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

PROTOCOL

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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

	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.**].

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).

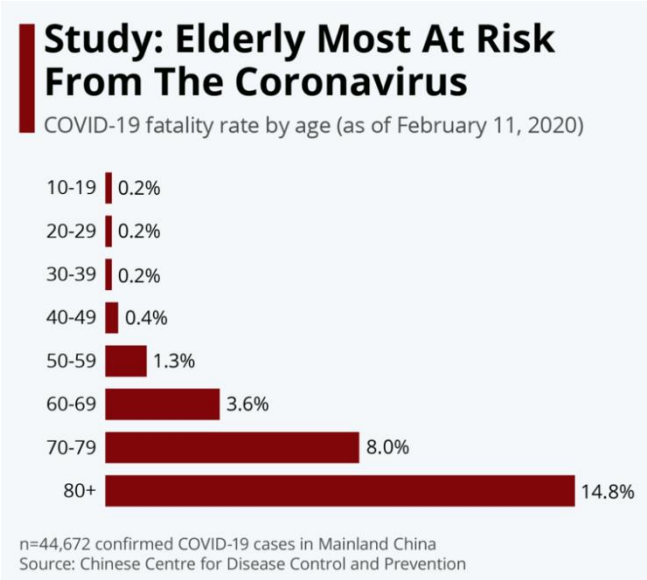


Figure 1 - Age-adjusted mortality

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

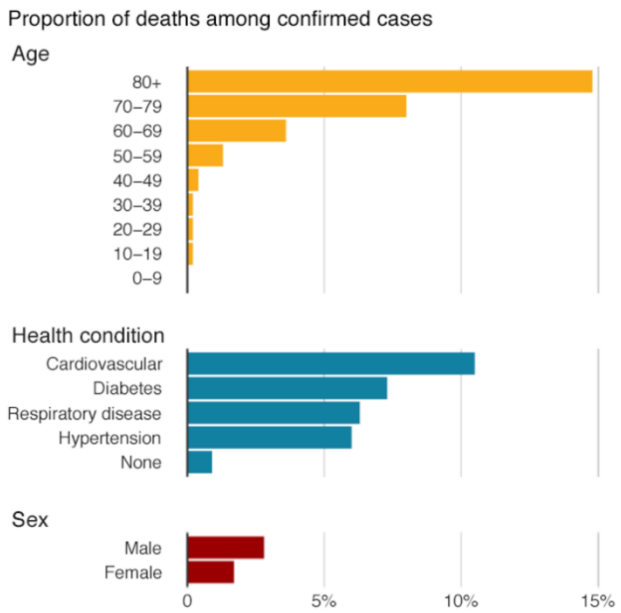


Figure 2 – Global Mortality by Age group – COVID-19

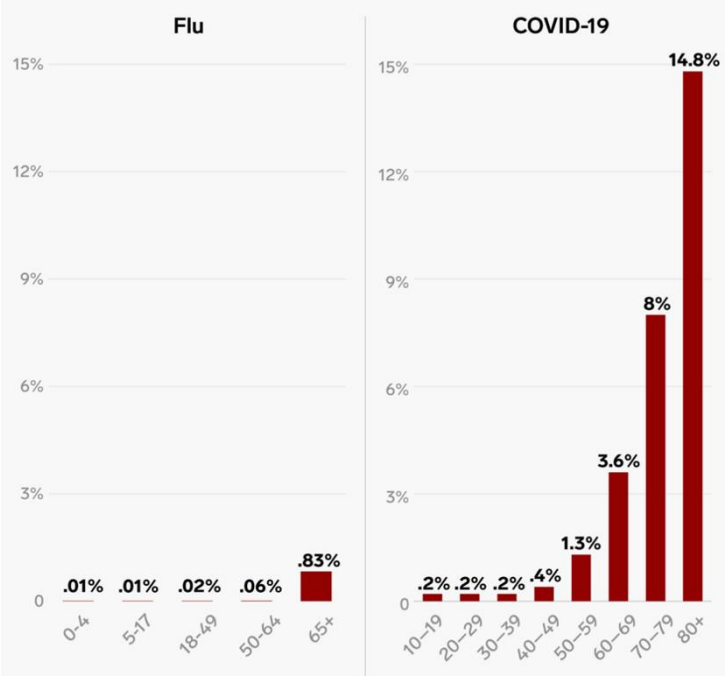


Figure 3 – Mortality from influenza and COVID-19

1.4 Mechanisms of infectivity

This global health emergency has intensified research efforts to understand better the pathogenesis, clinical manifestations and outcomes of people affected by this new viral strain. Coronavirus spike proteins, including those from SARS-CoV2, interact with Angiotensin-Converting Enzyme 2 (ACE2) and with type II transmembrane serine proteases to invade cells[14,16]. 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 (≥ 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 INVESTIGATIONAL PLAN

3.1 Study design

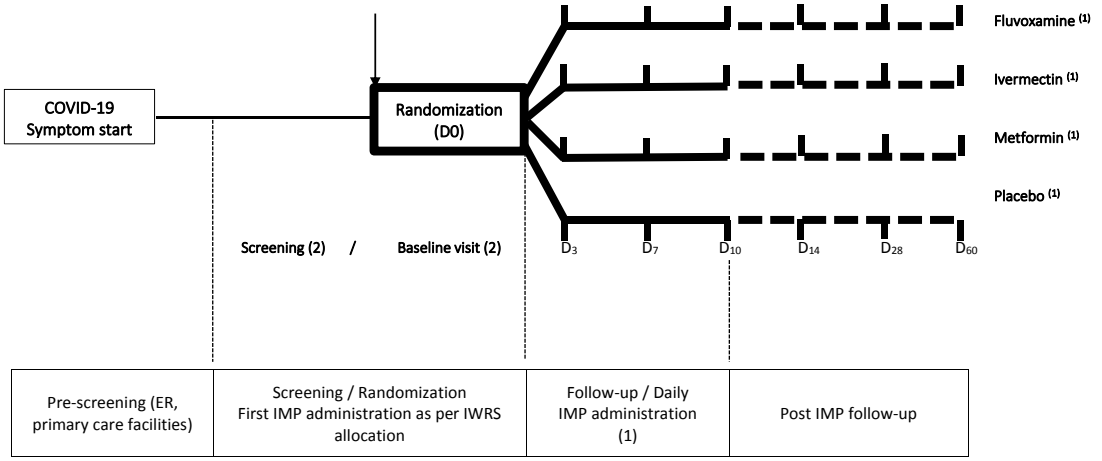
This is a multicenter, adaptive, double-blind, randomized, placebo-controlled study to assess the effect of fluvoxamine, ivermectin and metformin, in reducing hospitalization of patients with mild COVID-19 and high-risk for complications. The treatment groups are:

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 μM), CADs including fluvoxamine, have been shown to inhibit lysosomal acid sphingomyelinase and cause drug-induced phospholipidosis. This non-specific activity can globally deregulate lipid homeostasis, modulating autophagy via the mTOR nutrient detection pathway[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 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[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.

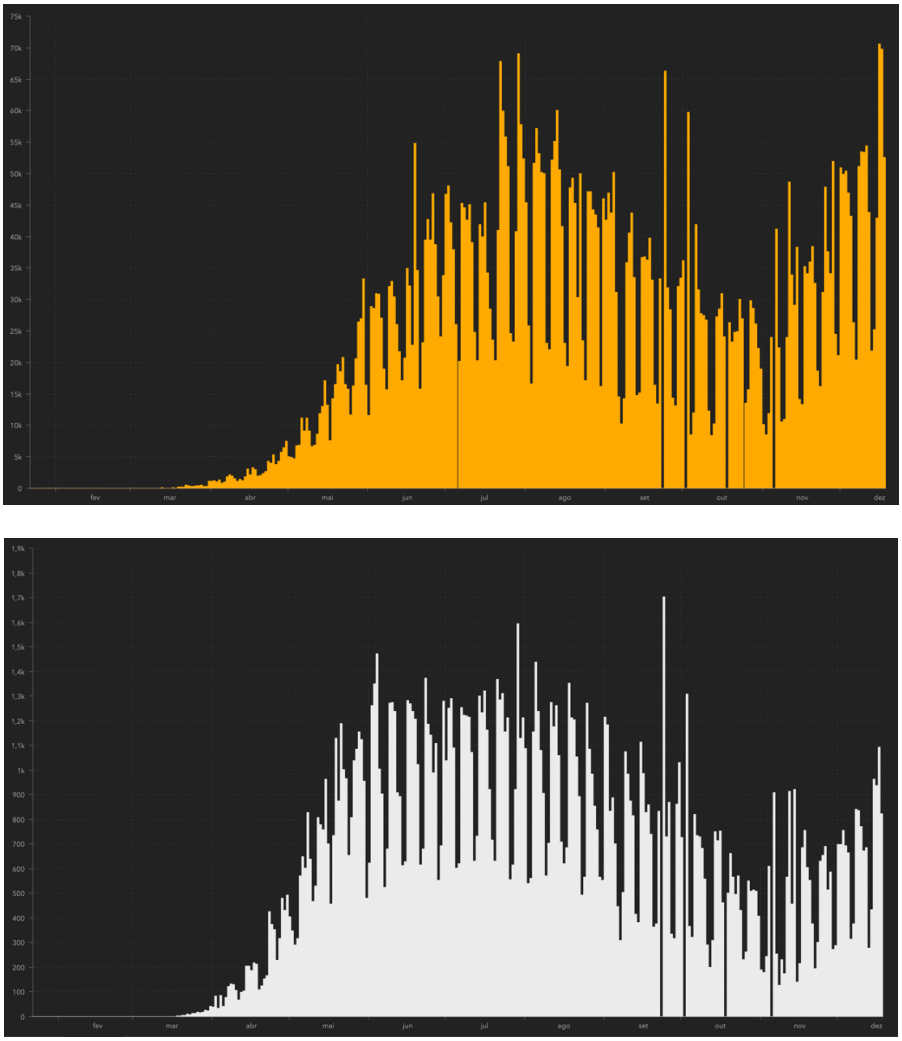
3.6.3 Metformin

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].

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 ≥ 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. SaO2 < 90% or < 93% on nasal oxygen therapy at 10 L / min;
    iii. PaO2 / FIO2 < 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);
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). 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 > 38.0º 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.

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

Vaccination Status										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.

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.

8.2.5 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 enrolment until receiving vaccination. The date and type of vaccination received will be documented.

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 (will be performed only at 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)[102]. 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[103]. 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 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)[104], 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.

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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