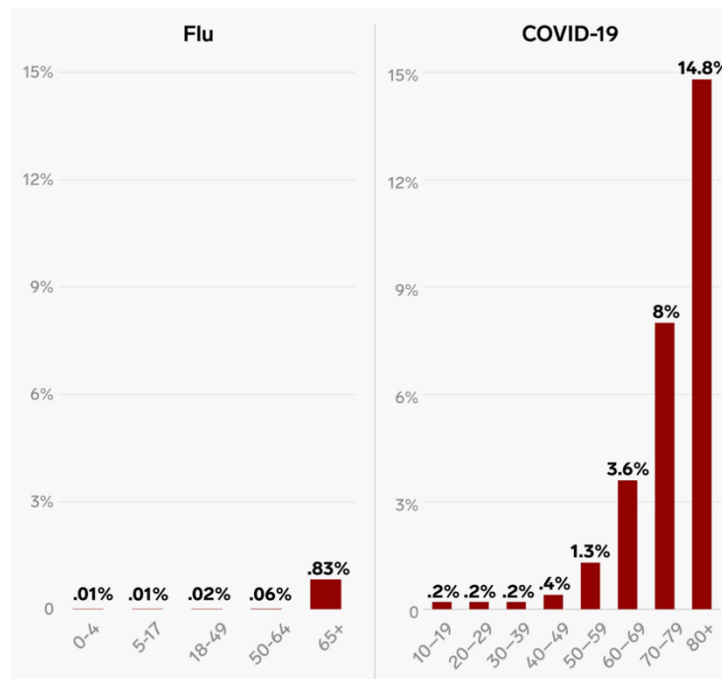
Figure 3 – Mortality from influenza and COVID-19

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[2,14]. 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[15]. 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) has pulmonary protective effects attenuating the inflammatory response[16]. 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 thus reducing pulmonary edema and the unwanted amplification of the inflammatory response resulting from COVID-19[14].

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 that 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[17,18], Swine Flu H1N1, which first appeared in Mexico in 2009[19] and the Coronavirus that causes the Midwest Respiratory Syndrome (MERS-CoV) which appeared in Saudi Arabia in 2012[20].

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.[11,21,22] Mortality associated with COVID-19 is apparently associated with Adult Respiratory Distress Syndrome, which, when associated with comorbidities, significantly increases mortality[23].

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.[24,25]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[26].

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[27]. 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. As a result, the WHO declared on January 30, 2020, that COVID-19 was a global public health emergency[28]. 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[29].

Since the onset of the outbreak, 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).
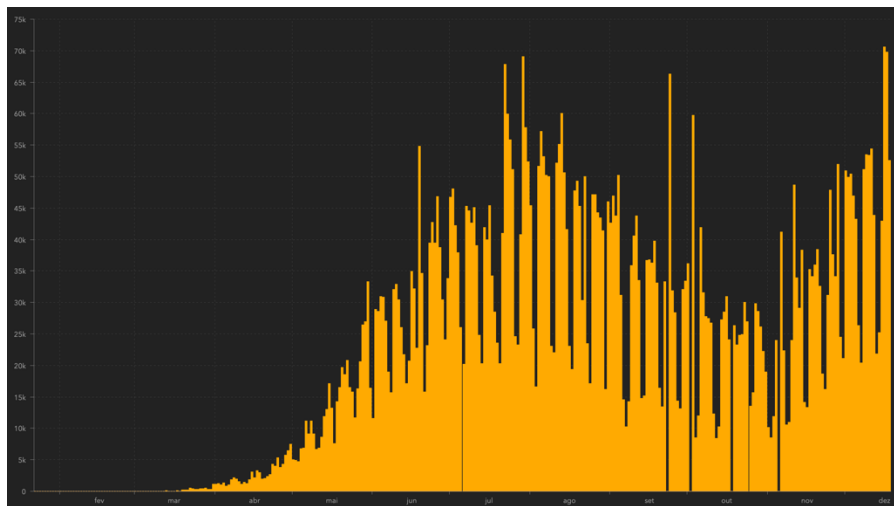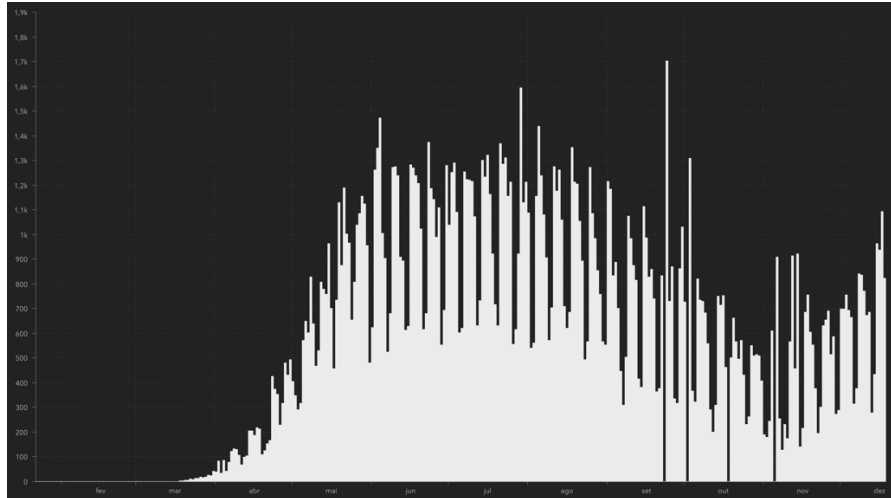
Figures 4 and 5 - Numbers of daily cases (yellow) and deaths (white)
associated with COVID-19
Source: Johns Hopkins University Data Center (12/17/2020)

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 the 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 who 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 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. Therefore, they have been selected for use in the study based on their known safety and efficacy profiles (see Appendix 1 for information on IPs).

This study aims 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 at 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 and Wisconsin Upper Respiratory Symptom Survey (WURSS-21)
- 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
- Oxygen saturation ≤ 93% after randomization

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

- Number of visits to primary care physicians/clinics

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 ($\geq$ 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 throughout the 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 replacing 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 local 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[30].

The trial consists of 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 on day 60 to assess long-term outcomes. Participants who prematurely discontinue the product under investigation remain in the trial. Unscheduled visits (during the treatment period) may occur at any time in case of adverse events.
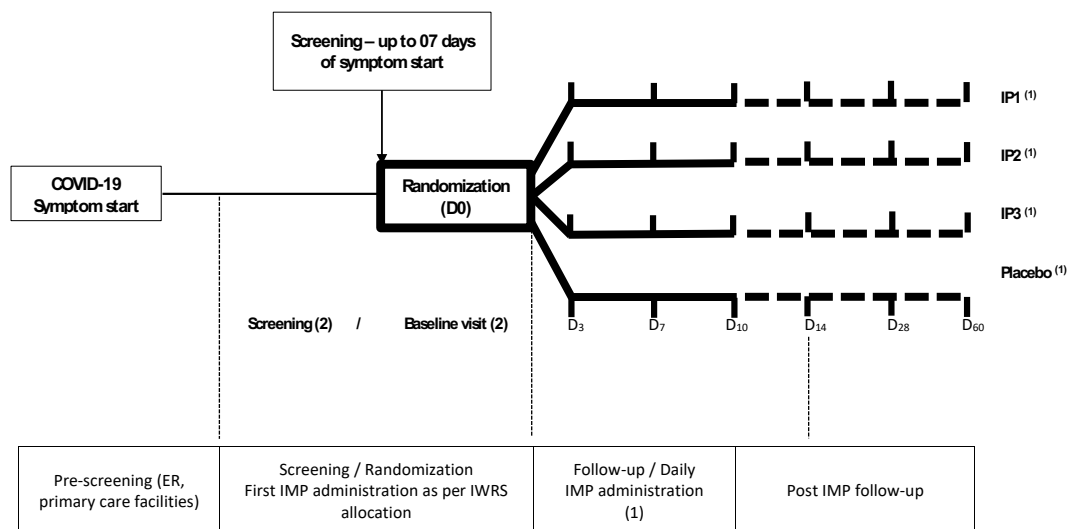
1. Treatment: IP 1, IP 2, IP 3 in parallel groups for the planned period. Discontinue if significant symptoms or adverse reactions.
2. Screening and Randomization (Baseline visit) must be performed on the same visit. Ensure that the patient is randomized when at the medical care facility. Patients with 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 a 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 given 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 the 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										
Oxygen Saturation		X	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	
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]	X[7]		
Hospitalization/Emergency Room Visits			X	X	X	X	X	X	X	X	X	X
Primary Care 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	
WURSS-21			X	X	X	X	X	X	X	X	X	

Legend

1. Screening and baseline visit: must be carried out simultaneously 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 presenting 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.
10. Oxygen saturation will be documented for participants that are hospitalized or visit the ER or primary care physician.

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 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 a 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 with 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 a 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 or oxygen saturation ≤ 93%;
3. Patients with acute respiratory condition due to other causes;
4. Dyspnea secondary to other acute and chronic respiratory causes or infections (e.g., decompensated COPD, acute bronchitis, pneumonia, primary pulmonary arterial hypertension);
    i. Antiretroviral agents
5. Continued use of monoamine oxide inhibitors (phenelzine, tranylcypromine, selegiline, isocarboxazide, moclobemide);
6. Pregnant or breastfeeding patients;
7. History of severe ventricular cardiac arrhythmia (ventricular tachycardia, patients with recovered ventricular fibrillation) or long QT syndrome;
8. History of diabetic ketoacidosis or clinical condition that maintains persistent metabolic acidosis;
9. Surgical procedure or use of contrast planned to occur during treatment or up to 05 days after the last dose of the study medication;

10. Current daily and/or uncontrolled alcoholism or drug addiction;
11. History of seizures in the last month or uncontrolled seizure;
12. Clinical history of moderate to severe hepatic deficiency or liver cirrhosis or Child-Pugh C classification;
13. Patients with known severe degenerative neurological diseases and/or severe mental illness;
14. Inability of the patient or representative to give informed consent or adhere to the procedures proposed in the protocol;
15. 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 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. one day, three days, ten 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 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 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 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. On visit Day 28, the participant will complete the Telephone Interview for Cognitive Status (TICS) questionnaire. The last visit can be in person, at the investigator's discretion (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 investigator's discretion or at the participant's need and can occur during the treatment period until the end of the 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 investigator's discretion 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 a 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. The center should do their utmost to ensure that the participant completes the described early termination procedures. In addition, 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 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

There is no provision for laboratory tests in this clinical research protocol 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. In addition, 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. Arterial oxygen saturation will also be documented for participants who are hospitalized or visit the emergency room or a primary care physician.

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. It is a procedure that adds transmission risks to the research team without a direct benefit from the data. In addition, heart rate can be obtained when ECG is performed using the Kardiamobile®. Therefore, we will not measure blood pressure or heart rate in the traditional 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 to prevent pregnancy. Participants who have had a vasectomy do not need to use 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 to collect information about the pregnancy, delivery, and the baby's health. As the effect of the study drugs on sperm is unknown, male participants will be instructed not to 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
- Primary care physician visits
- Viral clearance and viral load (first 150 participants randomized)
- Respiratory symptoms
- Oxygen saturation
- 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 an in-person visit to avoid influencing the answers from participants. Study coordinators will review the participant's answers immediately after completing 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: the 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 patients' global health status on days 0, 14 and 28 using the 10-item PROMIS global health scale (Patient-Reported Outcomes Measurement Information System 10)[31]. 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 questions 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[32], 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.

5.8.4   Wisconsin Upper Respiratory Symptom Survey (WURSS-21)

We will assess respiratory symptoms using the WURSS respiratory symptom scale. The WURSS is a flu-like symptom assessment tool developed by Barrett et al.,[33,34] is a disease-specific questionnaire instrument that assesses upper respiratory symptoms with an emphasis on patient-oriented outcomes. The WURSS is available in multiple languages, and its reliability and validity has been tested in previous studies.

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 companies 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 enrollment rate. 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. Other than those included in this specific clinical study, no patients 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 on 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. The study pharmacist or the qualified representative will carry out the accounting and verification of adherence to the study medication for all products under investigation 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 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 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

All participants will receive regular treatment following the guidelines during the treatment phase. Usual care includes recommendations for all aspects of treatment for patients with acute upper respiratory infections (i.e., recommendations for antipyretics for temperature $> 38.0^{\circ}$ C, frequent hydration, severe myalgia analgesics and looking 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 participant's health status, 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 that 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 and 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 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. Medications the investigator considers suitable for treating 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 to collect 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 using 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 a participant in this clinical study may experience.

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 until the end of the 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 can still perform them.
- Severe: The AE is disabling, and the participant cannot 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). An 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

To assess 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 when the AE results in death. The cause of death is necessary when known. If an autopsy is 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

The investigator should report a diagnosis instead of individual signs and symptoms or abnormal laboratory values whenever possible. However, if a set of signs and/or symptoms cannot be characterized clinically as a single diagnosis or syndrome at the time of reporting, each 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 corresponding to 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. Based on the above criteria and the participant's clinical condition, the investigator must decide 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 an accurate clinical term can characterize the laboratory abnormality 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.

The investigator should analyze all pathological laboratory values/findings diagnosed throughout the treatment period 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 related to the drugs used in this research is not expected.

Reference safety information (RSI) provides the basis for assessing the predictability of an 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 when 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).

Whether considered treatment-related or not, a death that occurs during the study period 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 justify the assessment of a causal relationship. All safety information 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

<u>7.8.1   Definition of special situations</u>

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.

<u>7.8.2   Recording and reporting of special situations</u>

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.

<u>7.8.3 Exposure during pregnancy and birth events</u>

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.

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

Placebo administration:
- o 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 ($10\,\mu$M), 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[17-19]. 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

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Appendix 1.2 Ivermectin

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

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

Ivermectin administration:
- o   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:
- o   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[22,24]. 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[25].

We also conducted an extensive review[26] 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

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Appendix 1.3 Metformin

Date IP (metformin) arm added: December 17, 2020

Date IP (metformin) arm closed: April 3, 2021

Metformin administration:
- o   750 mg dose twice daily for a period of 10 days

Placebo administration:
- o   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

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Appendix 1.4 Doxazosin

Date IP (doxazosin) arm added: 26-Jun-2021

Date IP (doxazosin) arm closed: 15-Nov-2021

Doxazosin administration:
- o Progressive dosing based on blood pressure, administered once per day for 14 days in form of 2mg tablets as detailed below.

Placebo administration:
- o 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

<u>First dose (day 1) for participants with SBP <120 mmHg at time of enrollment:</u>

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.

   o If the SBP is <90 mmHg on repeat spot measurement <u>*and*</u> 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 <u>*until symptoms resolve*</u>, 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).

- o An attempt to introduce the higher dose can be made if the participant remains asymptomatic on the highest previously tolerated dose for 24 hours.
- o Repeated occurrences of postural dizziness should trigger drug dose reduction of doxazosin.
- o Treatment is discontinued after 14 days of treatment.

<u>First dose (day 1) for participants with SBP ≥120 mmHg at time of enrollment</u>:
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.
   o 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).
   o An attempt to introduce the higher dose can be made if the participant remains asymptomatic on the highest previously tolerated dose for 24 hours.
   o Repeated occurrences of postural dizziness should trigger drug dose reduction of doxazosin.
   o 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[1,2]. In a subset of patients, the disease course can progress to a dysregulated immune state characterized by systemic hyperinflammation ("cytokine storm syndrome")[2-5]. This state can manifest clinically as ARDS, shock, and multi-organ failure. Resulting mortality equals or exceeds 50% in this population[6,7]. 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[8-11]. 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[12-14]. 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[3].

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[15]. 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[15,16]. 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[17,18]. 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[15]. Similar protection against a hyper-inflammatory stimulus was observed after prazosin administration[15], 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[19,20]. 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[21-23]. 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[24]. In humans, prazosin is a first-line treatment in scorpion envenomation, a process that involves dysregulated inflammatory responses that can progress to ARDS[25]. Expression of alpha-1 adrenergic receptors are increased during sepsis[26], and catecholamine levels are elevated in septic shock[27]. 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[16].

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[3]. Prazosin has a significant shorter half-life than doxazosin mesylate (2-3 hours versus 22 hours, respectively)[28,29]. As such, doxazosin mesylate may facilitate dosing in the outpatient setting, increase compliance, and thereby reduce subtherapeutic episodes[30]. While we have used prazosin in preclinical models of cytokine storm, doxazosin – like prazosin – inhibits all three alpha-1 adrenergic receptor subtypes[31]. 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)[15,32,33], 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[28]. Clinical trial data suggest a significant increase in adverse events (orthostasis) at doses >8 mg PO daily[28].

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)[15].

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[28], 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.

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Appendix 1.5 IFN Lambda

Date IP (IFN lambda) arm added: June 30, 2021

Date IP (IFN lambda) arm closed: TBD

Lambda administration:
- o One subcutaneous injection of 180μg peginterferon lambda (0.45ml) in the lower abdomen during the baseline/randomization visit

Placebo administration:
- o 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)[1]. 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[1]. 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[2]. 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[3], 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[4], hepatitis B virus[5] and most recently hepatitis delta virus[6] 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[7]. 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[8]. However, when the IFNs were given after infection, IFN-alpha worsened outcome, whereas IFN- lambda treatment improved survival[8]. 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[9], which would address intestinal and hepatic

involvement documented in patients with COVID-19[10,11]. Furthermore, the lack of the lambda receptor on hematopoietic cells limits concerns about the potential to worsen cytokine storm syndrome[12].

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[13]. 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[14]. 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.

Clinical activity in chronic HCV and HBV infection
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.

<u>Contraindications</u>
- 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.

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Appendix 1.6 Fluvoxamine and Fluvoxamine + Budesonide

Date IP (fluvoxamine and fluvoxamine/budesonide) arms added: 3-Jan-2022

Date IP (fluvoxamine and fluvoxamine/budesonide) arms closed: TBD

Fluvoxamine administration:
   o   100 mg fluvoxamine every 12 hours for a period of 10 days

Fluvoxamine + budesonide administration:
   o   Fluvoxamine 100 mg plus one inhaled dose of budesonide (400 μg) every 12 hours for a period of 10 days

Placebo administration (fluvoxamine + budesonide):
   o   Inactive placebo oral dose plus placebo inhaler

Rationale for evaluating fluvoxamine:
Please refer to appendix 1.1 for rationale for evaluating fluvoxamine.

Rationale for evaluating budesonide:
Budesonide is a second-generation, non-halogenated synthetic corticosteroid with potent glucocorticoid activity and weak mineralocorticoid activity. Initially patented in 1973 and used in humans since 1981, it is currently included in the list of essential medicines of the World Health Organization[1]. It has been approved by ANVISA for several years for the long-term treatment of bronchial asthma and chronic obstructive pulmonary disease.

The medication has an excellent anti-inflammatory activity when administered in an inhaled form and a low systemic activity, which provides a higher efficacy a higher efficacy and lower risk of adverse reactions resulting from the use of glucocorticoides. Its action is at several points of the inflammatory cascade, since the inhibition of the formation of specific antibodies; prevention of the formation, storage and release of chemical mediators by mast cells; interference in bronchoconstriction, inflammatory edema and also in mucosal secretion resulting from the inflammatory process[2].

Budesonide, which is of intermediate lipophilicity, is retained longer in the airways. It has been suggested that budesonide esterification contributes to its prolonged anti-inflammatory action and may explain why budesonide is so effective at similar doses compared to other ester formation corticosteroids[3].

Approximately 75% of episodes of chronic obstructive pulmonary disease decompensation are secondary to acute cases of viral airway infections. Similarly, viral infections have been considered an important cause of episodes of asthmatic decompensation in susceptible individuals. There is no evidence that the use of inhaled corticosteroid therapy is a predisposing factor for complications in patients with established asthma decompensation, and is considered an important therapeutic

weapon in cases of persistent symptoms, considering its beneficial role in restraining the triggered inflammatory process. Topical corticosteroid therapy or internal therapy is then considered the standard treatment in these conditions and recommended in virtually all consensus and positions of known allergy and pulmonology societies.

COVID-19 results in a severe involvement of the bronchial mucosa leading to intense inflammation, with consequent bronchospasm. To date, there is no evidence to associate the use of inhaled or nasal glucocorticoids and increased risk of SARS-CoV-2 infection or a more severe course of COVID-19 disease. These medications are expected to exercise effective anti-inflammatory control of the upper and lower airways and is a good protection against virus-triggered exacerbations for these patients. From today's perspective, there is sufficient data that patients with chronic inflammatory airway disease should receive guideline-based pharmacological treatment in the context of the COVID-19 pandemic, including glucocorticoids[4,5].

Clinical studies of budesonide in COVID-19 patients:
Ramakrishnan et al evaluated the use of 400 μg of instilled budesonide twice daily in patients with clinical picture of COVID 19 and mild symptoms within 07 days of symptom onset in a UK community[6]. The primary outcome criterion of the study was the visit to emergency care due to symptoms of COVID-19 after randomization and hospitalization. Important secondary outcomes were time to resolution of flu syndrome symptoms and evaluations through questionnaires of flu syndrome outcomes (FLUPro, CCQ), SpO2 evaluation and viral load. A total of 167 participants were recruited between July and December 2020, 73 of which were randomized patients for budesonide and 73 patients randomized for conventional treatment. In the "per protocol" analysis, a primary outcome was observed in ten (14%) of 70 participants in the usual care group and one (1%) of 69 participants in the budesonide group (difference in proportions 0.131; 95% CI: 0.043 to 0.218; p = 0.004). In the "intention to treat" analysis, the primary outcome occurred in 11 (15%) participants in the usual care group and two (3%) participants in the budesonide group (difference in proportions 0.123; 95% CI: 0.033 to 0.213; p = 0.09). Thus, the number needed to treat budesonide to achieve the reduction of a primary event was 8 participants. Although not statistically significant, recovery in the budesonide-treated group was faster (01 days) compared to the group with usual treatment (median of 7 days [95% CI 6 to 9] in the budesonide vs 8-day group [7 to 11] in the treatment group usual; log-rank test p = 0.07).

These data gave support for the performance of the phase III study using budesonide at a dose of 800 μg in two daily doses for 14 days in patients with COVID-19 and mild symptoms conducted by Yu et al. Eligible participants were older than 65 years or older than 50 years associated with some comorbidity and onset of symptoms up to 14 days, but not admitted for hospital treatment[7]. The primary outcome of the study was time for symptom recovery and hospital admission or Covid-19-associated death within 28 days of randomization. 4,700 participants were randomized to the budesonide group (n=1,073) or usual treatment (1,988) or other treatments (n=1,639). The primary analysis model included 2,530 participants positive for SARS-CoV-2, 787 in the budesonide group, 1,069 in the usual treatment group and 974 receiving other treatments.

A greater recovery of flu-like symptoms was observed in the budesonide-treated group of 2.44 days (Bayesian credibility range of 95% [BCI] 1.19 to 5.12) in the budesonide group versus the usual treatment group (11.8 days [95% BCI 10.0 to 14.1] vs 14.7 days [12.3 to 18.0]; RR 1.21

[95% BCI 1.08 to 1.36]), with a probability of superiority greater than 0.999, meeting the pre-specified limit of superiority of 0.99. For hospital admission or outcome of death, the estimated rate was 6.8% (95%; BCI 4.1 to 10.2) in the budesonide group versus 8.8% (5.5 to 12.7) in the usual care group (estimated absolute difference 2.0% [95% BCI -0.2 to 4.5]; odds ratio 0.75 [95% BCI 0.55 to 1.03]), with a 0.963 odds of superiority, below the pre-specified upper limit of 0.975.

Rationale for evaluating fluvoxamine plus budesonide:
Fluvoxamine and Budesonide have been approved medications for clinical use in specific situations in medicine for more than 30 years. To date, there are no reports of pharmacological interactions between the association of these SRIs with budesonide or other inhaled glucocorticoid, and there is no such recommendation in any package leaflet of these drugs available in Brazil.

To date, there are no published studies on the association between SSRIs and inhaled glucocorticoids for the treatment of patients with initial and outpatient COVID-19. Considering the potentially additive rationale of both pharmacological classes we are proposing the evaluation of these two pharmacological classes using fluvoxamine, a drug studied by this research program in previous stages, which showed significant action in improving the clinical picture of patients, with lower hospitalization rate, worsening and mortality, and with important action of functional inhibitors of acid sphingomyelinase, which can also contribute to its benefit. We chose budesonide because there are two clinical trials, one of which was large, which demonstrated the benefit of the use of this drug at this stage of the disease caused by the new coronavirus.

Justification of dose/regimen, route of administration and duration of treatment
Fluvoxamine:
Please refer to appendix 1.1 for justification of the dosing regimen and route of administration for fluvoxamine.

Budesonide:
The dose of budesonide approved for use by ANVISA in patients with bronchial asthma is 1,000 to 2,000μg (initial dose) followed by a aintenance dose which can range from 500μg to 4,000μg daily, depending on the therapeutic response.

We elected to use two daily doses of 400 μg administered by inhaler every12 hours for 10 days. We adopted 10 days to align with the dosing scheme for fluvoxamine.

Risks and precautions related to fluvoxamine
Please refer to appendix 1.1 for risks and precautions related to fluvoxamine

Risks and precautions related to budesonide
Most adverse reactions reported in clinical studies conducted with are self-limited and resolve with discontinuation of medication or non-pharmacological measures.

Common reactions to the use of inhaled budesonide include: nausea, headache, dysphonia, respiratory tract infection and sinusitis, palpitations, syncope, tachycardia, weight gain, abdominal pain, oral candidiasis, dyspepsia, vomiting, xerostomia, diffuse myalgias, asthenia, drowsiness, insomnia, migraine, cataracts, glaucoma, cough, epistaxis, nasal congestion, nasal irritation. Rare

reactions are: dermatitis, hives, Cushing's syndrome, hypoglycemia, dyslipidemia, anxiety, depression, irritability, behavior problems, psychoses (psychiatric disease), bronchospasm and throat irritation.

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.
- Selective Serotonin Reuptake Inhibitors (except sertraline)

Protocol modifications

Exclusion criteria:

- Chronic use of serotonin reuptake inhibitors except sertraline
- Chronic use of corticosteroid therapy with doses > 40 mg/day equivalent to prednisone.

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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 > 38° 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)

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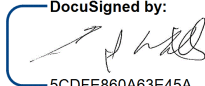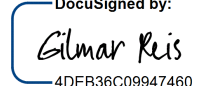
PROTOCOL

Version: 2.0

Date: 25-Mar-2021

This trial is funded by the Bill and Melinda Gates Foundation, Rainwater Charitable Foundation, and Fast Grants.

The TOGETHER Protocol is the confidential intellectual property of McMaster University and Platform Life Sciences and cannot be used in any form without their expressed permission.

Reviewed and Approved by:		
Edward Mills	*Signature:* DocuSigned by: 5CDFE860A63E45A...	*Date:* 3/26/2021
Gilmar Reis	*Signature:* DocuSigned by: Gilmar Reis 4DEB36C09947460...	*Date:* 3/28/2021

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
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
WHO	World Health Organization

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. Fluvoxamine, metformin, and ivermectin have shown promise in treating COVID-19. For this study, we will assess the efficacy of fluvoxamine, metformin, ivermectin, and possibly other repurposed drugs, as treatment for early COVID-19 among outpatients at a high risk for severe complications.
Primary Objective	The primary objective is to determine if each of the above repurposed drugs 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 in acutely affected patients with evidence of high risk for complications.
Secondary Objectives	The secondary objectives are to determine if the repurposed drugs reduce: • Viral clearance and viral load on day 3 and 7 after randomization • Time to clinical improvement, 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 since randomization • Hospitalization for any causes • Time to hospitalization due to COVID-19 progression • Mortality due to pulmonary complications • Cardiovascular mortality • Mortality from any causes • WHO clinical worsening scale scores over the follow-up period • WHO clinical worsening scale scores during the treatment phase This trial will also determine if each of the repurposed drugs improves health-related quality of life as assessed by PROMIS global health scale ("Global-10") scores (day 14 and day 28). Adverse events, adverse reactions

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	to the study medications and the proportion of participants who are non-adherent with the study drugs will also be assessed. Unless otherwise stated, the secondary objectives will be assessed up to day 28.
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 1 of the 4 treatment groups: 1) fluvoxamine, 2) ivermectin, 3) metformin and 4) placebo. Additional repurposed drugs may be added over the course of the trial.
Duration of Treatment	Up to 10 days.
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 • WHO clinical worsening scale • PROMIS global health scale • Hospitalization for any cause • Mortality, and cause of mortality • Viral clearance and viral load • Clinical progression of COVID-19 • Respiratory symptoms • Adverse events • Adverse drug reactions
Sample Size	Up to 3,200 participants

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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]**Error! Bookmark not defined.**.

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]**Error! Bookmark not defined.**.

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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].**Error! Bookmark not defined.**

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]**Error! Bookmark not defined.**. 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).

Study: Elderly Most At Risk From The Coronavirus
COVID-19 fatality rate by age (as of February 11, 2020)

Age	Fatality rate
10-19	0.2%
20-29	0.2%
30-39	0.2%
40-49	0.4%
50-59	1.3%
60-69	3.6%
70-79	8.0%
80+	14.8%

n=44,672 confirmed COVID-19 cases in Mainland China
Source: Chinese Centre for Disease Control and Prevention

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].
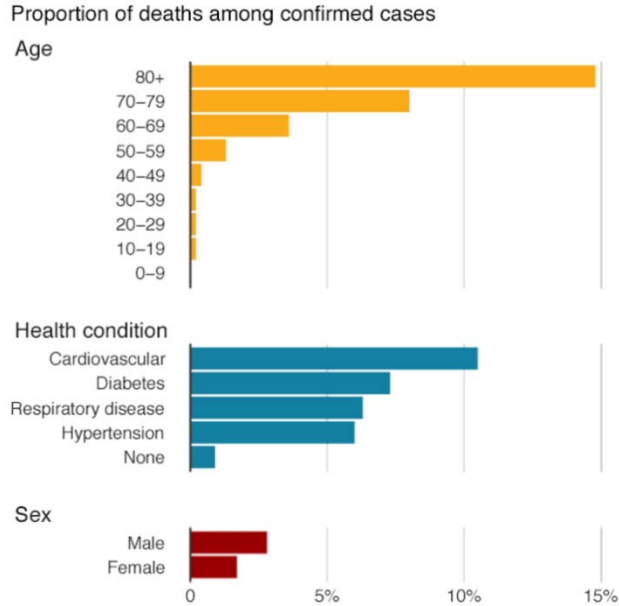
Proportion of deaths among confirmed cases

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[14,16]. 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[5].

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.

2.0   STUDY OBJECTIVES

The objective of this study is to evaluate the efficacy, safety, and benefit of the use of fluvoxamine, ivermectin, and metformin in patients acutely affected with COVID-19 presenting to outpatient settings with mild respiratory symptoms who are high-risk of experiencing complications. The research protocol has at least four treatment arms: (1) Fluvoxamine; (2) Ivermectin; (3) Metformin; and (4) Placebo. In addition to the above four treatment arms, there is an option to evaluate other repurposed drugs should one of the four listed treatments be stopped during interim analysis. The patient's participation period in the protocol is 60 days, with up to 10 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 above repurposed drugs 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 determine if each of the above repurposed drugs reduces:
- Viral clearance and viral load on day 03 and 07 after randomization (evaluation to be carried out on the first 600 randomized participants - 150 participants in each stratum)
- Time to clinical improvement, defined as the first day on which the participant reports a score of 0 on the WHO Clinical Worsening Scale
- Time to clinical failure, defined as time until the need for hospitalization due to clinical progression of COVID-19 (viral infection of the lower respiratory tract 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 causes
- Time to hospitalization due to COVID-19 progression
- Mortality due to pulmonary complications
- Cardiovascular mortality
- Mortality from any causes
- WHO clinical worsening scale scores over the follow-up period (day 1 to day 28)
- WHO clinical worsening scale scores during the treatment phase (day 1 to day 10)

This trial will also determine if each of the repurposed drugs improves health-related quality of life as assessed by PROMIS global health scale ("Global-10") scores (day 14 and 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 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 ($\geq$ 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)
    - HIV status (South Africa only)

3.0   INVESTIGATIONAL PLAN

3.1   Study design
This is a multicenter, adaptive, double-blind, randomized, placebo-controlled study to assess the effect of fluvoxamine, ivermectin and metformin, in reducing hospitalization of patients with mild COVID-19 and high-risk for complications. The treatment groups are:
1. Fluvoxamine
2. Ivermectin
3. Metformin
4. Placebo

Patients will be randomized to one of the 4 arms of the study using an interactive web response system (IWRS) (Figure 4). The protocol forecasts an adaptive phase to accommodate any needs for pre-specified modifications.

The protocol is designed to reach 800 patients in each of the 4 groups above, due to a 1: 1: 1: 1 randomization ratio. The protocol has an adaptive phase with blind interim analysis. A description of the interim analysis can be found in the Statistical Analysis Plan.

These interim evaluations will be reviewed by the Data and Safety Monitoring Committee, (DSMC), with decisions communicated to the Steering Committee.
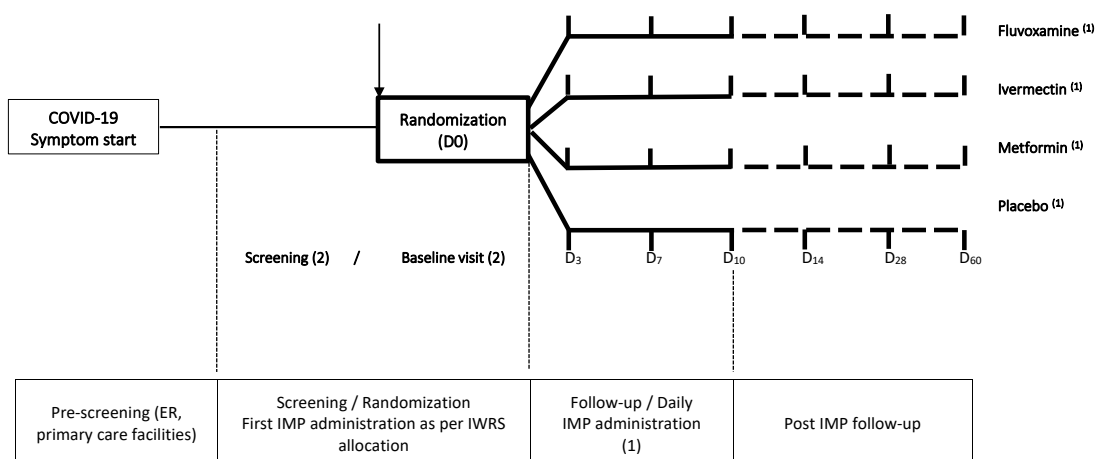
1. Treatment: Fluvoxamine, Ivermectin and Metformin in parallel groups for the planned period. Discontinue if significant symptoms or adverse reactions.
2. Screening and Randomization (Baseline visit) must be performed on the same visit. Ensure that the patient is randomized when at medical care facility. 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 by telefone 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 D_7 will be performed as per protocol.

Figure 4 - Research Flowchart

3.2. Rationale for the use of fluvoxamine

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) and an S1R receptor agonist[30]. 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.

3.2.1 Anti-inflammatory effects via the S1R – IRE1 route

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[31]. 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[32]. 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[33]. 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.

3.2.2 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[34,35]. 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[36,37]. Additional Nsp6 has been shown to physically associate with S1R[38]. 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[39]. 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[40,41].

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[42]. In COVID-19, this may increase the effects of treatment on the airway epithelium[43]. In high doses ($10\,\mu M$), 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[44,45].

3.2.3 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[46,47,48]. 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[49,50].

3.2.4 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[51,52].

3.2.5 Elevation of melatonin levels in the body

The SARS-CoV2 virus can activate the NLRP343 inflammasome, which can contribute to the cytokine storm[53,54]. Melatonin can act on this NLRP3 pathway to reduce inflammation[55,56]. Fluvoxamine inhibits melatonin metabolism, so it can increase the level of melatonin in the body, which can 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 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[58-66].

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[67-69].

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[70-73]; (2) accelerates clinical recovery, minimizing the evolution to complications in patients with mild and moderate clinical condition if treated soon after symptoms[74-76]; (3) accelerates recovery and prevents admission to the ICU and death of hospitalized patients[77-80] 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[81,82]. 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.

3.5 Rationale for the use 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[83]. Patients with body mass index $> 25 \text{ kg} / \text{m}^2$ or men with excess visceral adipose tissue are at higher risk of needing invasive ventilatory support in the case of COVID-19[84].

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[85,86]. 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[87].

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[88-90]. 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.[91]

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[92-95]. Recently, an observational study identified metformin as a potential mortality reducer in women[96].

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.

3.6 Justification of 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 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[97]. 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.

3.6.2 Ivermectin

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[98].

We also conducted an extensive review[99] 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.

3.6.3   Metformin

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.

3.7   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[100]. 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[101].

In South Africa, the first reported case of COVID-19 was reported in the province of KwaZulu-Natal[102]. Unfortunately, cases of COVID-19 have increased exponentially with a worrisome trend of community transmission. As of September 2020, >650,000 confirmed cases and >16,000 deaths were reported, and this pandemic has caused severe impact on both economy and life[103]. Since August of 2020, South Africa reported the highest number of cases on the African continent and measures aimed to contain the spread of COVID-19 were initiated by the South African Ministry of Health[104]. In addition to this unacceptable increase in cases, several novel South African variants

of COVID-19 have been identified (N501Y, E484K) which appear to enhance its spread and potential resistance to the currently available vaccines. These variants have now been identified in other countries, including Canada, United States and Britain and pose a serious health risk over and above the original COVID-19 strain. As a result, South Africa has currently closed 20 land boarder entry sites to try and reduce the spread of these new variants of COVID-19.

In Europe, wide variations in SARS-CoV-2 incidence and mortality have been reported. Northern Italy along with north-eastern French Regions, Switzerland and Belgium were among the most severely hit. In contrast, the majority of Balkan countries from Slovenia to Greece as well as the Islands of Malta and Cyprus had much fewer cases and deaths per capita, including deaths per number of cases[105]. However, the current rapid spread of COVID-19 in the Balkans has forced governments to implement a series of health guidelines to both reduce the spread of the virus while increasing the treatment of infected citizens[106]. Currently, Balkan nations have limited access to COVID-19 vaccines from multiple companies and programs, with no firm timeline for the start of their national inoculation drives. It is likely that Albania, Bosnia-Herzegovina, Kosovo, Montenegro, North Macedonia and Serbia – home to some 20 million people – will lag far behind other EU nations that are already in the process of vaccinating a large number of their people.

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 5,6).
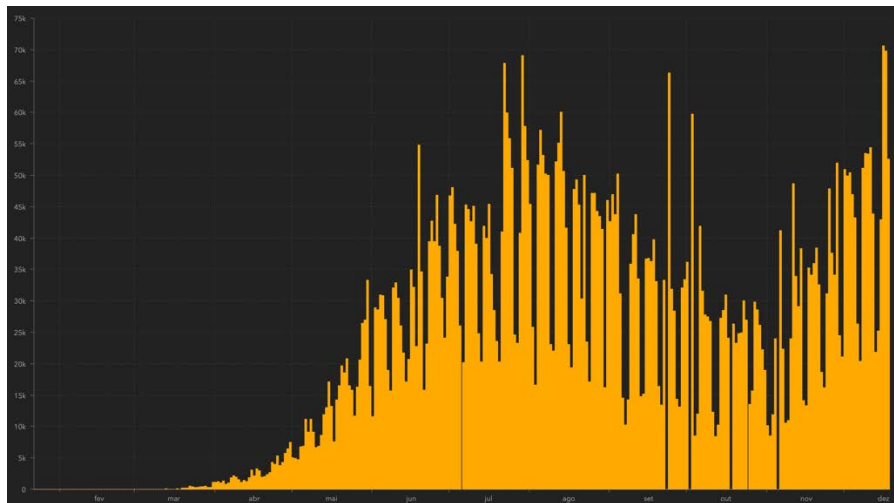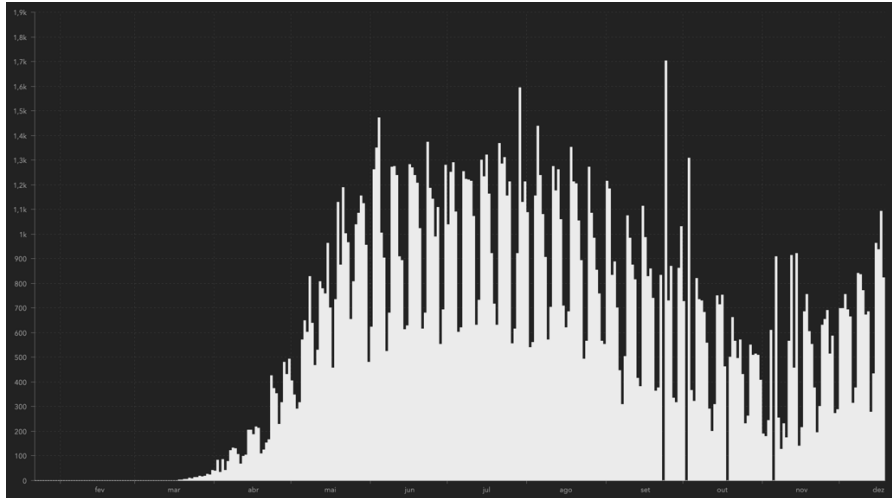
**Figures 5 and 6 - Numbers of daily cases (yellow) and deaths (white)
associated with COVID-19
Source: Johns Hopkins University data Center (12/17/2020)**

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.

4.0 RESEARCH PLAN

4.1   General trial design
The trial consists of a face-to-face screening and randomization visits, which will take place simultaneously, and follow-up visits completed through telephone contact and social media

applications using video-teleconferencing. 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 study. Unscheduled visit (during the treatment period) may occur at any time in case of adverse events.

During the screening visit, potentially eligible patients will be offered the possibility to participate in a research program to address experimental treatments for COVID-19. The informed consent form will be presented and after they agree to participate and sign the written consent, the screening procedures for the study will begin. Patients who test negative for COVID-19 during the screening visit will be considered a screen failure and patients who test positive will be enrolled and randomized.

After performing all the procedures of the screening and baseline visits, checking all the inclusion criteria and identifying that the patient does not meet any exclusion criteria from the study, the participants will be considered eligible for the treatment phase and will then be randomized to one of the four arms of the study (1: 1: 1: 1 ratio for treatment with the products under investigation). Participants will start their designated treatments as per randomization.

4.2 Duration of participation in the trial

Following completion of the screening and baseline visits, each participant will commence an up to 10-day treatment phase. Participants will then enter the follow-up phase, which continues until 60 days after randomization.

The primary outcome and all secondary outcomes will be assessed over 28 days post-randomization. To evaluate outcomes of late complications of COVID-19, post-study follow-up by telephone contact will be completed on day 60 post-randomization.

Patients who prematurely discontinue the investigated product will remain in the trial to collect data on trial outcomes and will receive the usual care.

5.0 PARTICIPANT SELECTION AND WITHDRAWAL

5.1 Inclusion criteria

The inclusion criteria are:
    a) Patients over 18 years old with the ability to provide free, prior and informed consent;
    b) 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;
    c) Patients over 18 and with at least ONE of the following criteria:
        1. Age $\geq$ 50 years (does not need any other risk criteria)
        2. *Diabetes mellitus* requiring oral medication or insulin
        3. Systemic arterial hypertension requiring at least 01 oral medication for treatment
        4. Known cardiovascular diseases (heart failure, congenital heart disease, valve disease, coronary artery disease, cardiomyopathies being treated, clinically manifested heart disease and with clinical repercussion)

5. Symptomatic lung disease and / or being treated (emphysema, fibrosing diseases)
6. Symptomatic asthma patients requiring chronic use of agents to control symptoms
7. Smoking
8. Obesity, defined as BMI> 30 kg / m2 (weight and height information provided by the patient)
9. Transplant patients
10. Patient with stage IV chronic kidney disease or on dialysis
11. Immunosuppressed patients / using corticosteroid therapy (equivalent to at least 10 mg of prednisone per day) and / or immunosuppressive therapy
12. Patients with a history of cancer in the last 05 years or undergoing current cancer treatment

d) 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
e) Willingness to use the proposed investigational treatment and follow the research procedures.

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.

5.2 Exclusion criteria

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 vaccination for SARS-CoV2;
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. $SaO_2 < 90\%$ or $< 93\%$ on nasal oxygen therapy at 10 L / min;
    iii. $PaO_2 / FIO_2 < 300$ mmHg;
7. Patients using serotonin receptor inhibitors: donepezil, sertraline;
8. Use of the following medications in the last 14 days:
    i. Monoamine Oxide Inhibitors (phenelzine, tranylcypromine, selegiline, isocarboxazide, moclobemide);
    ii. Use of iodinated contrasts during treatment until 05 days after the end;
    iii. Use of antiretroviral agents (Treatment of Acquired Immunodeficiency Syndrome - AIDS) – for clinical sites in Brazil only;

9. Patients with severe psychiatric disorders or major depression not controlled or controlled with any of the prohibited drugs (item above);
10. Pregnant or breastfeeding patients;
11. History of severe ventricular cardiac arrhythmia (ventricular tachycardia, patients with recovered ventricular fibrillation) or long QT syndrome;
12. History of diabetic ketoacidosis or clinical condition that maintains persistent metabolic acidosis;
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;
15. History of seizures in the last month or uncontrolled seizure;
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 informed consent or adhere to the procedures proposed in the protocol;
19. Known hypersensitivity and / or intolerance to fluvoxamine, ivermectin or metformin;
20. Inability to take oral medications;
21. Inability or unwillingness to follow research guidelines and procedures.

5.3   Randomization criteria

Patients can be randomized when they meet the inclusion criteria and have no exclusion criteria for the trial and have provided informed consent.

5.4   Discontinuation of the product under investigation or withdrawal of participants

5.4.1 Discontinuation of the product under investigation

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.

5.4.2   Withdrawal of consent

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. 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)

5.4.3 All early withdrawal participants

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.

6.0 STUDY TREATMENTS

6.1 Randomization

Each eligible participant will be assigned in a 1:1:1:1 ratio to receive 1 of the 4 treatment groups:
- Fluvoxamine
- Ivermectin
- Metformin
- Placebo (pills without medication)

The 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.

6.2 Posology and administration

The treatment groups and dosing regimens are:
- Fluvoxamine:
  - Dose of 100 mg twice daily for a period of 10 days
- Ivermectin:
  - 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 |

- ◆ Metformin:
  - ○ 750 mg dose twice daily for a period of 10 days
- ◆ Placebo: Once daily for 3 days or twice daily for 10 days

In addition to the 4 treatment arms described above, there will be an option to add additional repurposed study drugs.

Each participant will receive instructions on the proper dosage of medications and individual 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 dosing instructions agreed during the remainder of the study to encourage adherence. The investigator will determine if the study drug administration instructions require changes at each planned telephone contact visit and any changes will be communicated to the participant.

Participants will also be instructed to keep the empty / unused medication bottles which will be collected by the research staff at day 14 for compliance assessment at the treatment stage. Participants will be instructed to return the empty / unused medicine blisters to the containers in which they were originally supplied.

6.3   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. The patient must return with the blister cards to account for the medications delivered. The study medication used will come from pharmaceutical factories with commercial authorization for their production.

6.4   Supply, storage and accounting by the study center
6.4.1   Supply by the study center
Once a study center has been approved to receive the study drug, it will receive an initial shipment of drugs sufficient for 20 participants. 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.

6.4.2   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 at room temperature, not exceeding 30°C and away from direct sunlight exposure. All study drugs will be stored in a safe place. No participant, 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.

6.4.3   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.

6.5   **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 blocked. The study is blind, and the participant, investigator and team will not have access to the contents of the bottles, which are closed and hermetically sealed. Likewise, the sponsor and designees will not have access to randomization data. The treatment bottles will be dispensed through codes, kept by a non-blinded biostatistician not involved in the research. The DSMC and study management team will not have access to the participant's allocation during interim.

6.6   **Modification of drug dose**

6.6.1   Adverse reactions when using medications

The research participant should contact the research team when presenting any adverse reactions that the participant believes may be associated with the product under investigation. In the same way, the patient 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 patient should return to use the products under investigation.

6.6.2   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 $> 38.0^{\circ}$ C, frequent hydration, severe myalgia analgesics and look for medical help if needed). Usual care can also include educating the participants.

6.7 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.

6.8 Prohibited therapy, special considerations and concomitant treatment

6.8.1 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;
- Use of iodinated contrasts during treatment until 05 days after the end;
- Use of antiretroviral agents (Treatment of Acquired Immunodeficiency Syndrome-AIDS) – for clinical sites in Brazil only;
- Sertraline, donepezil.

6.8.2 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.

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7.0 RISKS AND PRECAUTIONS

7.1 Precautions

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.

7.2 Adverse reactions

7.2.1 Fluvoxamine

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.

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, vertigo and skin allergic reactions can occur in less than 1% of patients.

7.2.3 Metformin

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).

8.0 STUDY PROCEDURES

For a detailed assessment schedule (with all assessments, visits and visit windows required by the protocol) see schedule of events (Table 2).

Table 2. 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]			
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

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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.

8.1 Screening and baseline procedures

8.1.1 Screening procedures

The screening visit will be carried out in an outpatient care setting as shown in Figure 4. 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. 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, which will be generated on IWRS. Participants will be screened first to identify those who meet the eligibility criteria. As soon as a participant meets all the eligibility criteria, he will begin the baseline visit phase.

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

- The participant signs the informed consent form
- Review of eligibility criteria
- Demographics and medical history
- Pregnancy test for women of childbearing age
- WHO clinical worsening scale
- Performing the 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.

8.1.2 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 2. The participant will be provided with their medication as per randomization and two swab kits for the first 600 patients (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.

8.2 Treatment and follow-up phase procedures

Considering the transmissibility of COVID-19 and the need to quarantine cases, daily telephone contacts will be made between randomization until day 7.

8.2.1   Daily telephone contacts (Days 1 to 5 and Day 7)
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 2.

8.2.2   Day 3 and Day 7 visits
In addition to the procedures as described in the daily telephone contacts (Table 2), the collection of nasopharyngeal swab or sputum / saliva will be performed by the first 600 participants enrolled in the trial 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.

8.2.3   Day 10 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 3. They will also collect the medication kits for drug accountability and treatment compliance.

8.2.4   Day 14, 28, and 60 (End of the Study) visits
These visits will be performed through telephone contact. 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 2. At the end of the study, they will also advise the participant that their participation in the research study has ended.

8.3   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.

8.4 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.

9.0 STUDY EVALUATIONS AND OUTCOMES

9.1 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.

9.2 Arterial Oxygen Saturation (O$_2$) and Temperature

Considering the extremely transmissible characteristic of SARS-CoV2 and the isolation recommendations of positive individuals, limited vital sign data will be collected. Arterial O$_2$ saturation and temperature will be taken at the randomization visit.

9.3 Physical examination

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

9.4 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.

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

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.

9.6 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-19
- Hospitalization for any cause
- Mortality, and cause of mortality
- Viral clearance and viral load (nasopharyngeal swab associated with sputum sample collection / saliva collection in the first 600 enrolled participants – 150 per treatment group)
- Clinical progression of COVID-19
- Respiratory symptoms
- Adverse events (See section 10.0)
- Adverse drug reactions (See section 10.0)

9.7 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.

9.7.1 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.

9.7.2 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)[107]. 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.

10.0 ADVERSE EVENTS: EVALUATION, REGISTRATION AND REPORTING

10.1 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[108]. 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.

10.2   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.

10.3   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.

10.4   Assessment of adverse events

10.4.1 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).

10.4.2 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.

10.4.3 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.

10.5   Registration and reporting

10.5.1 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.

10.5.2 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.

10.5.3 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").

10.5.4 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.

10.5.5 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.

10.6   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.

10.7   Serious adverse event

10.7.1 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

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with the research coordination any AE for which the severity assessment is uncertain or questionable.

10.7.2 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)

10.7.3 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.

10.7.4   Composite study outcomes

All events potentially related to the primary outcome (i.e., attendance at emergency units and observation for a period > 6 hours associated with hospitalization for worsening of a lower respiratory tract infection) will be collected from the date on which the prior, free and informed consent was signed. For the purposes of this protocol, the following events are considered study outcomes and should be reported as previously described:

- Viral clearance and viral load on day 03 and 07 after randomization (first 600 patients);
- Clinical failure, defined as time until the need for hospitalization due to the progression of COVID-19 or attendance in the emergency room with permanence for treatment of COVID-19 progression for > 6 hours;
- Hospitalization for any causes
- Hospitalization due to COVID-19 progression
- Mortality due to pulmonary complications
- Cardiovascular mortality
- Specific adverse reactions to fluvoxamine;
- Specific adverse reactions to ivermectin; and
- Specific adverse reactions to metformin.

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.

10.7.5 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.

10.8   Special situations

10.8.1 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 a PEF 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 a PEF 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.

10.8.2 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.

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 in pregnant patients without a careful assessment of the risks and benefits of using them during this phase. Thus, pregnancy is not expected to occur during the treatment phase (10 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).

10.8.3.2 Exposure during pregnancy and registration and reporting of birth events
Pregnancies should be reported throughout the course of the study, including up to 4 weeks after the last dose of the study drug is received. Notification of pregnancy 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 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).

11.0   STUDY COMMITTEES

11.1   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.

11.2   Event Adjudication Committee
The independent Event Adjudication Committee (EAC) will evaluate all events related to the primary outcome based on pre-established criteria and prospectively and blindly. EAC members must not be direct research members, and there must be at least two qualified members among them. The EAC will operate blindly to the study's treatment allocations to assess events. Outcome adjudication will occur continuously throughout the blind treatment phase of the study.

12.0   STATISTICAL CONSIDERATIONS

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

13.0   ETHICAL CONSIDERATIONS OF THE STUDY

13.1   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)[109], 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

13.2   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.

13.3   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.

14.0   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

14.1   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

15.0   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.

15.1   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.

15.2   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).

15.3   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.

15.4   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.

16.0   PROCEDURE FOR MODIFYING THE PROTOCOL OR PREMATURE

CLOSURE OF THE STUDY

16.1   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.

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16.2   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.

16.3   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.

17.0   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.

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TOGETHER Protocol Revision History

Please note that there is no version 1.0 of the TOGETHER protocol. Please note that changes to the protocol was first submitted to the relevant Brazilian boards and authorities for approval before the Master Protocol was submitted for approval to HiREB.

Version 2.0 (March 25, 2021)
- Initial version of the English protocol
- Corresponds with version 2.0 of the protocol approved in Brazil
- Submitted to HiREB, who requested minor revisions
- Resubmitted to HiREB as version 2.1 (see below)

Version 2.1 (May 5, 2021)
- Revision requested following HiREB's initial review
- Approved by HiREB on June 25, 2021

Version 3.0 (June 22, 2021)
- Reformatted into the master protocol format

Version 3.1 (November 16, 2021)
- Approved by HiREB on December 20, 2021

Version 4.0 (February 8, 2022)
- Approved by HiREB on February 14, 2022

Important Changes Between Versions 2.0 and 2.1:

Change	Explanation
Removed references to clinical sites in South Africa throughout the protocol	Trial team made the decision not to initiate sites in South Africa at that time
Added section 8.2.5 on vaccination status	Clarified that participation in the trial would not preclude vaccination

Important Changes Between Versions 2.1 and 3.0:

Change	Explanation
Reformatted into a master protocol.	The master protocol format easily allows new treatments to be added into this ongoing platform trial, and existing treatments to be discontinued. It also allows participating jurisdictions to adapt the information contained within the master protocol to their local protocol format requirements. In other words, the master protocol will serve as an internal document, which clinical sites will take and adapt for their local use. It also allows the flexibility required for countries to simultaneously participate in different treatment arms.
Addition of two investigational products (doxazocin and IFN lambda).	The master protocol allows for the evaluation of multiple repurposed medications. Both treatments received regulatory and ethics committee approval in Brazil prior to implementation.
Addition of the Telephone Interview for Cognitive Status questionnaire.	This questionnaire was added so that we can determine if the IPs reduce the risk of cognitive impairment and memory loss.
Addition of the following criteria to the inclusion criteria: - Documented fever (>38C) - 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)	These criteria were added as participants presenting with these symptoms are at high risk for complications due to COVID-19.
Addition of the following criteria to the inclusion criteria: 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.	While contraceptive requirements were described in the previous version of the protocol, we formalized this into an inclusion criterion in the master protocol.
Addition of exploratory objectives.	Exploratory objectives were added as we developed the master protocol.
Secondary objectives were clarified as we revised the protocol changes.	Secondary objectives were clarified as we developed the master protocol.
Addition of exploratory objectives.	Exploratory objectives were added as we developed the master protocol.
Wording clarifications were made to the exclusion criteria to adapt it to the master protocol format.	To allow for the flexibility of the master protocol.

Important Changes Between Versions 3.0 and 3.1:

Change	Explanation
Addition of the number of visits to primary care physicians/clinics as an exploratory outcome.	This change was made so that we can explore if the IPs reduce the number of visits to primary care physicians/clinics.
Clarified that the investigational product is administered at the baseline visit.	This is the correction of an administrative error in the initial protocol.
Multiple wording clarifications were made throughout the protocol.	These changes make the protocol easier to understand and follow.

Important Changes Between Versions 3.1 and 4.0:

Change	Explanation

Exclusion Criteria:
• Patients with acute respiratory condition compatible with COVID-19 treated in the primary care and with hospitalization need or *oxygen saturation ≤ 93%* **[revised]**
• Patients who have received at least one dose of vaccination for SARS CoV2>14 days prior to screening **[removed]**
• 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 **[removed]**
• Continued use of monoamine oxide inhibitors (phenelzine, tranylcypromine, selegiline, isocarboxazide, moclobemide) **[revised]**
	• Added the oxygen saturation ≤ 93% as an exclusion criteria as it is associated with hospitalization.
	• To permit the enrollment of vaccinated participants, as they are also contracting COVID-19.
	• Updated to align with investigational products

Addition of the Wisconsin Upper Respiratory Symptom Survey at baseline and each follow-up visit.	To better document and define respiratory symptoms.
Collection of oxygen saturation levels for participants who present to the emergency room or hospital and to document the	To better document the participant's health status over the course of the study and in the emergency room and hospital.

Change	Explanation
participant's lowest oxygen saturation level at Day 28.	
Closed Doxazosin treatment arm to enrollment.	Trigger was met at a planned interim analysis.
Added investigational products (Fluvoxamine and Fluvoxamine + Budesonide).	The master protocol allows for the evaluation of multiple repurposed medications. Both treatments received regulatory and ethics committee approval in Brazil prior to implementation.
Multiple wording clarifications were made throughout the protocol.	These changes make the protocol easier to understand and follow.
Tidied references throughout the protocol.	References were added to Endnote and any duplicate references were removed.

together•COVID-19
clinical trials

Statistical Analysis Plan

Sponsor:	McMaster University		
Protocol:	TOGETHER MP		
Document Version No.:	4.0	Document Date:	3-May-2022

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Statistical Analysis Plan

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Protocol

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

Protocol Number:
(Version Date)

TOGETHER Trial Master Protocol V5.0

29-Apr-2022

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

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Document Date:

3-May-2022

Document Version:

TOGETHER MP SAP Version 4.0

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Statistical Analysis Plan

Sponsor:	McMaster University		
Protocol:	TOGETHER MP		
Document Version No.:	4.0	Document Date:	3-May-2022

SIGNATURE PAGE

Protocol Title: Master Clinical Trial Protocol: Repurposed Approved Therapies for Outpatient Treatment of Patients with Early-Onset COVID-19 and Mild Symptoms

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Protocol Number: Version 5.0

Document Date/Version: 29-Apr-2022

Steve Kanters, PhD

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Associate Director, RainCity Analytics

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Date:_____

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Statistical Analysis Plan

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Document Version No.:	4.0	Document Date:	3-May-2022

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: millsej@mcmaster.ca

Signature:_____

Date:_____

Principal Investigator Signatory:

Gilmar Reis

Email:
administrador@cardresearch.org

Signature:_____

Date:_____

Statistical Analysis Plan

Sponsor:	McMaster University		
Protocol:	TOGETHER MP		
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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

Statistical Analysis Plan

Sponsor:	McMaster University		
Protocol:	TOGETHER MP		
Document Version No.:	4.0	Document Date:	3-May-2022

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.

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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 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.

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2.5 Efficacy and Safety Variables

2.5.1 Efficacy Variables

Primary endpoint:

- Emergency room visit due to the clinical worsening of COVID-19 within 28 days of randomization AND/OR

- Hospitalization due to the progression of COVID-19 (defined as worsening of viral pneumonia) and/or complications within 28 days of randomization

Secondary endpoints:

- Time to recovery (defined as the first instance that the participant reports feeling fully recovered from the illness)

- 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

- Symptoms as assessed by the Wisconsin Upper Respiratory Symptom Survey (WURSS-21)

- Oxygen saturation ≤ 93% whilst under medical supervision

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- 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.

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- Modified intent-to-treat (mITT): Randomized patients who did not have a primary outcome event within 24 hours of receiving IP.

- 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 mITT and PP populations (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 RainCity Analytics 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 per-protocol 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

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- 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

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.

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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 and/or frequentist Kaplan-Meier estimates.

Bayesian bivariate analysis will be performed on the primary efficacy outcome. Bayesian and/or frequentist bivariate analysis will be performed secondary efficacy endpoints outlined in section 2.5. 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) or R (Version 4.1.0), 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).

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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

$$\log p(\beta, \gamma | \boldsymbol{y}) = \log p(\beta, \gamma) + \sum_{i=1}^{n} \log p(y_i | \beta, \gamma)$$

$$= \sum_{i=1}^{n} \{y_i (x_i^T \beta + \gamma T_i) - log[1 + exp(x_i^T \beta + \gamma T_i)]\}, (1)$$

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

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$$h_0(t; \boldsymbol{\lambda}) = \sum_{j=1}^{J} \lambda_j \, \mathbb{I}\big(t \in (a_{j-1}, a_j]\big) \quad (1)$$

as in Ibrahim et al.[4] for $\lambda_1, \dots \lambda_J \geq 0$ 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 $\boldsymbol{t} = [t_1, \dots, t_n]^{\mathrm{T}}$ 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 ith 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.

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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).

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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

Refer to the protocol for treatment periods, follow-up periods, and visit windows, as these vary by IP.

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

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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*.

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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, mITT, 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	
• Reduction in the need for emergency room visits due to the clinical worsening of COVID-19 within 28 days of randomization in	• Proportion of those in need of emergency care under observation for more than 6 hours for COVID-19

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acutely affected patients and with evidence of high-risk for complications	
• 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 time to recovery, defined as the first instance that the participant reports feeling fully recovered from the illness.	• Time to recovery
• 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 • Proportion of patients with change in the Wisconsin Upper Respiratory Symptom

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	Survey (WURSS-21) over the treatment period and over the follow-up period
• 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 oxygen saturation ≤ 93	• If oxygen saturation ≤ 93 over the course of the follow-up period
• 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

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• To test whether any of the IPS are associated with the number of days using oxygen therapy	• Number of days using oxygen therapy

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.

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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.

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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.

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.

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APPENDIX

1. Interim analysis in an even-based Bayesian adaptive clinical trial

Suppose that we have I active treatments, such that

$$y_{ij}|p_i \sim \text{Binom}(n_{ij}, p_i), \qquad i = 1, \ldots, I,$$

where $j = 1, \ldots, J$ denotes the number of interim analysis, n_{ij} is the number of patients randomized to the ith 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.

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- 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%

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Figure 2: a graphical illustration of Table 2.
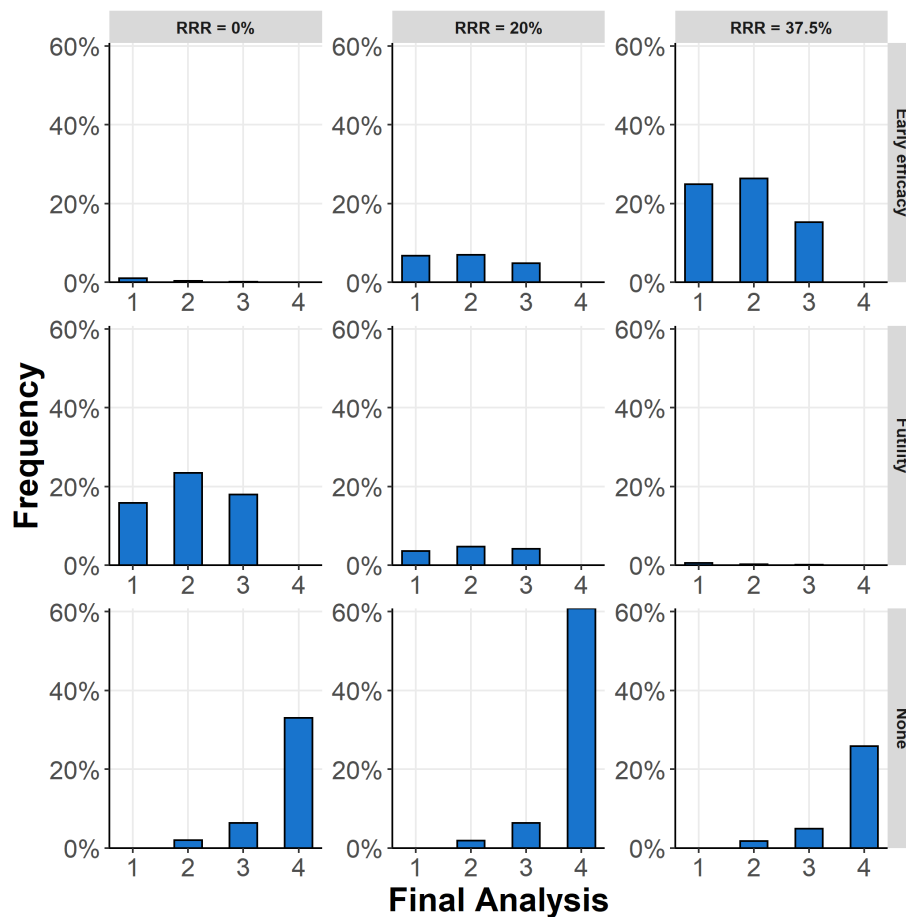
Example: a simulated 4-arm trial

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 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

together • COVID-19
clinical trials

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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 ($i \in \{Control, 1,2,3\}$) 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			

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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.

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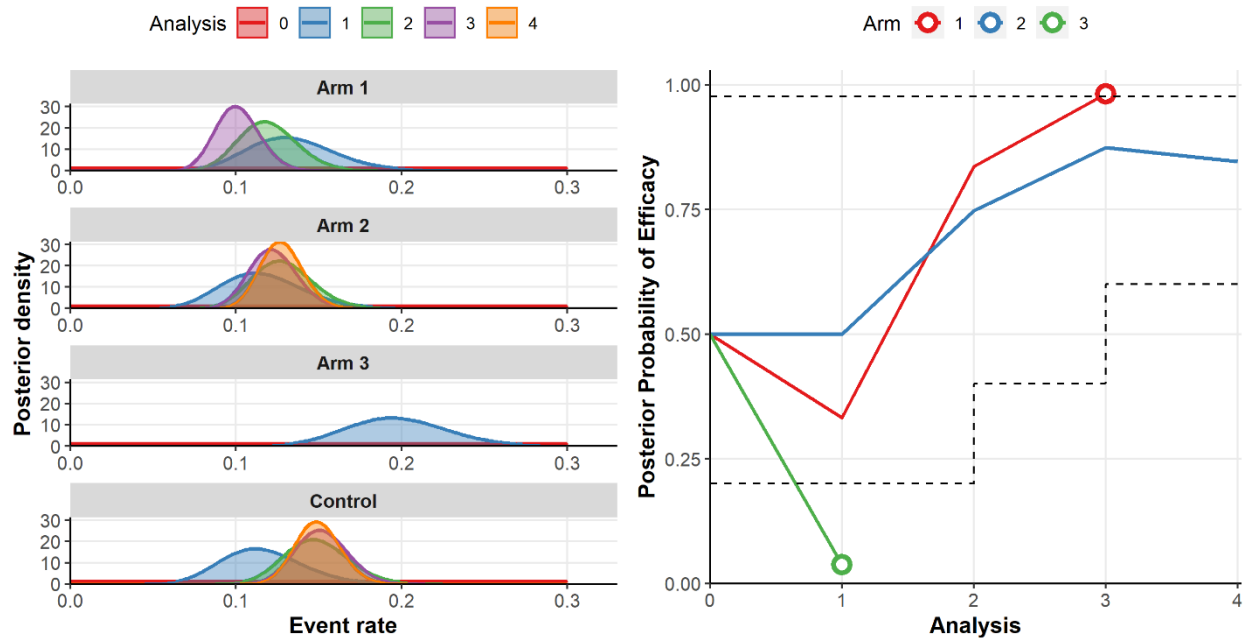
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Protocol

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

Protocol Number: **(Version Date)**	TOGETHER trial V2.0 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

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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

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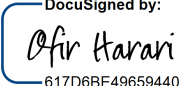
Protocol Number: Version 2.0

Document Date/Version: March 25, 2021

Cytel, Inc. Author:
Ofir Harari
Cytel, Inc.

Signature: *Ofir Harari*
DocuSigned by:
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Date: 4/8/2021

Cytel, Inc. Author:
Hinda Ruton
Cytel, Inc.

Signature: *Hinda Ruton*
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Date: 4/8/2021

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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:_____
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Date: 3/29/2021
_____

Principal Investigator Signatory:
Gilmar Reis

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administrador@cardresearch.org

Signature:_____
Gilmar Reis
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Date: 3/29/2021
_____

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LIST OF IN-TEXT TABLES

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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

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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

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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.**.

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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]			

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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.

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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).

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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

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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%.

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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).

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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

$$\log p(\beta, \gamma | \boldsymbol{y}) = \log p(\beta, \gamma) + \sum_{i=1}^{n} \log p(y_i | \beta, \gamma)$$

$$= \sum_{i=1}^{n} \{ y_i(x_i^T \beta + \gamma T_i) - \log[1 + \exp(x_i^T \beta + \gamma T_i)] \}, (1)$$

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

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$$h_0(t; \boldsymbol{\lambda}) = \sum_{j=1}^{J} \lambda_j \, \mathbb{I}\big(t \in (a_{j-1}, a_j]\big) \quad (1)$$

as in Ibrahim et al.[4] for $\lambda_1, \dots \lambda_J \geq 0$ 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 $\boldsymbol{t} = [t_1, \dots, t_n]^{\mathsf{T}}$ the vector of event times, the log-likelihood function is given by

$$\ell(\boldsymbol{t}; \beta, \gamma, \boldsymbol{\lambda}) = \sum_{i=1}^{n} [(1 - \delta_i) \log h_0(t_i; \boldsymbol{\lambda}) + x_i^{\mathsf{T}} \beta + \gamma T_i + \log S_0(t_i; \boldsymbol{\lambda}) + \exp(x_i^{\mathsf{T}} \beta + \gamma T_i)], \quad (3)$$

where δ_i is an indicator assuming the value of 1 if the ith 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.

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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:

    o ≥50 years or <50 years

- Sex: Male or female

- Time from onset of symptoms:

    o ≥ 120 hours or < 120 hours

- Comorbidity in screening

    o Diabetes mellitus (yes or no);

    o Cardiovascular disease (yes or no);

    o Lung disease (yes or no);

    o Immunosuppressed patients / use of corticosteroid therapy (Yes or No);

    o Other special categories (solid organ transplantation, end-stage kidney disease);

    o HIV status (clinical sites in South Africa).

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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.

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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

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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.

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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

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	• 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.

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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.

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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.

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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 ith 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.

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- 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%

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Figure 2: a graphical illustration of Table 2.
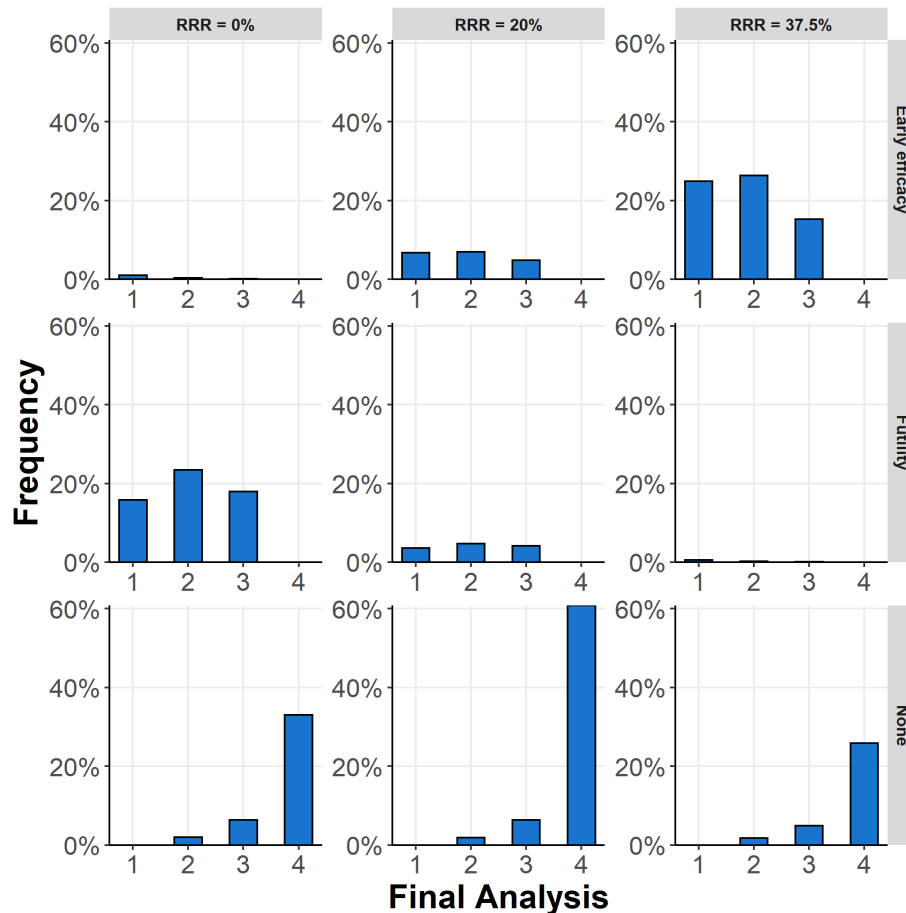
Example: a simulated 4-arm trial

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

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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 ($i \in \{$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			

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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*
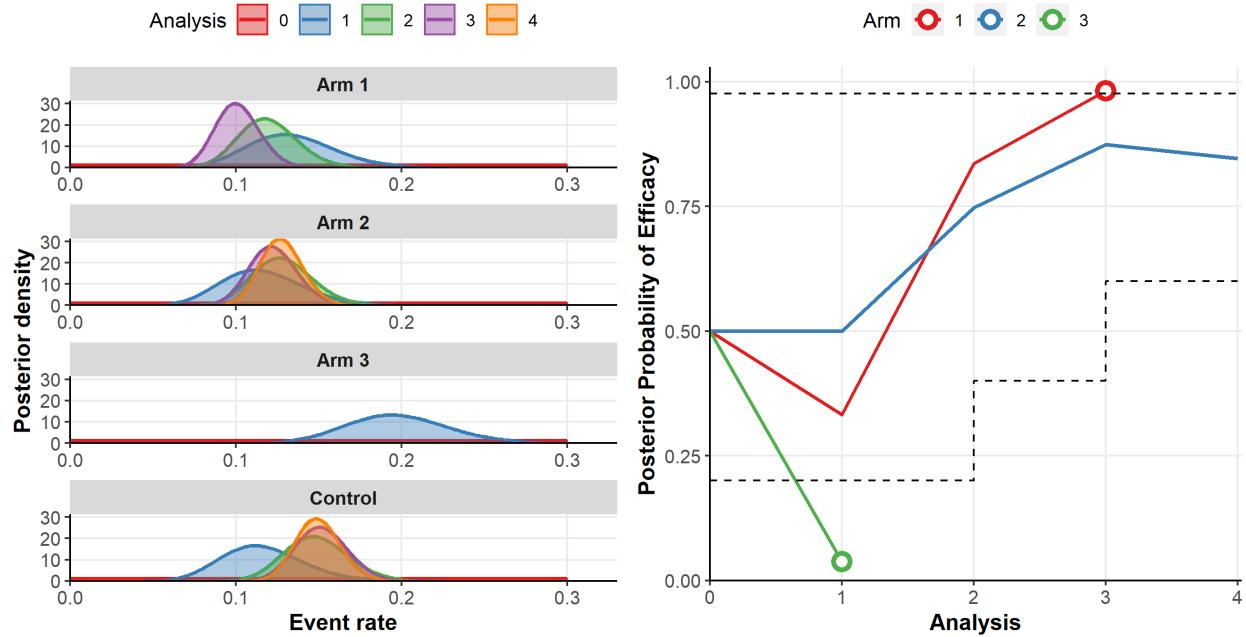
*The dashed lines mark the decision boundaries.

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
3.0	8 Feb 2022	• Updated secondary and exploratory endpoints to correspond with the master protocol (WURSS-21 and oxygen saturation) • Updated analysis population definitions to include modified ITT • Updated analysis of secondary/exploratory outcomes to include Bayesian analyses
4.0	3 May 2022	• Updated secondary and exploratory endpoints to correspond with the master protocol (self-reported time to recovery