# Clinical Trial Protocol

# COVID19_AMB_Brazil

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

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## LIST OF ABBREVIATIONS

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

## GLOSSARY OF TERMS

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

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

# PROTOCOL OVERVIEW

**Protocol – COVID-19_MG_AMB_2**

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

<table>
<tr><td></td><td>
<ul>
<li>Time from start of treatment to death in 14, 28 days, and 60 days.</li>
<li>Safety and tolerability</li>
</ul>
</td></tr>
<tr><td>Design:</td><td>Multicenter, double-blind, adaptive, prospective, randomized, parallel-group, placebo-controlled, 8-week follow-up after randomization.</td></tr>
<tr><td>Treatment:</td><td>
Table 1 - Study treatment regimen
<table>
<tr><th></th><th colspan="3">Treatment Scheme</th></tr>
<tr><th>Visit<br>Clinic</th><th>Fluvoxamine</th><th>Ivermectin</th><th>Metformin XR</th></tr>
<tr><td>$D_0$ – randomization</td><td>100 mg</td><td>See Table 2 and 3</td><td>750 mg BID</td></tr>
<tr><td>$D_1$ to $D_2$</td><td>100 mg BID</td><td>See Table 2 and 3</td><td>750 mg BID</td></tr>
<tr><td>$D_3$ to $D_9$</td><td>100 mg BID</td><td>No medication</td><td>750 mg BID</td></tr>
</table>
<table>
<tr><th>Peso (kg)</th><th>Número de comprimidos de 06 mg</th><th>Dose total mg</th><th>Dose (mcg kg)</th></tr>
<tr><td>40 - 45</td><td>3</td><td>18</td><td>400 – 450</td></tr>
<tr><td>46 – 50</td><td>3</td><td>18</td><td>360 - 391</td></tr>
<tr><td>51 - 55</td><td>4</td><td>24</td><td>436 - 470</td></tr>
<tr><td>56 – 60</td><td>4</td><td>24</td><td>400 - 428</td></tr>
<tr><td>61 – 65</td><td>4</td><td>24</td><td>369 - 393</td></tr>
<tr><td>66 – 70</td><td>5</td><td>30</td><td>428 - 450</td></tr>
<tr><td>71 - 80</td><td>5</td><td>30</td><td>422 - 375</td></tr>
<tr><td>80 - 90</td><td>6</td><td>36</td><td>400 - 450</td></tr>
<tr><td>> 91</td><td>6</td><td>36</td><td>Até 400</td></tr>
</table>
Tabela 2 – Posologia considerando comprimidos de ivermectina 06 mg
</td></tr>
</table>

Treatment (continued):

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

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

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

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

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| Inclusion Criteria | 1. Patients over 18 years of age with the capacity to provide informed consent |

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| Inclusion Criteria (continued) | 2. Patients seen at a Primary Care Unit of the Brazilian National Health System (SUS), or patients seen at SUS or supplementary care units with an acute clinical picture compatible with COVID 19 and symptoms beginning within 7 days of the screening date;<br>3. Patients over 18 years of age and with at least ONE of the following criteria<br>a. Age 50≥ years (do not need any of the other criteria)<br>b. *Diabetes mellitus* requiring oral medication or insulin<br>c. Hypertension requiring at least 01 oral medication for treatment<br>d. Known cardiovascular diseases (heart failure, congenital heart disease, valve disease, coronary artery disease, myocardiopathy under treatment, clinically manifest heart diseases with clinical repercussions)<br>e. Lung disease symptomatic and/or under treatment (emphysema, fibrosing diseases)<br>f. Patients with symptomatic asthma requiring chronic use of agents for symptom control.<br>g. Smoking<br>h. Obesity, defined as BMI > 30 kg/m$^2$ on weight and height information provided by the patient;<br>i. Transplant Patients<br>j. Patient with stage IV chronic kidney disease or on dialysis.<br>k. Immunosuppressed patients/in use of corticotherapy (equivalent to at least 10 mg prednisone per day) and/or immunosuppressive therapy)<br>l. Patients with a history of Cancer in the past 05 years or currently undergoing oncological treatment<br>4. Patient with a positive rapid test for SARS-CoV2 antigen performed at the time of screening or patient with a positive diagnostic test for SARS-CoV2 within 7 days of symptom onset.<br>5. Willingness to use the proposed investigational treatment and follow the procedures foreseen in the research |
| Exclusion Criteria: | 1. negative diagnostic test for SARS-CoV2 associated with acute influenza symptoms (patient with a negative test taken early and becomes positive a few days later is eligible, provided he/she is < 07 days from the onset of influenza symptoms);<br>2. Patients with an acute respiratory condition compatible with COVID-19 seen in the primary care network and with a decision to hospitalize;<br>3. Patients with an acute respiratory condition due to other causes;<br>4. Patients Vaccinated for SARS-CoV-2<br>5. Dyspnea secondary to other acute and chronic respiratory causes or infections (e.g., decompensated COPD, acute bronchitis, pneumonia, primary pulmonary arterial hypertension);<br>6. Acute influenza presenting at least ONE of the criteria below: |

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| Criteria for Exclusion (continued) | a. Respiratory Rate > 28/min;<br>b. SaO2 < 90% or < 93% on nasal oxygen therapy at 10 l/ min;<br>c. $PaO/_2$ $FIO_2$ < 300 mmHg<br>7. Patients taking serotonin reuptake inhibitors (Donepezil, Sertraline)<br>8. Use of the following medications in the last 14 days:<br>a. Monoamine-Oxidase-Inhibitors (MAOI): Phenelzine, Tranylcypromine, Selegiline, Isocarboxazid, moclobemide;<br>b. Use of iodinated contrasts during the treatment until 05 days after the end;<br>c. Use of Antiretroviral Agents (Treatment of Acquired Immune Deficiency Syndrome – AIDS)<br>9. Patients with severe psychiatric disorders or major depression not controlled or controlled with any of the prohibited drugs (item above);<br>10. Pregnant or nursing patients;<br>11. History of severe ventricular cardiac arrhythmia (ventricular tachycardia, recovered ventricular fibrillation patients) or Long QT Syndrome;<br>12. History of diabetic ketoacidosis or a clinical condition that maintains persistent metabolic acidosis;<br>13. Surgical or contrast use planned to occur during treatment or within 5 days of the last dose of study medication;<br>14. Current daily and/or uncontrolled alcoholism;<br>15. History of seizures in the last month or an uncontrolled convulsional condition;<br>16. Clinical history of Liver Cirrhosis or Child-Pugh C classification;<br>17. Patients with known severe degenerative neurological diseases and/or severe mental illness;<br>18. Inability of the patient or representative to give consent or adhere to the procedures proposed in the protocol;<br>19. Hypersensitivity and/or known intolerance to Fluvoxamine, Ivermectin or Metformin;<br>20. Inability to take oral medications; |
| Primary and Secondary Outcomes: | <u>Primary endpoint:</u><br>• To evaluate the effect of fluvoxamine, ivermectin, and metformin in reducing the need for emergency care AND observation for longer than 06h due to worsening COVID-19;<br>• To evaluate the effect of fluvoxamine, ivermectin and metformin in reducing the need for Hospitalization due to complications and/or worsening of COVID-19<br><br><u>Co-primary Outcome:</u><br>To evaluate the effect of Fluvoxamine, Ivermectin and Metformin in reducing mortality associated with COVID-19 up to 28 days from randomization. |

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| Primary and Secondary Outcomes: (continued) | <u>Secondary outcomes:</u><br>The secondary endpoints will assess, relative to the placebo group:<br>• Change in viral load on day 03 and 07 after randomization (Evaluation to be performed on the first 600 randomized patients – 150 patients in each stratum);<br>• Time to clinical improvement (up to 28 days from randomization), defined as greater than 50% improvement in reference to symptoms at the time of randomization;<br>• Time to clinical failure, defined as the time until hospitalization due to clinical progression of COVID-19 (lower respiratory tract viral infection associated with dyspnea requiring oxygen therapy; hospitalization due to progression of COVID-19) or complications directly associated with COVID-19;<br>• Number of days with respiratory symptoms since randomization<br>• Hospitalization for any cause<br>• Hospitalization due to progression of COVID-19<br>• Mortality due to pulmonary complications<br>• Cardiovascular mortality<br>• Mortality from any cause<br>• Adverse events (up to 28 days);<br>• COVID-19 symptom scale assessment ($D_1$ to $D_{28}$)<br>• WHO Clinical Worsening Scale Assessment ($D_1$ to $D_{10}$)<br>• Assessment of the PROMIS Global Health Scale (“Global-10”) days 14 and after60 randomization<br>• Mortality rate of patients at day 14 and 28 days;<br>• Proportion of non-adherent patients with the product under investigation;<br>• Specific adverse reactions to the study medications: fluvoxamine, ivermectin and metformin. |
| Procedures | See study procedure schedule for details and applicable visits.<br><br><u>Visit 1 – screening visit ($D_1$).</u><br>Patients seen in the primary care network or in SUS emergency care units or patients seen in supplementary medicine emergency care units with clinical criteria for presumptive diagnosis of COVID-19, without fulfilling hospitalization indication criteria, will be invited to participate in this research.<br>• obtaining the informed consent form (ICF) for potentially eligible subjects prior to any procedures related to this protocol<br>• checking the inclusion/exclusion criteria<br>• documentation of screening procedures (demographics, high-risk criteria for covid-19, and concomitant medications) as described in the protocol. Serious adverse events observed will be reported within 24 hours of knowledge of the event<br>• sample collection for rapid antigen testing for SARS-CoV2 in undiagnosed patients. Patients with a confirmed diagnosis of COVID-19 within 7 days of screening do not need to be tested at screening |

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| Procedures (continued) | <u>Visit 2 – baseline visit, randomization, and administration of the first dose of the investigational drug ($D_1$)</u><br>• The randomization visit should be performed immediately after the screening visit, at the same assessment<br>• Performing the baseline visit procedures, according to the research flowchart:<br>  ○ airway secretion sample for RT-PCR for Sars-CoV2 in the first 800 patients (viral load assessment – expected in the first 200 patients in each stratum)<br>• Urinary pregnancy test for women with at least one menstrual period in the last 12 months<br>• Checking the inclusion/exclusion criteria<br>• Randomization in the IWRS system<br>• Completion of the WHO acute influenza syndrome questionnaire<br>• Digital oximetry measurement<br>• Randomization and delivery of the investigational drug as allocated by the IWRS. All patients will receive the standard treatment for COVID-19 as adopted by the health units to which they are linked, as defined by the medical team. All patients will also receive 24-hour telephone contact, to be activated in case of need and will be oriented about the daily telephone contact that will be carried out by the research team until $D_{10}$. The 800 initial patients will have their own nasal swab and saliva swab collected for RT-PCR at randomization, $_3$ from $D_7$ to treatment. The patients will be oriented about this home collection and logistics for collecting the samples at their homes<br><br><u>Evaluations after randomization</u><br>• all patient assessments will be conducted by telephone contact, social media applications, video calls, or telemedicine. No in-person visits are planned, especially due to the fact that the virus is highly transmissible, following the guidelines of the health authorities regarding recommendations for confinement and distancing from cases.<br>• Daily evaluations by telephone contact: between $D_1$ and $D_{10,}$ the patient will be monitored daily by telephone and/or video calls, and the WHO flu symptoms questionnaire will be carried out. In the initial 600 patients, there will be additional information on the occasion of telephone contact on days $D_2$ and $D_6$, when the patient will be oriented about the self-collection of samples for viral load research (nasal swab + saliva) to be performed the next day.<br>• Assessment of $D_{14}$ – telephone contact/video call to assess the evolution of the clinical picture and verify outcomes.<br>• Evaluation of $D_{28}$ – telephone/video call contact for evaluation of the evolution of the clinical picture and verification of in-person outcomes. Possible persistence of symptoms that appeared at the time of COVID-19 diagnosis will be evaluated. |

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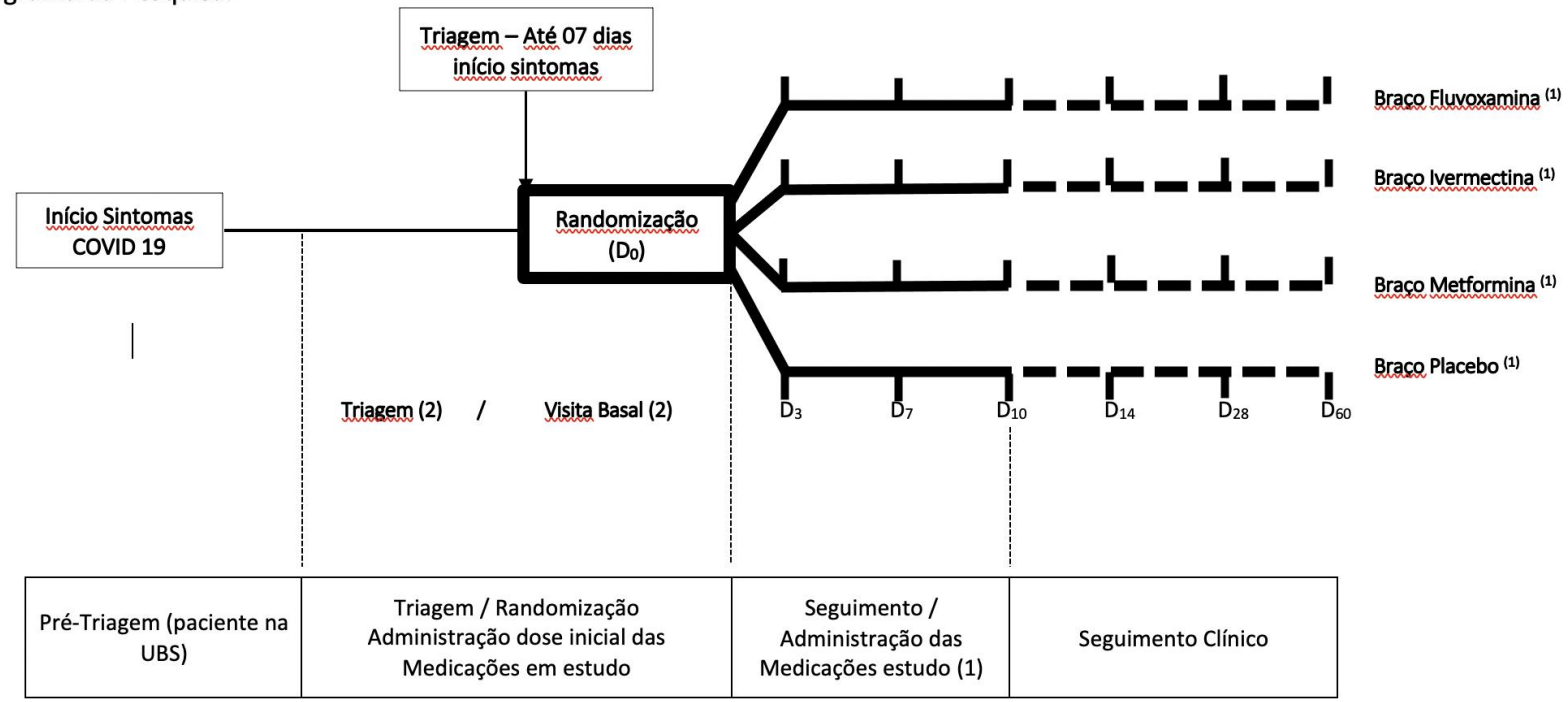
| | Research Monitoring Committee<br>A research steering committee, an independent data and safety monitoring committee, and an endpoint monitoring committee will be established in a blinded manner until the end of the study is defined.<br><br>The research steering committee will ensure the scientific integrity of the study in addition to operational care for the proper conduct of the research. The safety monitoring committee will consist of experienced external researchers to ensure the overall safety of the participating research subjects and group data in a blinded manner. The endpoint monitoring committee will reassess identified clinical endpoints and ensure that they indeed fall within the intended endpoints of the trial, using predefined event classification criteria. |
| Sample Size | It is planned to randomize a total of 2,724 patients distributed in the four treatment arms |
| Statistical Methods | This study will be conducted in two phases: (1) Internal pilot phase, which will be considered for the first 100 patients. This phase is necessary due to the rapidly evolving scientific information, requiring responses from the public health systems, and considering the need for eventual adjustments in order for the study to be successful. At this time, there will be no analysis, and the patients' data will be included for analysis as planned; and (2) Main Study, which involves the full implementation of the research protocol with hospitalization as the primary endpoint of the study. This phase is also an adaptive phase, where there will be three (3) interim analyses to assess the effects of the interventions compared to the placebo arm, at 25, 50 and 75% of the total planned sample.<br><br>Critical adjustments involve (a) withdrawing the placebo arm if there is great benefit from the others and (b) withdrawing any arm that does not show benefit or meets futility criteria. The sample size was calculated at 681 participants per group, for a total of 2,724, maintaining a power of 80% and a two-sided alpha of 0.05 to demonstrate a statistical significance ratio of 0.80 (20% reduction in hospitalization between groups and reduction in deaths compared with the COVID-19 population). The statistical software SAS version 9.4 was used for this sample calculation.<br>The protocol design will be adaptive, with provision for blinded interim analyses comprising 25, 50 and 75% of the initially projected sample of participants. The sample size will be revised based on the outcomes that occurred in the placebo group at the time of the interim analyses. Blinded outcome analysis will be performed with simulations to limit type I errors within the 5% tolerance range (97.5% or greater probability of superiority over the control group). Decisions may be made at this point to terminate arms of the study if there are not acceptable projections of benefit over futility. |

Fluxograma da Pesquisa:




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

**Table 4 – Procedure Flowchart**

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

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

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

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

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

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

5 After signing the Informed Consent Form.

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

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

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

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

# 1 INTRODUCTION

## 1.1 Background

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

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

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

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

## 1.2 Transmission

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

Evidence from initial epidemiological studies conformed that COVID-19 has higher levels of transmissibility and pandemic risk than SARS-CoV since the effective reproductive number ($R_0$)

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

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

### 1.3 Clinical manifestations and risk profile

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

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

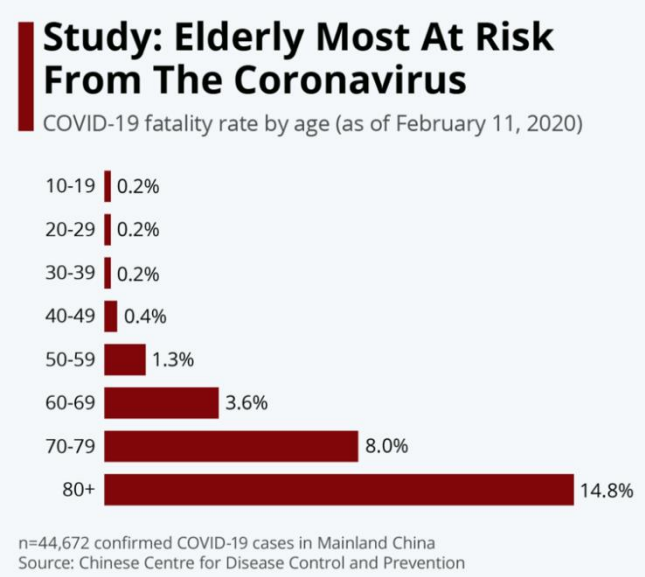



**Figure 1 - Age-adjusted mortality rate**

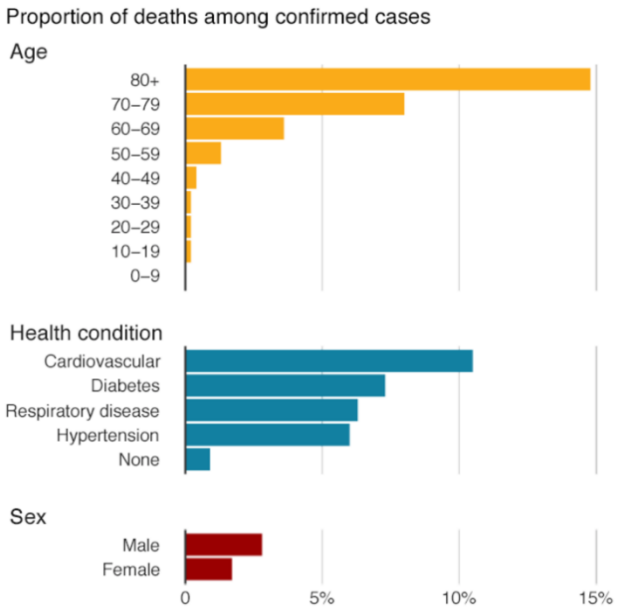



**Figure 2 - Global mortality by age group - COVID-19**

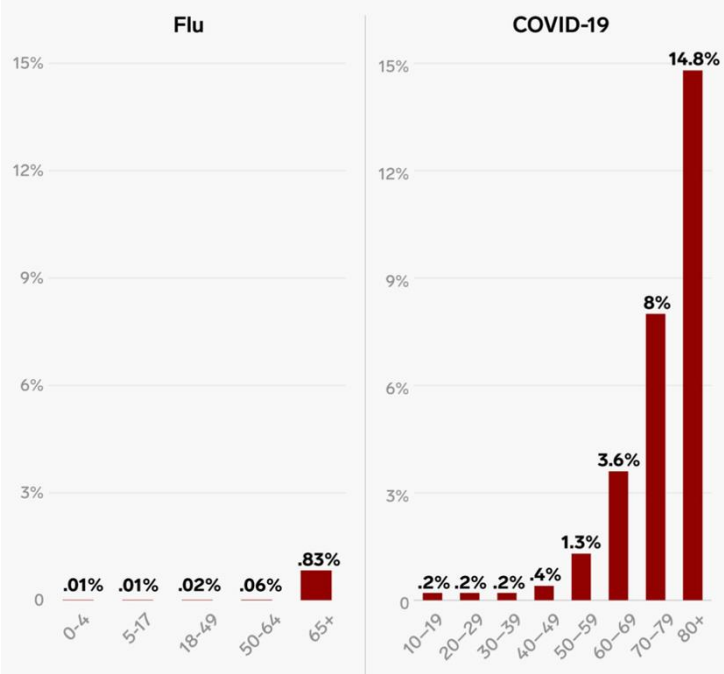



**Figure 3 - Influenza and COVID-19 mortality**

### 1.4 Mechanisms of infectivity

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

### 1.5 Need for studies to treat COVID-19

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

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

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

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

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

## 2 OBJECTIVES OF THE STUDY

The objective of this study was to evaluate the efficacy, safety, and benefit of the use of Fluvoxamine, Ivermectin, and Metformin in patients acutely affected with COVID-19 and presenting mild respiratory symptoms, seen at emergency care units and/or Basic Health Units of the Brazilian Unified Health System, through a research protocol designed with 04 treatment arms: (1) Fluvoxamine; (2) Ivermectin; (3) Metformin and (4) Placebo.
The research subject's participation in the protocol is for 60 days, with the first 10 days being the treatment phase and the remaining period for follow-up after the end of treatment.

### 2.1 Objectives/primary endpoint

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

Goal/co-primary endpoint:

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

### 2.2 Objectives/secondary outcomes

The proposed secondary objectives are:

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

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

**2.3 Exploratory Objectives**

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

# 3 INVESTIGATIONAL PLAN

## 3.1 Study design

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

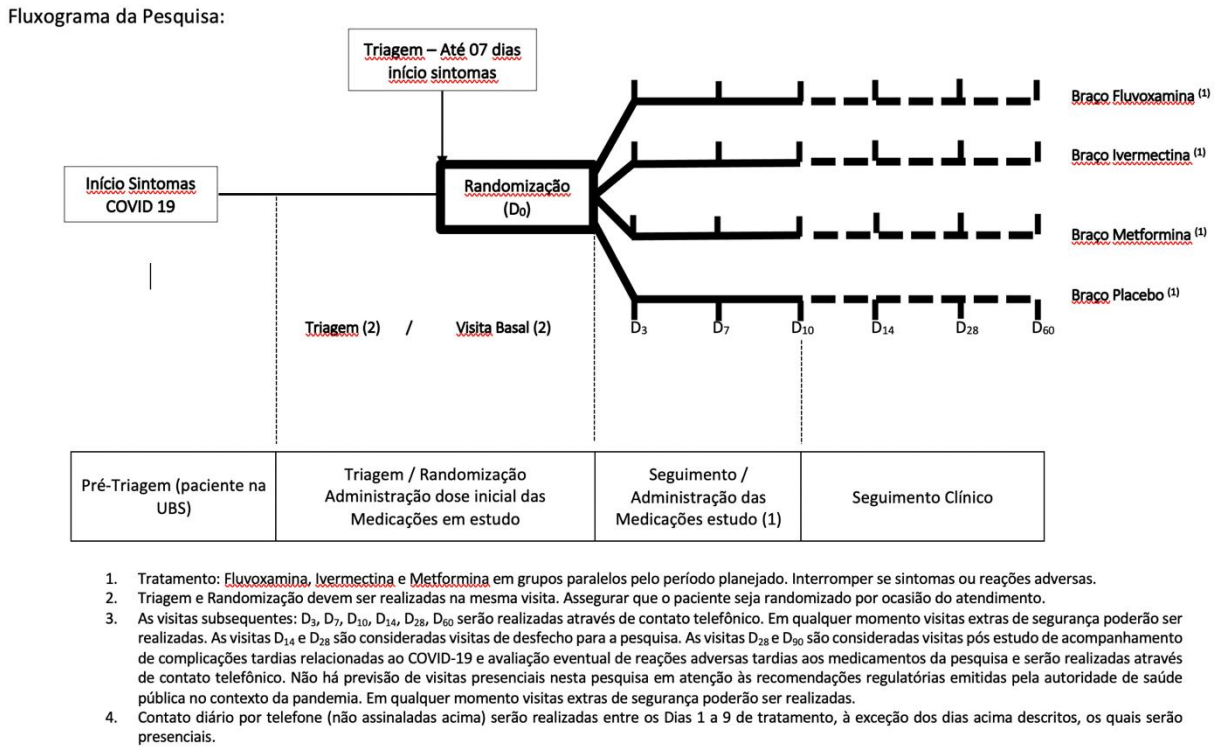
The groups will be as follows:

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

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

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

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




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

**Figure 3 - Flowchart of the research**

### 3.2 Justification of the study design

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

### 3.3 Rationale for the use of fluvoxamine

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

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

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

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

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

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

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

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

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

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

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

### 3.3.4 Antiplatelet effects (common to all SSRIs).

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

### 3.3.5 Elevation of melatonin levels in the body.

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

## 3.4 Rationale for the use of ivermectin

*In vitro* studies have shown that ivermectin inhibits the replication of many viruses, including influenza, zika, dengue and others. It has also been seen to inhibit the replication of SARS-CoV2 in infected cell cultures, leading to the absence of almost all viral material within 48h. In addition to these, in several animal models, when infected with SARS-CoV2 or similar coronaviruses, the use of ivermectin in several preclinical and clinical studies resulted in a significant drop in viral

load and blocked several inflammatory pathways associated with proteolysis, cell lysis, and consequent reduction of organ damage[58,59,60,61,62,63,64,65,66].

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

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

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

### 3.5 Rationale for the use of metformin

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

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

levels are reduced, with a direct relationship between these changes and the intensity of insulin resistance observed in these patients[87].

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

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

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

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

#### 3.6.1 Fluvoxamine

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

#### 3.6.2 Ivermectin

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

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

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

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

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

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

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

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

Such a dosing regimen was discussed extensively between the co-authors and the study steering committee a few weeks before the original version of this clinical trial was finalized. Moreover, the

data made available by the authors of the ongoing clinical trials did not contain a significant number of participants. Even though pharmacokinetic studies evaluating higher doses in other clinical conditions are already in the public domain, we have chosen to initially maintain the dose of 400 mcg/ kg in a single dose in the trial.

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

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

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

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

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

**Table 2** - Dosage considering ivermectin 06 mg tablets

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

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

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

### 3.6.3 Metformin

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

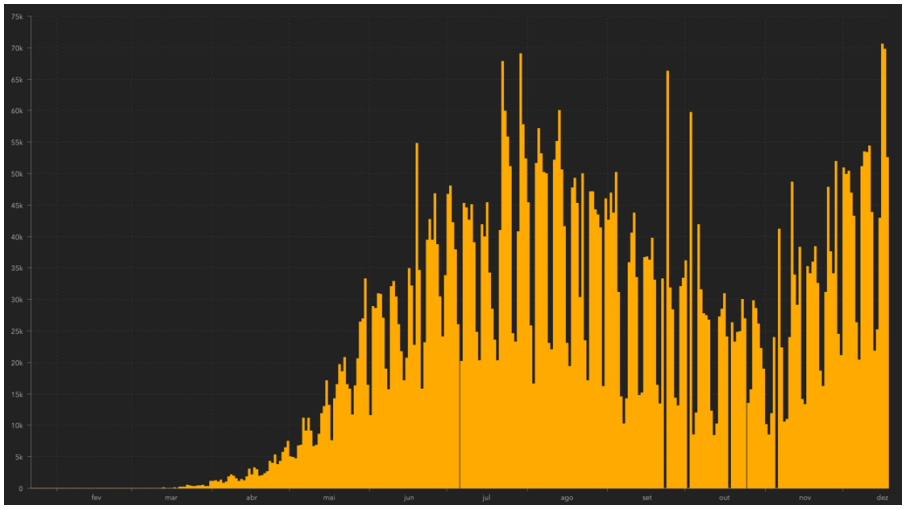
We chose to use the extended-release formulation because it causes fewer gastrointestinal adverse effects, and the bioavailability is more consistent and stable, which becomes an advantage by providing a uniform serum dose.

### 3.7 Justification for the study

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

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

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



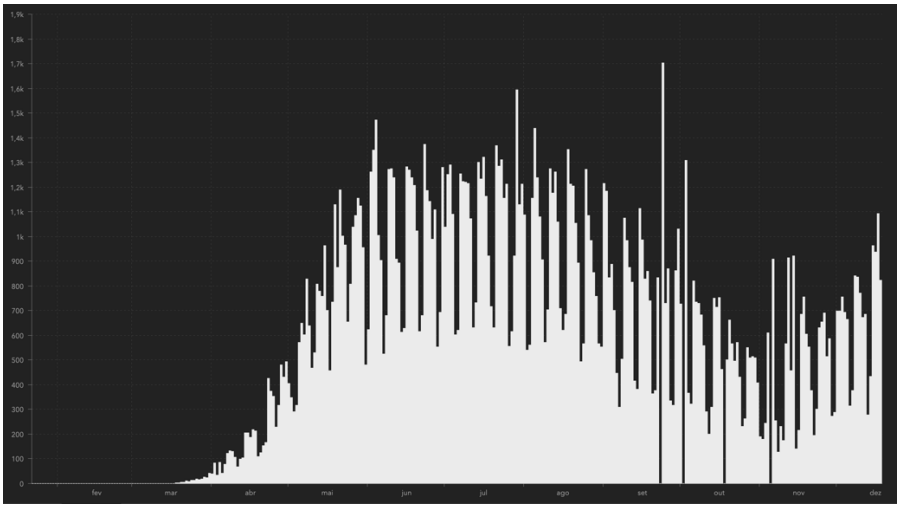


**Figure 5 and 6 - Number of cases (yellow) and deaths (white) diaries associated with COVID-19**
**Source: Johns Hopkins University Data Center (12/17/2020)**

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

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

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

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

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

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

# 4 RESEARCH PLAN

## 4.1 Overall study design

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

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

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

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

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

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

**Treatment phase (Randomization):**

After all baseline visit procedures have been performed, all inclusion criteria have been checked, and it has been identified that the patient does not meet any exclusion criteria for the study, the participants will be considered eligible for the treatment phase and then randomized to one of the four arms of the trial in a 1:1:1:1 ratio for treatment with the investigational product(s).

This randomization process will be performed centrally using the IWRS system, and treatment kits will be allocated and identified by random numbering. The KITs will be made available in such a way that no individual will be able to identify the study medication.
Participants will start their assigned treatments (Fluvoxamine; Ivermectin; Metformin or placebo).

### 4.2 Duration of participation in the study

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

## 5 SELECTION AND WITHDRAWAL OF PARTICIPANTS

### 5.1 Number of participants

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

### 5.2 Inclusion criteria

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

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

### 5.3 Exclusion criteria

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

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

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

1.

**5.4 Randomization criteria**

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

**5.5 Discontinuation of the product under investigation or withdrawal of participants**

**5.5.1 Discontinuation of the product under investigation**

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

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

**5.5.2 Withdrawal from the study**

**5.5.2.1 Withdrawal of consent**

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

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

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

**5.5.2.2 Participant withdrawn by the researcher**

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

**5.5.2.3 All early withdrawal participants**

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

# 6 STUDY TREATMENTS

## 6.1 Concealment of treatment

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

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

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

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

## 6.2 Dosage form/formulation administration

### 6.2.1 Fluvoxamine

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

### 6.2.2 Ivermectin

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

### 6.2.3 Metformin

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

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

### 6.3 Dosage and administration

#### 6.3.1 Treatment groups

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

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

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

**Tabela 2** – Posologia considerando comprimidos de ivermectina 06 mg

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

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

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

### 6.3.2 Dosage and administration guidelines

#### 6.3.2.1 Fluvoxamine

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

#### 6.3.2.2 Ivermectin

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

#### 6.3.2.3 Metformin

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

### 6.4 Packaging and labelling

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

### 6.5 Study treatment allocation

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

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

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

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

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

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

### 6.6 Delivery, storage, and accounting by the study center

#### 6.6.1 Delivery from the study center

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

#### 6.6.2 Storage

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

### 6.6.3 Accounting

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

## 6.7 Changing the dose of the drug

### 6.7.1 Adverse reactions during the use of medications

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

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

### 6.7.2 Usual care

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

### 6.8 Prohibited therapy, special considerations, and concomitant treatment

#### 6.8.1 Prohibited medications

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

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

#### 6.8.2 Concomitant medications

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

# 7 RISKS AND PRECAUTIONS

## 7.1 Precautions

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

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

## 7.2 Adverse reactions

### 7.2.1 Fluvoxamine

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

### 7.2.2 Ivermectin

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

### 7.2.3 Metformin

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

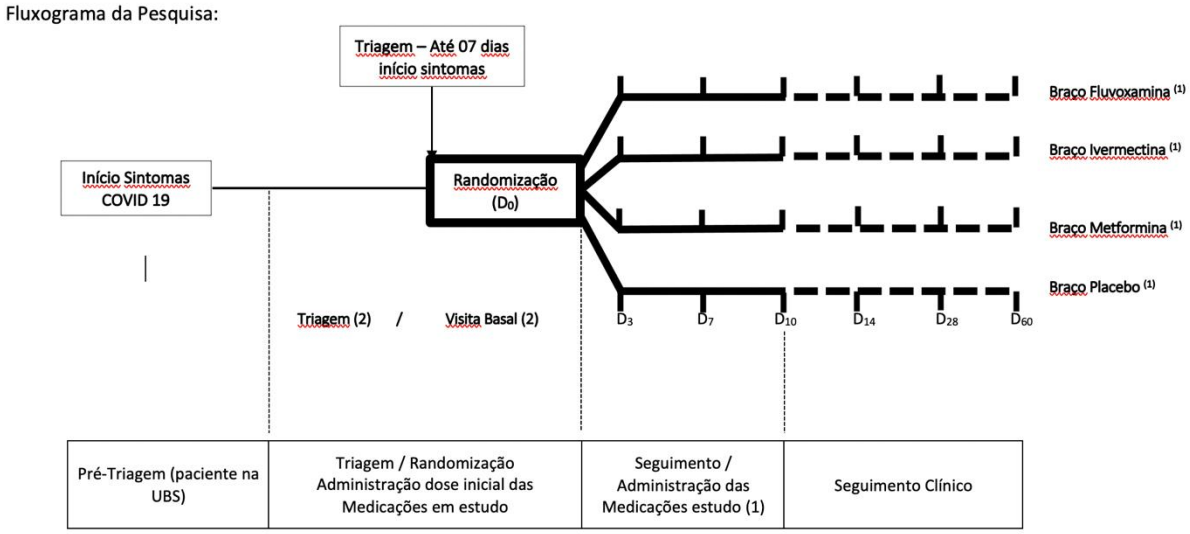
# 8 STUDY PROCEDURES

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

## 8.1 Screening procedures

### 8.1.1 Screening procedures

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




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

Table 1 - Procedure flowchart

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

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

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

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

#### 8.1.1.1 Retrying participants

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

### 8.1.2 Visit 2: Baseline visit procedures/randomization

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

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

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

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

### 8.2.1 Daily telephone contacts ($D_2$ to $D_7$)

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

- Tolerance to the product under investigation
- Adverse effects/adverse reactions which may arise
- Clinical progress regarding COVID-19 and any emergency room visits or hospitalizations
- WHO Ordinal Scale of Clinical Improvement Questionnaire

- For the first 600 patients in the study, during the contact made at the $D_2$ and $D_6$ visits, the participant will be instructed about the collection of nasopharyngeal SWAB or sputum/saliva, which will be performed by the participant himself on the following day ($D_3$ and $D_7$). In the D telephone contact, $_7$the participant will be oriented about the collection of the SWAB samples (it will be collected at the patient's home) or at a place to be arranged, in case of impossibility of access by the delivery service (hard to reach the place, area of high social vulnerability). In these cases, a designated person will go to a known point at an agreed time to collect the sample

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

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

In addition to this, the following procedures will be checked in these visits:

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

### 8.2.3 Visit 5 ($D_{10}$)

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

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

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

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

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

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

### 8.3 Unscheduled visit procedures

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

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

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

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

### 8.4 Proceedings of the $D_{28}$ visit

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

### 8.5 Early termination procedures (ET)

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

# 9 EVALUATIONS OF THE STUDY

## 9.1 Laboratory examinations

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

## 9.2 Vital signs

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

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

### 9.2.1 Heart rate and blood pressure

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

## 9.3 Physical examination

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

### 9.4 ECG evaluation

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

### 9.5 Patient-reported outcomes

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

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

PROMIS Global Health Questionnaire (Global-10)

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

The 10 questions on the Global-10 were largely adapted from older measures, such as the SF-36 and the EQ-5D, with modifications that resulted in greater sensitivity and accuracy than the questions originally formulated.

### 9.6 Contraception in women of childbearing potential

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

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

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

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

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

## 10 EVALUATION, RECORDING AND REPORTING OF ADVERSE EVENTS

### 10.1 Definition of adverse events

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

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

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

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

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

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

### 10.2 Adverse event reporting period

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

### 10.3 Obtaining adverse events

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

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

### 10.4 Evaluation of adverse events

#### 10.4.1 Intensity/severity

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

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

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

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

**10.4.2 Causality and reporting**

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

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

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

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

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

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

### 10.4.3 Outcome categorization

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

### 10.5 Recording and Reporting

#### 10.5.1 Persistent or recurrent adverse events

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

### 10.5.2 Diagnosis versus signs and symptoms

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

### 10.5.3 Pre-existing clinical conditions

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

### 10.5.4 Clinical laboratory analysis

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

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

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

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

### 10.5.5 Abnormal vital signs and other abnormalities

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

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

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

## 10.6 Adverse drug reaction and reference safety information

### 10.6.1 Adverse drug reaction

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

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

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

### 10.6.2 Reference safety information

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

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

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

## 10.7 Serious Adverse Event

### 10.7.1 Definition of serious adverse event

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

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

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

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

#### 10.7.1.1 Situations that are not considered serious adverse events

The following situations are not considered SAEs:

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

### 10.7.2 Serious adverse event reporting

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

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

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

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

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

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

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

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

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

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

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

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

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

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

#### 10.7.2.1 Composite study endpoints

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

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

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

### 10.7.3 SUSARs

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

## 10.8 Special Situations

### 10.8.1 Definition of special situations

The following situations are defined as special:

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

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

### 10.8.2 Registration and special situation reporting

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

### 10.8.3 Exposure during pregnancy and birth events

#### 10.8.3.1 Definition of exposure during pregnancy and birth events

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

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

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

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

**10.8.3.2 Exposure during pregnancy and recording and reporting of birth events**

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

# 11 STUDY COMMITTEES

## 11.1 Data Security Monitoring Committee (DSMC)

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

## 11.2 Event Adjudication Committee

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

# 12 STATISTICAL CONSIDERATIONS

## 12.1 Study Design

The study will be conducted in two phases:

### 12.1.1 Internal pilot phase

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

### 12.1.2 The main clinical trial

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

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

## 12.2 Randomization

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

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

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

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

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

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

**12.3 Sample Calculation**

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

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

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

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

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

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

### 12.4 Statistical Analysis

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

### 12.5 Analysis of the feasibility results

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

### 12.6 Analysis of primary and secondary results

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

**12.7 Sensitivity analysis**

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

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

**12.8 Subgroup analysis**

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

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

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

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

**12.9 Lost data**

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

**12.10 Combined studies analysis policy**

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

**12.11 Summary table of events**

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

| | | | |
|---|---|---|---|
| 3) **Subgroup Analysis:**<br>i) age (young vs. old)<br><br>ii) Sex (male vs. woman)<br><br>iv) Diabetes<br><br>v) Hypertension<br><br>vi) Chronic kidney disease KDIGO IV or hemodialysis<br>vii) Chronic lung disease<br>viii) Solid-organ transplantation<br><br>ix) Heart Failure | The elderly have a higher risk of complications<br><br>Men have a higher risk<br><br>Diabetes has a higher risk<br><br>Hypertensives have a higher risk<br><br>Kidney disease carries a higher risk<br><br>Lung disease has a higher risk<br>Transplantation has a higher risk<br><br>Heart failure carries a higher risk | Risk Measurement | Regression methods with appropriate interaction terms. |
| 4) **Sensitivity Analysis** | Results remain robust | The primary and co-primary outcome | |
| IMPORTANT REMARKS:<br>• In all analyses, results will be expressed as estimated effect (corresponding to 95%) and associated p-values.<br>• The quality of fit will be assessed by examining the residuals for the model assumptions and chi-square test of goodness of fit | | | |

## 13 ETHICAL CONSIDERATIONS OF THE STUDY

### 13.1 Ethical conduct of the study

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

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

All anonymous data remains the property of the research Steering Committee

### 13.2 Informed consent

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

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

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

**13.3 REB**

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

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

## 14 QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

### 14.1Quality management: critical processes and data

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

#### 14.1.1 Critical processes

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

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

## 15 REPORTING AND RECORDING DATA

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

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

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

### 15.1 Source documentation

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

The medical history, prior to participation in the study;

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

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

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

**15.2 Medical records**

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

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

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

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

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

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

### 15.3 Records Retention

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

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

### 15.4 Plant documentation

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

# 16 PROCEDURES FOR PROTOCOL MODIFICATION OR PREMATURE TERMINATION OF THE STUDY

## 16.1 Protocol Deviation

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

## 16.2 Protocol Amendments

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

## 16.3 Study Closure

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

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

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

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

## 17 DATA SUBMISSION AND PUBLICATION POLICY

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

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

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