Clinical Trial Protocol

COVID19_AMB_Brazil_2

A multicenter, adaptive, double-blind, randomized, placebo-controlled study to evaluate the effect of pegylated lambda interferon, fluvoxamine, a combination of fluvoxamine and budesonide, and a combination of fluoxetine and budesonide on reducing complications in patients with COVID-19 and high-risk conditions.

Authors: Gilmar Reis MD, PhD[1,2]; Eduardo Augusto dos Santos Moreira Silva MD, PhD[1,21,2]; Daniela Carla Medeiros Silva MD, PhD; Edward J Mills, PhD[3]; Lehana Thabane, PhD[3], Gordon H. Guyatt MD[3].

ANTICOV Collaboration Nathalie Strub-Wourgaft

Document Type	Clinical Trial Protocol
Study Code	COVID19_AMB_Brazil_2
Registration Number	None
Version number	v.6.0 (Amendment 5)
Development Phase	III (New Indication)
Release Date	03-JAN-2022

1. Cardresearch - Cardiology Care and Research, Belo Horizonte, Brazil
2. Pontificia Universidade Católica de Minas Gerais, Belo Horizonte, Brazil
3. McMaster University, Hamilton, Canada

INDEX

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

RAM	Adverse reactions to the drug
EA	Adverse event
PA	Blood pressure
IC	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Group
CMSD	Data security monitoring committee
EAC	Event adjudication committee
REC	Research ethics committee
CONEP	National Commission for Ethics in Research
ECG	Electrocardiogram
EOS	End of study
EP	Early termination
BPC	Good clinical practice
HR	Hazard ratio
TCLE	Informed consent form
ICH	International Council for Harmonisation
IWRS	Interactive Internet response system
SAE	Serious adverse event
PAE	Statistical analysis plan
DP	Standard deviation
EP	Standard error
SUS	Single health system
SUSAR	Suspected unexpected serious adverse reaction
EADT	Adverse event resulting from treatment
AESI	Adverse event of special interest

GLOSSARY OF TERMS

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

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

PROTOCOL OVERVIEW

Protocol - COVID19_MG_AMB_2

Title:	**A multicenter, adaptive, double-blind, randomized, placebo-controlled trial to evaluate the effect of pegylated interferon lambda, fluvoxamine, the combination of fluvoxamine and budesonide, and the combination of fluoxetine and budesonide in reducing complications in patients with COVID-19 and high risk: TOGETHER Study**
Short Title:	Repositioning of approved and in-development medications for outpatient treatment of patients with COVID-19: The TOGETHER Study
Product under Investigation:	Interferon pegylated lambda, fluvoxamine, fluvoxamine + budesonide combination, fluoxetine and budesonide combination
Indication:	COVID-19 Infection in Outpatients
Phase:	PHASE III - New indication
Sponsor	CARDRESEARCH - Cardiology Care and Research LTDA ANTICOV Consortium
Study code	COVID19_AMB_2 - TOGETHER Study
Coordinating Researchers:	Gilmar Reis, Eduardo Augusto dos Santos Moreira Silva, Daniela Carla Medeiros Silva, Edward J Mills, Lehana Thabane, Gordon H Guyatt
Proposing Institution:	Cardresearch - Cardiology Care and Research LTDA
Researchers / Collaborating Institutions	Ed. J Mills PhD Lehana Thabane PhD Gordon H Guyatt MD McMaster University, Hamilton, Canada
Objectives:	<u>Primary Objective(s)</u> • To evaluate the effect of pegylated interferon lambda, fluvoxamine, combination of fluvoxamine + budesonide, and combination of fluoxetine and budesonide in reducing the need for emergency care AND observation for longer than 06h due to worsening COVID-19; • To evaluate the effect of interferon pegylated lambda, fluvoxamine, combination of fluvoxamine + budesonide, and combination of fluoxetine and budesonide in reducing the need for hospitalization due to COVID-19 related complications <u>Co-primary Objective:</u> To evaluate the effect of pegylated interferon lambda, fluvoxamine, combination of fluvoxamine + budesonide, and combination of fluoxetine and budesonide in reducing mortality associated with COVID-19 up to 28 days from randomization. <u>Secondary objective(s)</u> • Evaluate, compared to placebo, the effect of pegylated interferon lambda, fluvoxamine, combination of fluvoxamine + budesonide, and combination of fluoxetine and budesonide on the following parameters up to 28 days after randomization: o Time to clinical improvement, defined as greater than 50% improvement in reference to symptoms at the time of randomization;

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

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.
Obtaining SpO2 ≤ 93% after randomization
Number of days with respiratory symptoms after randomization/ WURSS-21 Scale;
Number of days in Intensive Care Center
Number of days on invasive mechanical ventilation
Number of days of hospitalization
Mean and incidence rate of serious adverse events after randomization;
Rate of discontinuations or temporary suspension of study drugs
Disease-free status: disease-free based on normalization of pre-existing symptoms (based on mMRC scale, clinical improvement scale and clinical symptoms) and SpO2> 94% by D28.
Time from start of treatment to need for hospital admission/emergency care due to progression of COVID-19
Time from start of treatment to the need for hospitalization for any cause;
Safety and tolerability of the proposed treatment regimens;
Quality of life and symptoms scale (PROMIS-10 Scale and WHO Scale).
TICSM Scale for memory assessment after COVID-19
Time from start of treatment until death.
Adverse reactions associated with the proposed treatment regimens

</td></tr>
<tr><td>Design:</td><td>Multicenter, double-blind, adaptive, prospective, randomized, parallel-group, placebo-controlled, 8-week follow-up after randomization, with the fluoxetine + budesonide arm paired with active paracetamol open control.</td></tr>
<tr><td>Treatment:</td><td>
Table 1 - Study treatment regimen - pegylated interferon lambda
<table>
<tr><th></th><th>Treatment Scheme</th></tr>
<tr><td>Visit Clinic</td><td>pegylated interferon lambda</td></tr>
<tr><td>D0 - DRand.</td><td>180µg SC dose (single dose)</td></tr>
</table>
SC - subcutaneous injection

Table 2 - Study treatment regimen: fluvoxamine, fluvoxamine + budesonide combination, and fluoxetine + budesonide combination
*Oral and inhalation medications
</td></tr>
</table>

Treatment (continued):

For the oral + inhaled medication arms, there will be a placebo control arm with medications of the same appearance and shape, including an inhaler placebo control similar to the inhaler with active medication. As per the ANTICOV protocol design approved by the ethics committee of the World Health Organization (documents attached), the placebo arm will be replaced by paracetamol 500 mg BID (active control). For the injectable medication treatment arms, there will be a placebo control arm of subcutaneous injection of 0.9% saline solution in the subcutaneous injection of the same volume and appearance. Considering the results of previous studies of the effects of medications on viral load reduction and in current studies in patients with COVID-19, where there are indications of benefit (non-randomized, or open-label randomized and non-placebo controlled studies) and the current situation of the virtual absence of effective treatment approved by the regulatory authorities, The placebo arm will be re-evaluated through blinded interim analysis, by a committee independent from the research, when we reach 25, 50, and 75% of the sample of participants initially designed including for each new arm of the research, as recommended by the Data Safety and Analysis Committee. The initial interim analysis (25% of the planned sample - active principle and placebo group) will focus primarily on the safety, and potential adverse events presented. This analysis will also evaluate primary clinical endpoint and adverse event data obtained for futility. Subsequent interim analyses will include the analysis of the trial's primary endpoints.

	Treatment Scheme*		
Visit Clinic	**Fluvoxamine**	**Fluvoxamine + Budesonide**	**Fluoxetine + Budesonide**
D_{0} - DRand.	**01 pack of 100 mg**	**01 comp (100 mg) + 01 inhalation (400 mcg)**	**02 comp (40 mg) + 01 inhalation (400 mcg)**
D_{1} to D_{7}	**01 comp (100 mg) de (12/ 12 hs)**	**01 comp (100 mg) de (12/ 12 hs) + 01 inhalation (400 mcg) every 12 hours**	**02 comp (40 mg morning dose) + 01 inhalation (400 mcg) every 12 hours**
D_{1} to D_{10}	**01 comp (100 mg) de (12/ 12 hs)**	**01 comp (100 mg) de (12/ 12 hs) + 01 inhalation (400 mcg) every 12 hours**	**No medication**

	Interim analyses will occur in a blinded, independent manner, evaluating outcomes 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) recommending stopping any arm of the trial if there are no acceptable projections of benefit over futility, (2) recommending stopping the protocol if futility criteria are met for all proposed arms, (3) recommending stopping any arm of the trial due to adverse events, (4) recommending stopping any arm of the trial due to superiority of treatment, and (5) recommending continuing the clinical trial unchanged. 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)combination of fluvoxamine + budesonide, (3)pegylated interferon lambda, (4)combination of fluoxetine and budesonide and (5)placebo (or paracetamol 500 mg BID for 07 days as the active control group for the fluoxetine + budesonide arm - in collaboration with the ANTICOV protocol), with doses as described in the clinical protocol and exemplified in table 1 and 2. This day will be considered as D_0 (Randomization). This will be followed by daily administration of the investigational products according to the proposed treatment as per the trial arms, being single dose at randomization for the injectable medication arms, until D_7 for the fluoxetine + budesonide combination arm (and corresponding placebo) or 10 days of treatment D_{10} for the fluvoxamine and fluvoxamine + budesonide combination arms (and corresponding placebo). All patients will undergo a rapid test for confirmation of COVID-19 at the time of screening. Viral load will be assessed qualitatively and semi-quantitatively in all randomized patients in the subcutaneous medication arm (interferon and interferon placebo). Samples for rapid testing (COVID-19 diagnosis) will be collected nasopharyngeally and/or orally at the time of screening. Samples for RT-PCR will be collected after randomization and immediately before administration of the first dose of injectable medication, on D_3 and on D_7 for RT-PCR. In the participants of the injectable arms, the search for variants of the new coronavirus will be performed, using the same samples collected for RT-PCR. No RT-PCR testing will be performed for patients included in the 7-day or 10-day treatment arms (including the corresponding placebo).
Inclusion Criteria	**Inclusion criteria:** A - Inclusion criteria for the injectable medication arms (single dose at randomization), fluvoxamine, and fluvoxamine + budesonide combination (10-day treatment):

Inclusion Criteria (Continued)	1. Patients over 18 years of age with the capacity to provide informed consent 2. Patients seen at a Primary Care Unit of the Brazilian National Health System (SUS) or patients seen at SUS or supplementary care units with an acute clinical picture compatible with COVID 19 and symptoms beginning within 7 full days of the randomization date; 3. Patients over 18 years of age and with at least ONE of the following criteria a. Age 50≥ years (do not need any of the other criteria) b. *Diabetes mellitus* requiring oral medication or insulin c. Hypertension requiring at least 01 oral medication for treatment d. Known cardiovascular diseases (heart failure, congenital heart disease, valve disease, coronary artery disease, myocardiopathy under treatment, clinically manifest heart diseases with clinical repercussions) e. Lung disease symptomatic and/or under treatment (emphysema, fibrosing diseases) f. Patients with symptomatic asthma requiring chronic use of agents for symptom control g. Obesity defined as BMI > 30 kg/m^2 on weight and height information provided by the patient h. Transplant Patients i. Patient with stage IV chronic kidney disease or on dialysis j. Patient with fever thermometry at screening > 38º C k. Patients with at least one of the following symptoms: Cough, Dyspnea, ventilator-dependent chest pain or myalgias with limitation of daily activities (Criterion limited to 25% of randomizations) l. Immunosuppressed patients/in use of corticotherapy (equivalent to a maximum of 10 mg prednisone per day) and/or immunosuppressive therapy) m. 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 positive SARS-CoV2 diagnostic test within 07 days of symptom onset (antigen test or RT-PCR) 5. Willingness to use the proposed investigational treatment and follow the procedures foreseen in the research 6. Signing the Informed Consent Form prior to any research procedures 7. Specific inclusion criteria for the fluvoxamine arm: Present with significant dyspnea, hypotension, severe dehydration, or SpO2 below 49% on admission and be released home later, with an observation period no longer than 12 hours. B - Inclusion criteria for the Fluoxetine + Budesonide combination arm (07-day treatment - in collaboration with the "ANTICOV Consortium"): 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; 3. Patients over 18 years of age and a history of at least ONE of the following criteria a) *Diabetes mellitus*, heart disease, chronic kidney disease, chronic obstructive pulmonary disease, cerebrovascular disease, or patients considered underweight or overweight as judged by the investigator (BMI ≤ 16 or BMI > 25); **OR** b) Individuals aged ≥ 60 years without co-morbidities 4. COVID-19 confirmed by molecular or antigenic testing for SARS-CoV-2 within 24 hours prior to screening and no later than 2 days after sample collection 5. Viral syndrome with or without pneumonia and Arterial O2 saturation ≥ 94% 6. Signing the Informed Consent Form prior to any research procedures 7. Willingness to use the proposed investigational treatment and follow the procedures foreseen in the research
	Exclusion Criteria: 1. negative diagnostic test for SARS-CoV2 associated with acute influenza symptoms (patient with a negative test taken early and becomes positive a few days later is eligible, provided he/she is < 07 days from the onset of influenza symptoms) 2. Patients with an acute respiratory condition compatible with COVID-19 seen in the primary care network and with a decision to hospitalize 3. Patients with an acute respiratory condition due to other causes 4. Dyspnea secondary to other acute and chronic respiratory causes or infections (e.g., decompensated COPD, acute bronchitis, pneumonia other than viral, primary pulmonary arterial hypertension); 5. Patients with a need for hospitalization due to COVID-19 or SpO_2 ≤ 93% NOTE: Patients allocated to the fluvoxamine arm alone may be included if SpO_2 is below 94% with no evidence of acute respiratory failure, provided the attending physician decides to discharge them from the unit and continue treatment on an outpatient basis 6. Exclusion criteria applicable to injectable medication arms: a. Patients in chronic use of prednisone, prednisolone or another corticosteroid

Criteria for Exclusion (cont.)	with doses > 10 mg/day prednisone equivalent 7. Exclusion criteria applicable to the 07-day treatment arms: a. Abnormal findings on physical examination: respiratory rate ≥ 25 bpm; blood pressure < 90/ 60 mmHg or > 160/ 100 mmHg; Weight < 45 kg; recent episodes of vomiting in the past 24 hours or recurrent diarrhea or serum potassium below 3.5 mEq/L b. Severe organ damage requiring resuscitation and ongoing treatment. c. Use of corticotherapy chronically with equivalent doses of prednisone of > 40 mg/day d. Ongoing immunosuppressive treatment e. History of known pulmonary arterial hypertension or pulmonary fibrosis f. Patients who have received any dose of previous SARS-CoV-2 vaccine g. Use of serotonin reuptake inhibitors (all) 8. Exclusion criteria applicable to 10-day treatment arms: a. Chronic use of serotonin reuptake inhibitors except for sertraline b. Use of corticotherapy chronically with equivalent doses of prednisone of > 40 mg/day 9. Continued use of monoamine oxidase inhibitors (MAOI): Phenelzine, Tranylcypromine, Selegiline, Isocarboxazid, moclobemide 10. Patients with severe psychiatric disorders - schizophrenia, uncontrolled bipolar disorder, major depression with suicidal ideation 11. Pregnant or nursing patients 12. History of severe ventricular cardiac arrhythmia (ventricular tachycardia, recovered ventricular fibrillation patients) or Long QT Syndrome 13. Known history of decompensated heart failure (NYHA III or IV), recent myocardial infarction (event < 90 days from screening), unstable angina, recent coronary bypass surgery (procedure < 90 days from screening), recent stroke (event < 90 days from screening), symptomatic carotid disease, or moderate to severe mitral or aortic stenosis 14. Surgical procedure or hospitalization planned (for other indications) to occur during treatment or up to 05 days after the last dose of study medication 15. Current daily and/or uncontrolled alcoholism, which in the view of the investigator could compromise participation in the study 16. History of seizures in the last month or an uncontrolled seizure condition 17. Clinical history of moderate to severe liver impairment or cirrhosis of the liver with a Child-Pugh C classification 18. Patients with known severe degenerative neurological diseases and/or severe mental illnesses as assessed by the investigator 19. Inability of the patient or representative to give consent or adhere to the procedures proposed in the protocol 20. Any medical conditions, including psychiatric conditions, which in the investigator's view would preclude the use of the investigational medicinal products

	21. Hypersensitivity and/or known intolerance to fluvoxamine, budesonide, pegylated interferon lambda and fluoxetine 22. Use of drugs that have a known interaction with fluvoxamine, budesonide, pegylated interferon lambda and fluoxetine 23. Inability to use the drugs and formulations provided in this research
Primary and Secondary Outcomes: Primary and Secondary Outcomes:	<u>Primary endpoint:</u> o To evaluate the effect of pegylated interferon lambda, combination of fluvoxamine + budesonide, and combination of fluoxetine and budesonide in reducing the need for urgent care associated with observation + medication for longer than 06h due to worsening COVID-19; o To evaluate the effect of interferon pegylated lambda, fluvoxamine, combination of fluvoxamine and budesonide, and combination of fluoxetine and budesonide in reducing the need for hospitalization due to complications and/or worsening of COVID-19. <u>Co-primary Outcome:</u> To evaluate the effect of pegylated interferon lambda, fluvoxamine, combination of fluvoxamine and budesonide, and combination of fluoxetine and budesonide on reducing mortality associated with COVID-19 up to 28 days from randomization. <u>Secondary outcomes:</u> The secondary endpoints will assess relative to the placebo group in a period up to 28 days after randomization: o Change in viral load at randomization, Day 03 and Day 07 after randomization in patients receiving investigational medical product subcutaneously; o Time to clinical improvement, defined as greater than 50% improvement in reference to symptoms at the time of randomization (WHO scale); o Time to clinical improvement, defined as greater than 50% improvement in reference to symptoms at the time of randomization (WURSS-21 scale); o Time to clinical failure, defined as the time until need for hospitalization due to clinical progression of COVID-19 (lower respiratory tract viral infection associated with dyspnea requiring oxygen therapy OR hospitalization due to progression of COVID-19) or complications directly associated with COVID-19; o Time to worsening of peripheral arterial O_2 saturation (achieving a $SpO_2 \leq 93\%$) until day 28 post-randomization o Number of days with respiratory symptoms until day 28 after randomization. o Hospitalization for any cause up to day 28 after randomization

	○ Mortality due to pulmonary complications by day 28 after randomization ○ Cardiovascular mortality up to day 28 after randomization ○ All-cause mortality up to day 28 after randomization ○ Mean and rate of adverse events up to day 28 after randomization; ○ Rate of discontinuations or temporary suspension of study drugs ○ Disease-free status: disease-free based on normalization of pre-existing symptoms (based on mMRC scale, clinical improvement scale and clinical symptoms) and SpO2> 94% by D28. ○ COVID-19 symptom scale assessment (WURSS-21) by day 28 after randomization ○ WHO Clinical Worsening Scale assessment by day 28 after randomization ○ Assessment of the PROMIS Global Health Scale ("Global-10") days 14 and 28 after randomization. ○ TICSM scale assessment on day 28 after randomization. ○ Proportion of non-adherent patients with the product under investigation; ○ Specific adverse reactions to the study medications: fluvoxamine, budesonide, interferon pegylate lambda, and fluoxetine. The same primary and secondary endpoints will be evaluated for the interferon lambda 1st substudy in patients with acute influenza syndrome and COVID-19 NEGATIVE.
Procedures	See study procedure schedule for details and applicable visits. <u>Visit 1 - screening visit (D_0).</u> Patients seen in the primary care network or in SUS emergency care units, patients seen in supplementary medicine emergency care units, or patients referred for evaluation to participate in the research with clinical criteria for presumptive diagnosis of COVID-19, without fulfilling hospitalization indication criteria, will be invited to participate in this research. • obtaining the informed consent form (ICF) for potentially eligible subjects prior to any procedures related to this protocol. • checking the inclusion/exclusion criteria • documentation of screening procedures (demographics, high-risk criteria for covid-19, and concomitant medications) as described in the protocol. Serious adverse events observed will be reported within 24 hours of knowledge of the event. • sample collection for rapid antigen testing for SARS-CoV2 in undiagnosed patients. Patients with a confirmed diagnosis of COVID-19 within 7 days of screening do not need to be tested. <u>Visit 2 - baseline visit, randomization and administration of the first dose of the investigational drug (D_0)</u>

Procedures (continued)	• The randomization visit should be performed immediately after the screening visit, at the same assessment.
	• performing the baseline visit procedures, according to the research flowchart:
	  ○ sample of airway secretions to perform RT-PCR for Sars-CoV2 in patients allocated for single-dose subcutaneous medication;
	  ○ airway secretion sample for RT-PCR for viral panel and viral load in patients allocated to single-dose subcutaneous medication and SARS-CoV-2 antigen test negative;
	• urinary pregnancy test for women with at least one menstrual period in the last 12 months;
	• checking the inclusion/exclusion criteria
	• randomization in a centralized system
	• completion of the WHO acute influenza syndrome questionnaire
	• completion of the PROMIS-10 and WURSS- questionnaire21
	• digital oximetry measurement to obtain SpO_2
	• randomization and delivery of the investigational drug according to IWRS allocation. All patients will receive the standard treatment for acute influenza syndrome or COVID-19 if there is a provision according to the protocols adopted by the health units to which they are linked, according to the definition of the medical team and protocols defined by the institution and/or participating city. All patients will also receive 24-hour phone contact, to be activated in case of need and will be oriented about the phone contact as foreseen in the protocol, which the research team will carry out until the D_{60}. Patients will receive the initial contact through the phone number provided, where a welcome video will be sent. Patients allocated for subcutaneous medication to self-collect nasal swab and/or saliva for RT-PCR at randomization, D_3, and D_7 treatment. Patients may receive home visits for in-person evaluation at D_7, D_{14}, D_2 and D_{28} if necessary. In this situation, the samples and research materials will eventually be collected.
	
	<u>Evaluations after randomization</u>
	• all patient assessments will be conducted by telephone contact, social media applications, video calls, or telemedicine. No in-person visits are planned, especially due to the fact that the virus is highly transmissible, the increasing reports of developing COVID-19 in even vaccinated healthcare personnel, and following the guidelines of health authorities regarding recommendations for confinement and distancing from cases. Home visits after randomization may be made to eventually evaluate patients who are evolving unfavourably, always in agreement with the participant and/or family members.
	• Daily telephone contact assessments: between D_1 and D_5, the patient will be monitored daily via telephone contact and/or video calls, and the WHO influenza syndrome symptoms questionnaire will be administered. Further telephone contact is planned according to the study flow chart;
	• Evaluation of D_7, D_{10} and D_{14} telephone contact/video call to evaluate the evolution of the clinical picture and verify outcomes.

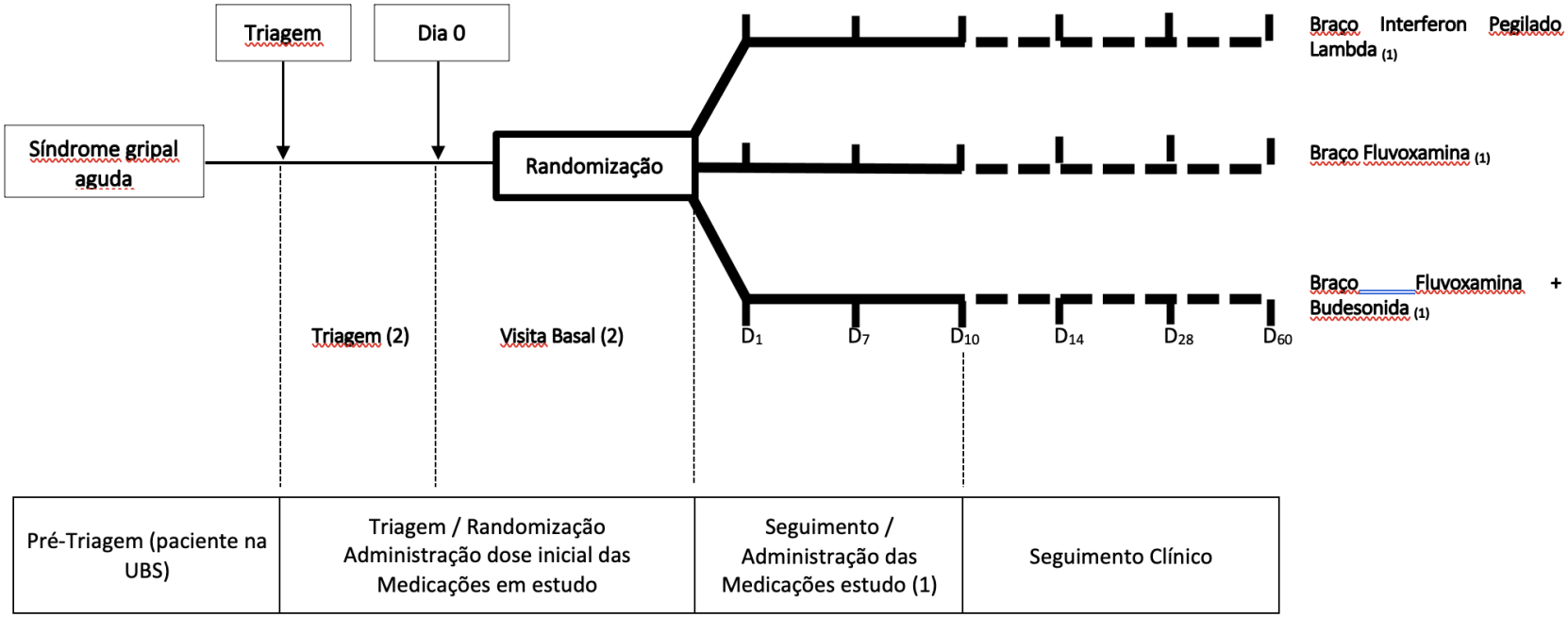
	• Evaluation of D_{28} - telephone/video call contact to evaluate the evolution of the clinical picture and verify outcomes. Possible persistence of symptoms that appeared at the time of COVID-19 diagnosis will be evaluated. • Evaluation of D_{60} - telephone/video call to evaluate the evolution of the clinical picture after the study and to check for persistence of symptoms after 28 days. Possible late complications regarding COVID-19 (late COVID) will also be evaluated. <u>Research Monitoring Committee</u> The research has an events adjudication committee responsible for ensuring that the source documents supporting the event/outcome of the study are adequate and that the diagnosis of adverse events is correct and supported by supporting documentation. In its absence, the events will be analyzed according to good research practices and the information certified by each center's principal investigator and attached to the research record. The research already has an independent data and safety review committee that has conducted four (4) interim reviews. This committee has a pre-defined plan for statistical analysis of data and research safety-approved prior to this clinical trial. The analyses follow good clinical practices, being conducted in a blinded manner and with possible breaking of the blind referring to the indicated research arms if the pre-specified criteria for such are met (see committee composition in the document attached to the regulatory file). The research steering committee is constituted from the beginning of the clinical trial, and its purpose is to ensure the scientific integrity of the study in addition to operational care for the proper conduct of the research. The safety monitoring committee consists of experienced external investigators to ensure the overall safety of the participating research subjects and group data in a blinded manner (see committee composition in the document attached to the regulatory filing). 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	As per the last approved amendment, this clinical trial is expected to randomize 4,989 patients, distributed in 05 treatment arms. On August 5, 2021, the Independent Safety and Data Review Committee recommended (1) discontinuation of the fluvoxamine arm due to superiority over the placebo group and (2) discontinuation of the ivermectin arm due to futility over the placebo arm. In early September, the committee met for safety and adverse event analysis for the Doxasozine arm as pre-specified in the approved amendment and recommended discontinuation of this arm due to excess adverse events occurring in the doxazosin arm. Initially, the clinical trial was planned to include 2,724 patients in 04 initial arms. With the approved amendments, 3.584 patients have been randomized to date by 12/16/2021 in all arms proposed in the previous amendments. With the current amendment in proposition once approved, considering the addition of new arms, it is anticipated that we will randomize 2,662 additional patients, totaling 6,246 patients, from the beginning of this research program.
Statistical Methods	This study is ongoing and considered two phases: (1) Internal pilot phase, which considered the first 100 patients. This phase was 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, the patients' data were not analyzed and were included for the first interim 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 sample planned for each research arm. Critical adjustments involve (a) withdrawal of the placebo arm if there is great benefit from the others and (b) withdrawal of any arm that does not show benefit or meets futility criteria, and (c) the addition of a new medication arm. At the start of this research program, the sample size was initially calculated at 681 participants per group, for a total of 2,724, with a power of 80% and a two-sided alpha of 0.05 being maintained to demonstrate a statistical significance ratio of 0.80 (20% reduction in hospitalization between groups and reduction in deaths compared to the COVID-19 population). The statistical software SAS version 9.4 was used for this sample calculation. In the two interim analyses performed, the primary and co-primary outcomes of the study had an overall incidence rate above that projected in the initial calculations, and it was recommended by the independent data and safety review committee that no changes to the sample size calculation be made at this time and that the possibility of a change in the sample size calculation be reevaluated in the next interim analysis. On November 12, 2021, the research protocol registered the randomization of patients 3,105. On the occasion of the 4ª interim analysis that took place on August 5, 2021, and after blinded data analysis recommended:

Statistical Methods (cont.)	(1) The Ivermectin arm was discontinued due to futility compared to the placebo group; (2) The suspension of the fluvoxamine arm for superiority over the placebo group; (3) The maintenance of the pegylated interferon lambda arm without modification; (4) The definitive suspension of the pegylated interferon lambda arm considering that the sponsor has withdrawn the proposal to sponsor the drug, thus making it unfeasible to perform this arm; (5) The conduct of a specific interim analysis to evaluate adverse events associated with the doxazosin arm, since there will be a projection of at least 125 patients included in the doxazosin arm (considering 1:1 randomization), to be scheduled by September 15. On September 12, 2012, the 5th interim analysis was conducted specifically to assess adverse events regarding the doxazosin arm, and the trial's independent data and safety review committee recommended discontinuation of the 14-day treatment arms. Considering (1) the discontinuation of the fluvoxamine, Ivermectin arms as described above, (2) the discontinuation of the Doxasozin arm due to undesirable ad verse reactions, (3)the maintenance of the Beta 1A Pegylated Interferon arm and (4) the proposed initiation of the following arms: fluvoxamine, fluvoxamine + budesonide combination, and fluoxetine + budesonide combination, we estimate that the study sample will need to be readjusted for patients6.246, necessary for us to reach the threshold needed for validation of clinical outcomes data (the randomization of 2.662additional patients). An evaluation of events in the placebo group points to the maintenance of the event rate as predicted in the initial sample calculation, and therefore no change in the number of participants required for each arm of the trial is recommended. The protocol design will be adaptive, with provision for blinded interim analysis comprising 25% of the sample (analysis of adverse events and safety), and analysis upon reaching 50 and 75% of the initially projected sample of participants (analysis of adverse events, safety, efficacy and futility). The sample size calculation may 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

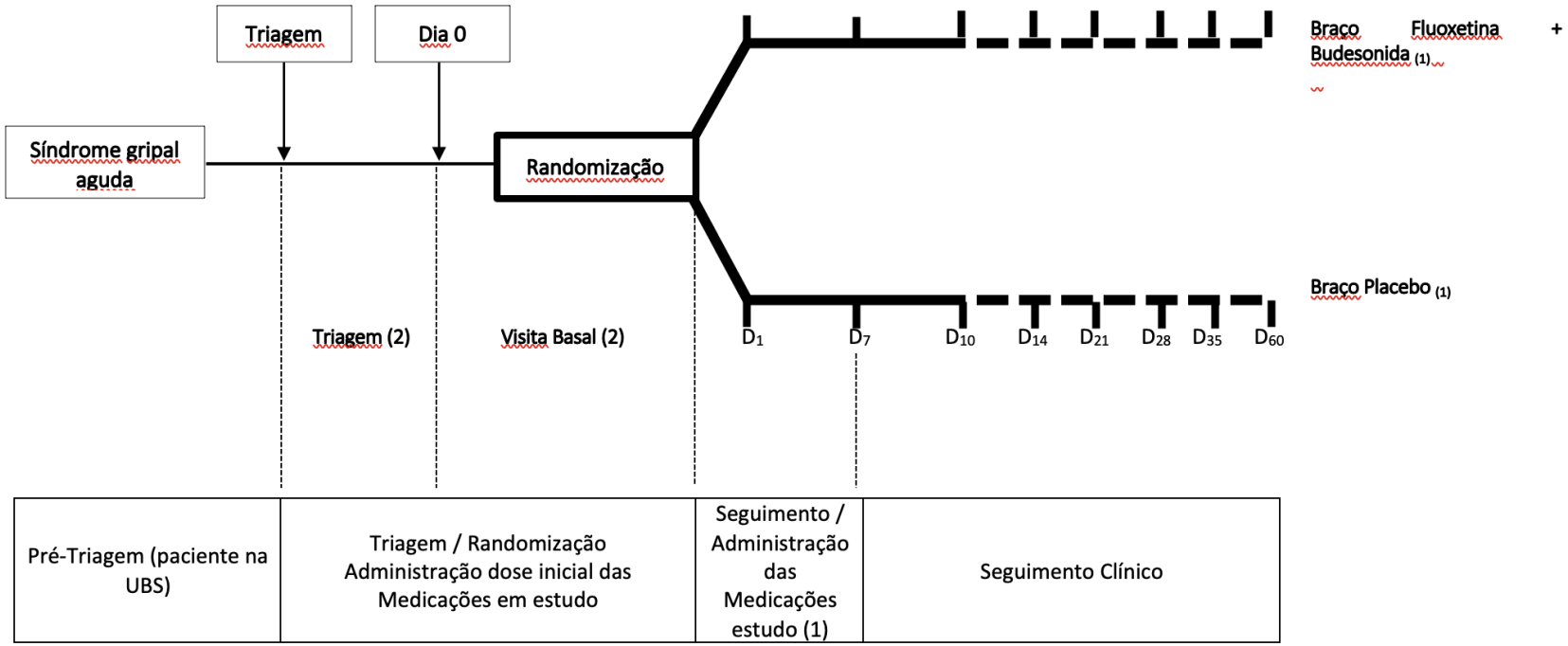
Braços Interferon pegilado Lambda, Fluvoxamina, combinação de Fluvoxamina + budesonida



1. Tratamento: Interferon Pegilado Lambda, Fluvoxamina e combinação de Fluvoxamina + Budesonida em grupos paralelos pelo período planejado. Posologia das medicações varia conforme a alocação do paciente em um braço do estudo (interferon pegilado lambda: dose única; fluvoxamina: 10 dias; combinado de fluvoxamina + budesonida: 10 dias). Para cada braço há o correspondente placebo, na mesma formulação e posologia. Medicações serão interrompidas a qualquer momento se houver evidência de reação adversa, a critério do sujeito da pesquisa ou por recomendação do DSMB (eficácia, futilidade ou segurança do participante).
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_1 a D_7, D_{10}, D_{14}, D_{28}, D_{60} serão realizadas através de contato telefônico, entretanto com possibilidade de visitas presenciais, caso necessário. Em qualquer momento visitas extras de segurança poderão ser realizadas, inclusive presenciais. A visita D_{28} é considerada a visita de desfecho para a pesquisa. A visita D_{60} é considerada visita pós-estudo, para acompanhamento de eventuais complicações tardias/ persistência de sintomas relacionados ao COVID-19 e também para avaliação eventual de reações adversas tardias aos medicamentos da pesquisa. Esta será realizada através de contato telefônico. Não há previsão de visitas presenciais regulares 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, inclusive presenciais, caso seja identificado alguma complicação e/ou evolução do COVID-19 que possa justificar nossa ida ao domicílio para avaliação do paciente.
4. Contato diário por telefone serão realizados entre os Dias 1 a 10 de tratamento, incluindo para sintomas clínicos de alarme. Outros contatos telefônicos poderão ser realizados, independentemente dos programados acima, tanto a pedido do paciente ou por nossa avaliação, visando a segurança do sujeito da pesquisa.

Fluxograma da Pesquisa - 2

Braços combinação de fluoxetina + budesonida e correspondente placebo



1. Tratamento: Combinação de Fluoxetina + budesonida e correspondente placebo em grupos paralelos pelo período planejado. Posologia das medicações varia conforme a alocação do paciente em um braço do estudo (combinação de fluoxetina + budesonida e correspondente placebo : 07 dias. Medicações serão interrompidas a qualquer momento se houver evidência de reação adversa, a critério do sujeito da pesquisa ou por recomendação do DSMB (eficácia, futilidade ou segurança do participante).
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_1 a D_7, D_{10}, D_{24}, D_{21}, D_{28}, D_{35} e D_{60} serão realizadas através de contato telefônico, entretanto com possibilidade de visitas presenciais, caso necessário. Em qualquer momento visitas extras de segurança poderão ser realizadas, inclusive presenciais. A visita D_{35} e D_{60} é considerada visita pós-estudo, para acompanhamento de eventuais complicações tardias/ persistência de sintomas relacionados ao COVID-19 e também para avaliação eventual de reações adversas tardias aos medicamentos da pesquisa. Esta será realizada através de contato telefônico. Não há previsão de visitas presenciais regulares 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, inclusive presenciais, caso seja identificado alguma complicação e/ou evolução do COVID-19 que possa justificar nossa ida ao domicílio para avaliação do paciente.
4. Contato diário por telefone serão realizados entre os Dias 1 a 21 após randomização para identificação de sintomas de alarme. Outros contatos telefônicos poderão ser realizados, independentemente dos programados acima, tanto a pedido do paciente ou por nossa avaliação, visando a segurança do sujeito da pesquisa.

Table 3 - Procedure flowchart: fluvoxamine arm, pegylated interferon lambda 1A, combination of fluvoxamine + budesonide

FLOWCHART		**STUDY VISIT SCHEDULE (Fluvoxamine arm, pegylated interferon lambda 1A and combination of fluvoxamine + budesonide)**						
	V1Triage [(1)]	V2Basal/ Randomization[(2)]	V3-V7 Day 1-5	V8 Day 7	V9 Day 10	V10 Day 14	V11 Day 28	V12 Day 60 (EoS or Early Termination
			V3-V7+1[(3)] day	V8+1[(3)] day	V9 ± 2 days	V10 [(3)] ±2 days	V11 [(3)] ± 3 days	V12 ± 5 days
Free and Informed Consent	X							
Revision of Eligibility Criteria	X	X						
Demography	X							
Medical History		X						
Physical Exam		X						
Weight / Height		X						
WURSS- Respiratory Symptoms Scale21		X	X	X	X	X	X	X
ECG (QT measurement)		X						
Oximetry		X						
Pregnancy Test	X[(4)]							
Adverse Events		X[(5)]	X	X	X	X	X	X
Previous concomitant 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)]	X[(6,7)]	X[(6,7)]
PROMIS Global Health Scale (Global-10)		X[(6,7)]				X[(6,7)]		X[(6,7)]
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]

FLOWCHART		STUDY VISIT SCHEDULE (Fluvoxamine arm, pegylated interferon lambda 1A and combination of fluvoxamine + budesonide)						
	V1Triage [(1)]	V2Basal/ Randomization[(2)]	V3-V7 Day 1-5	V8 Day 7	V9 Day 10	V10 Day 14	V11 Day 28	V12 Day 60 (EoS or Early Termination
			V3-V7+1[(3)] day	V8+1[(3)] day	V9 ± 2 days	V10 [(3)] ±2 days	V11 [(3)] ± 3 days	V12 ± 5 days
TICSM Scale - memory assessment							X	
Rapid Test for SARS-CoV2	X[(1)]							
Patient ID Card / Phone Contact		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 as randomization (immediately after randomizing). Single-dose for injectable arms

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.

Table 4 - Procedure flowchart: fluoxetine + budesonide combination arm

FLOWCHART			**STUDY VISIT SCHEDULE (Fluoxetine + budesonide arm)**						
	V1Triage [(1)]	V2Basal/ Randomization[(2)]	V3-V8 Day 1-6	V9 Day 7	V10-15 Day 8-13	V16 Day 14	V17-V22 Day 16-20	V23-25 Day 21, 28 and 35	V26 Day 60 (EoS or Early Termination
			V3-V8+1[(3)] day	V+19[(3)] day	V10-V15 ± 2 days	V16 [(3)] ± 2 days	V17-V22 [(3)] ±days2	V23-25 [(3)] ± 3 days	V26 ± 5 days
Free and Informed Consent	X								
Revision of Eligibility Criteria	X	X							
Demography	X								
Medical History		X							
Physical Exam		X							
Weight / Height		X							
WURSS-11 respiratory symptoms scale and mRC dyspnea		X	X	X	X	X	X		X
ECG (QT measurement)		X							
Oximetry		X[(3)]	X[(3)]	X[(3)]	X[(3)]	X[(3)]	X[(3)]	X[(3)]	
Pregnancy Test	X[(4)]								
Adverse Events (including pregnancy)		X[(5)]	X	X	X	X	X		X
Previous concomitant 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)]	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 (Fluoxetine + budesonide arm)						
	V1Triage [(1)]	V2Basal/ Randomization[(2)]	V3-V8 Day 1-6	V9 Day 7	V10-15 Day 8-13	V16 Day 14	V17-V22 Day 16-20	V23-25 Day 21, 28 and 35	V26 Day 60 (EoS or Early Termination
			V3-V8+1[(3)] day	V+19[(3)] day	V10-V15 ± 2 days	V16 [(3)] ± 2 days	V17-V22 [(3)] ±days2	V23-25 [(3)] ± 3 days	V26 ± 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	X[13]
TICSM Scale - memory assessment							X		
Rapid Test for SARS-CoV2	X[(1)]								
Patient ID Card / Phone Contact		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. Obtaining SpO2 if there is medical care or if the patient has a digital oximeter until D21.
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 as randomization (immediately after randomizing). Single-dose for injectable arms
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 genus betacoronavirus, 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[6,7] pandemic.

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_0 of COVID-19 is situated somewhere between 2.6 and 4.71[12]. The estimated mean incubation period until the first symptoms appear is 4.8 ± 2.6 days (CI 4.1-7.0; median 5.2)[9,10]. The most recent guidelines from the Chinese health authorities stated a mean incubation duration of 7 days, ranging from 2 to 14 days[12].

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

1.3 Clinical manifestations and risk profile

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

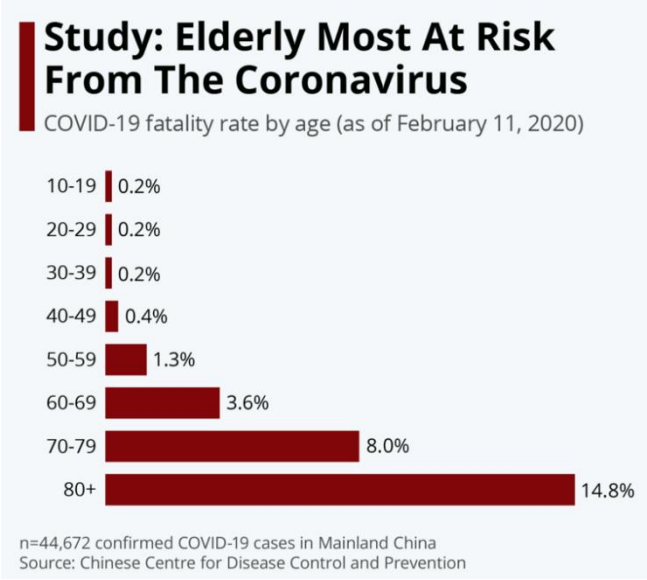


Figure 1 - Age-adjusted mortality rate

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

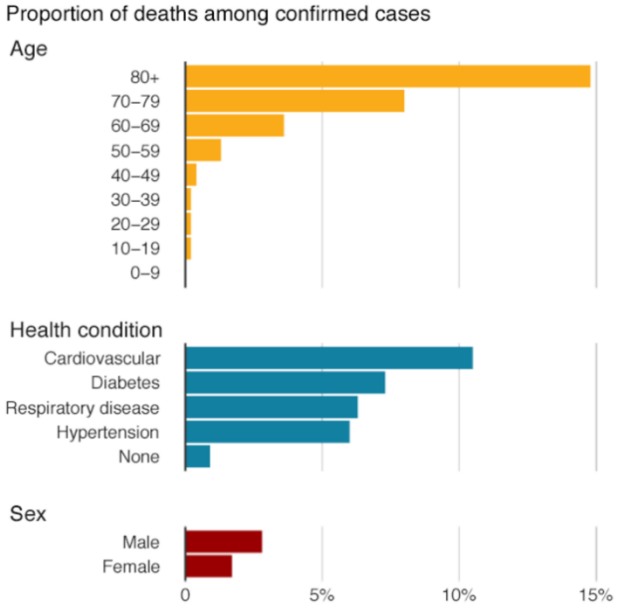


Figure 2 - Global Mortality by Age Group - COVID-19

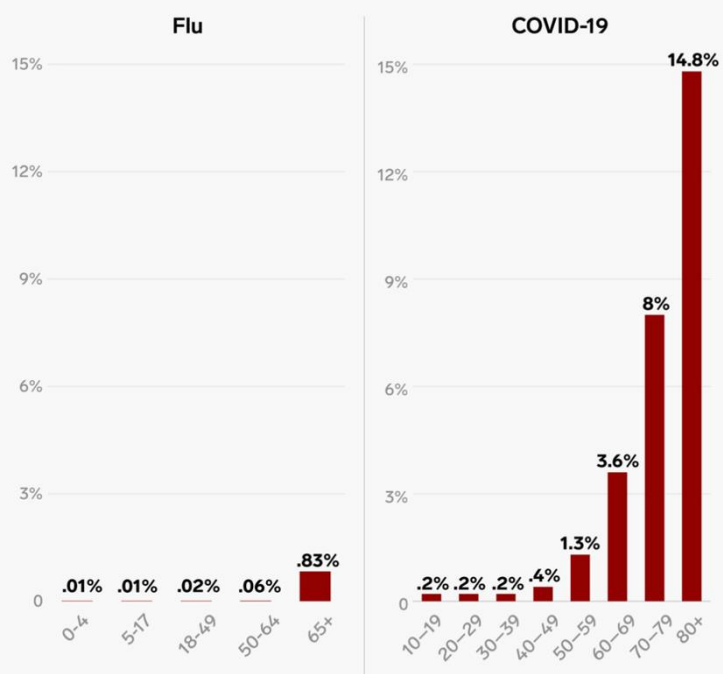


Figure 3 - Influenza and COVID-19 mortality

1.4 Mechanisms of infectivity

This global health emergency has intensified research efforts to better understand the pathogenesis, clinical manifestations, and outcomes of people affected by this new viral strain. It is known that the "spike proteins" of coronaviruses, including SARS-CoV2, interact with Angiotensin-converting enzyme 2 (ACE2) and type II transmembrane serine proteases to invade cells[14,15]. Thus, cells expressing ACE2, including pneumocytes and lung ciliated cells of the tracheobronchial tree, cardiac endothelial cells, intestinal mucosal cells and renal epithelial cells, can be affected and could partly explain 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 Immune Response in COVID-19

In the early stages of SARS-CoV-2 infection, an appropriate immune response is initiated against the virus, as occurs against similar SARS-CoV-1 and MERS- CoV coronavirus infections[18,19]. In a subset of patients, the disease course may progress to a dysregulated immune state characterized by systemic hyperinflammation ("cytokine storm syndrome")[20,21,22,23]. This state can manifest clinically as ARDS, shock, and multiple organ failure. The resulting mortality is 50% or more in this population[24,25]. Interventions that address this subset of patients are sorely needed. Current approaches are limited to still experimental immunosuppressive therapies in patients who have already developed the advanced disease[26,27]. Disease-modifying therapies that address the underlying pathophysiology and *prevent* progression to the hyperinflammatory state will be essential to mitigate morbidity and mortality due to COVID-19 at a population level[20].

Biomarkers of advanced stages and poor outcomes of COVID-19 support models of immunopathology and suggest routes of intervention. Absolute counts and relative proportions of immune cells and lymphocyte subsets are aberrant in COVID-19, especially in severe cases[24,28,29,30,31,32,33,34]. Inflammatory cytokines, chemokines, and other markers of inflammation including IL-2, IL-6, IL-7, IL-8, soluble IL-2 receptor, interferon-inducible protein 10, monocyte chemoattractant protein granulocyte-colony 1, stimulating factor, inflammatory macrophage protein 1-α, tumor necrosis factor-α, C-reactive protein, ferritin, and D-dimer, among others, are also increased in severe cases[11,28,29,30,31,32,33,34,35,36,37,38]. IL-6 diverges specifically between nonsurvivors and survivors and is predictive of COVID-19 severity and in-hospital mortality[28,36,37]. The levels of these markers mirror those observed in the cytokine storm induced by SARS-CoV-1 and MERS- CoV[39,40,41,42] infection.

The cytokine storm is associated with ARDS, the main driver of mortality in SARS and MERS[43,44]. COVID-19 cytokine profiles also resemble the hyperinflammatory state seen in primary hemophagocytic lymphohistiocytosis (HLH), a hyperinflammatory syndrome caused by underlying defects in perforin signaling pathways, and the macrophage activation syndrome (MAS) seen in a

subset of patients with autoimmune rheumatic disease[38,45,46,47,48]. Furthermore, the immune dysregulation profile of COVID-19 shares similarities with CRS seen as an adverse effect of cellular immunotherapies, including CAR-T cell therapy[49,50,51,52].

Data from randomized controlled trials, retrospective case series of patients with severe or critical COVID-19 treated with tocilizumab or siltuximab suggest that inhibition of the IL-6 signaling axis may be effective[26,53]. However, preliminary findings from a randomized, blinded, placebo-controlled trial of sarilumab in COVID-19 suggest that targeting the IL-6 signaling axis in patients with already advanced disease may not be as effective as observational[54] data suggest. Although immunosuppressive treatments likely play an important role in COVID-19[27], considerable cost, limited availability, and the potential for serious adverse events limit the application of biological therapies targeting different cytokine axes in COVID-19.

Another disadvantage of biologic therapies targeting the IL-6 axis is their half-life and the innate risk of prolonged immunosuppression. Their use too early in the disease course could lead to impaired viral clearance, favor secondary bacterial infection, and increase the risk of viral reactivation or co-infection[55,56,57,58]. Because secondary infections are a predictor of mortality with COVID-191, broadly immunosuppressive therapies such as glucocorticoids, anti-IL-6 (receptor) antibodies, Janus kinase (JAK) inhibitors, or anti-interferon gamma monoclonal antibodies pose no insignificant risk in the COVID-19patient[59,60,61]. In fact, the use of glucocorticoids in SARS and MERS was associated with delayed viral clearance and did not reduce mortality [57,58,59].

Hospital and critical care capacity has been exceeded in some regions and remains at risk of being exceeded in the coming months as regional blockades are lifted, and seasonal infectious diseases may overlap with the current SARS-CoV-2 pandemic[62,63]. Preventive therapies that could reduce the risk of progression to moderate or severe COVID-19 would acutely alleviate hospital capacity, critical care capacity, and the need for advanced support measures. Furthermore, in those patients who survive ARDS associated with COVID-19 and other organ damage, reducing the long-term morbidity of secondary pulmonary fibrosis, heart failure and chronic kidney disease, and other sequelae to be quantified from COVID-19 may prevent functional disability while increasing quality of life[51,52,53]. Considering the pathophysiology of severe COVID-19 and the limitations of current treatments, there is a critical need for preventive host-directed therapies[64]. Targeting the

catecholamine axis is a promising avenue to reduce disease severity while mitigating treatment-related risk to the patient[20,65].

1.6 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[66,67], the HN_{11} Swine Flu that first appeared in Mexico in 2009[68], and the Midwestern Respiratory Syndrome Coronavirus (MERS-CoV) that emerged in Saudi Arabia in 2012[69].

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[11,70,71]. The mortality associated with COVID - 19 is apparently associated with Adult Respiratory Distress Syndrome, which, when associated with co-morbidities, significantly elevates mortality[72,73].

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[74,75]. Data about COVID-19 continues to grow at alarming rates. Since January 31 and to date, March 23, 2020, 332,930 cases and 14,510 deaths have been confirmed, with community transmission present in virtually every country around the globe[76].

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 disease[77]. Given the high mortality expected in this pandemic and the high potential for transmission of the infection affecting entire populations and countries, it is imperative that treatments be sought for this disease, for which so far only supportive treatments exist.

2 OBJECTIVES OF THE STUDY

The objective of this study was to evaluate the efficacy, safety, and benefit of the use of fluvoxamine, pegylated interferon lambda, combination of fluvoxamine + budesonide, and combination of fluoxetine + budesonide in patients acutely affected with COVID-19 and 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 (including placebo): (1) fluvoxamine; (2) pegylated interferon lambda; (3) fluvoxamine + budesonide combination; (4) fluoxetine + budesonide combination and (5)placebo (or active control with paracetamol for the fluoxetine + budesonide arm).

The research subject's participation in the protocol is 60 days, with an initial phase of up to 10 days considered the treatment phase and the period up to 28 days considered the clinical outcomes period of the study. Visits after this period are considered post-study visits and are aimed at (1)identifying late symptoms related to COVId-19 and (2) monitoring possible late adverse events associated with the drugs under evaluation.

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 associated with this disease;
- Reducing the need for hospitalization due to progression of COVID-19 (worsening of viral pneumonia) and/or complications resulting from it in acutely affected patients with evidence of high risk for complications; associated with this disease

Goal/co-primary endpoint:

To evaluate the effect of the proposed treatments in reducing mortality associated with COVID-19 up to 28 days from randomization.

2.2 Secondary endpoints/objectives

The proposed secondary objectives are to evaluate, in comparison with the placebo arm, the effect of the drugs proposed in this amendment (pegylated

interferon lambda, fluvoxamine, combination of fluvoxamine + budesonide and combination of fluoxetine + budesonide on the following parameters:

- Reduction in viral load after randomization (D_3 and D_7) (only arm injectable medications);
- Number of days with respiratory symptoms since randomization
- Mean and rate of serious adverse events after randomization;
- Rate of discontinuations or temporary suspension of study drugs
- Disease-free status: disease-free based on normalization of pre-existing symptoms (based on mMRC scale, clinical improvement scale and clinical symptoms) and SpO2> 94% by D28.
- Time from start of treatment to need for hospital admission/emergency care due to progression of COVID-19
- Time from start of treatment to the need for hospitalization for any cause;
- Safety and tolerability of the proposed treatment regimens;
- Quality of life and symptoms scales (WURSS-21, PROMIS-10 and WHO Scale).
- Daily evaluation of symptoms considered an alarm
- Identification of patients with $SpO_2 \leq 93$ within 28 days post-randomization
- TICSM Memory Assessment Scale on day 28 post-randomization
- Time from start of treatment until death (randomization up to 28 days).
- Adverse reactions associated with the proposed treatment regimens

2.3 Exploratory objectives

- Complication rate stratified by age
- Number of days in the intensive care unit
- Number of days on invasive mechanical ventilation
- Number of days of hospitalization
- Number of days of hospitalization in a ward
- Number of days using oxygen therapy
- Number of days survival without hospitalization

3 INVESTIGATIONAL PLAN

3.1 Study design

This is a multicenter, adaptive, double-blind, randomized, placebo-controlled study to evaluate the effect of pegylated interferon lambda, fluvoxamine, and a combination of fluvoxamine + budesonide on reducing hospitalization in patients with mild COVID-19 and high risk for complications.

The groups will be as follows:

1. Pegylated interferon lambda
2. Fluvoxamine
3. Combination of fluvoxamine + budesonide
4. Combination of fluoxetine + budesonide
5. Placebo (or active control with paracetamol for the fluoxetine + budesonide arm)

Patients will be randomized to one of the study arms 5 via an iterative automatic centralized randomization system (IVRS or IWRS). The protocol provides for an adaptive phase to accommodate any pre-specified modification needs.

The protocol was re-evaluated, and the initial planning was maintained, which estimated the number of participants needed to demonstrate the hypotheses in 681patients in each arm of the research as described above, in a randomization ratio of 1:1:1:1 (total: patients 3,405 for the arms above). This re-evaluation considered the current event rate in the Brazilian population, data from participating cities in the trial, and data from patients vaccinated in participating cities. There was no significant variation in hospitalization rates once COVID-19 was developed, with the exception of mortality, which was reduced by 80-85%. Thus, for the primary endpoint, the sample size calculation was maintained (see detailed description in section 12). This will require the additional randomization of 2,662 patients.

The pandemic of the new coronavirus has demanded from the entire academic community an unprecedented effort in the history of medicine. A deadly pandemic with a high morbidity and mortality rate caused by a virus that has a high transmissibility rate and enormous mutagenic potential. Researchers from virtually every area of knowledge have come together in the search for understanding and knowledge of the disease, its pathophysiology and disease mechanisms, and of treatments (prophylactic or disease-specific, including vaccines). While much

progress has been made in the development of vaccines and treatments for the hospital phase of the disease, little has been achieved in the treatment of the early phase of the disease before the development of immuno-inflammatory activation.

Today it is clear that most research groups have made a futile effort since although thousands of publications have appeared, most of them lack a consistent methodology, present important biases, and significant flaws in the conduct and obtaining of the results. The pandemic of COVID-19 has re-emphasized not only the importance of randomized studies following an adequate methodology and adopting consistent practices in planning, conducting, and analyzing the data obtained, but above all, it has demonstrated the need for the development of large-scale clinical trials structured according to a master protocol in a coordinated and collaborative global manner[78].

Within this perspective, we proposed an adaptive clinical research protocol, aiming at a more efficient evaluation of the clinical benefits of new therapies for the initial outpatient phase of the new coronavirus[1]. Protocols with adaptive design, by studying more than one therapeutic intervention, in a "perpetual" manner which can be evaluated and discarded (through a robust statistical analysis plan) if they lack evidence of benefit[79]. These studies create opportunities for more efficient knowledge generation, where it can be incorporated into routine clinical practice and drive continuous improvement. With their common platform and infrastructure, their efficient use of control arms, and their ability to expedite the launch of new study interventions, adaptive clinical trials can offer numerous advantages in identifying effective drugs and devices to combat COVID-19 and comparative effectiveness settings with speed and agility and without losing the quality of a randomized[80,81,82,83] clinical trial.

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, a 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 or to

add a new drug to the clinical trial will be subject to immediate notification to the regulatory authorities and the ministry of health, according to current regulations and approval when applicable.

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

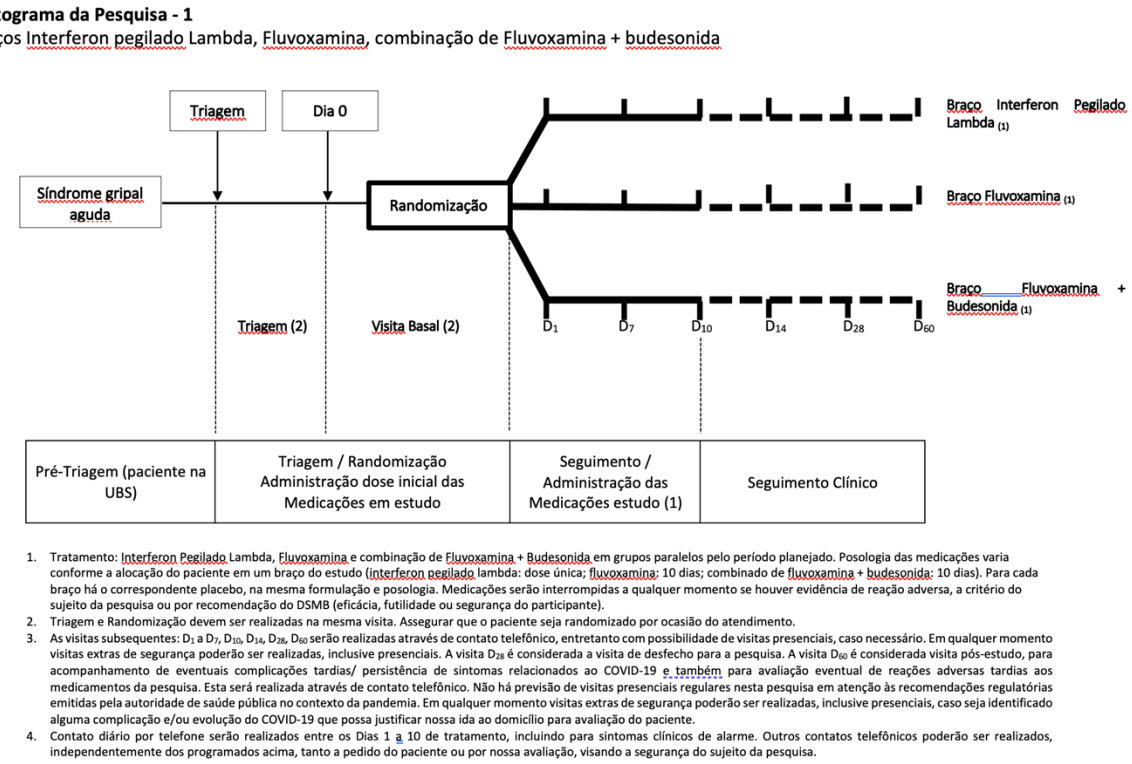
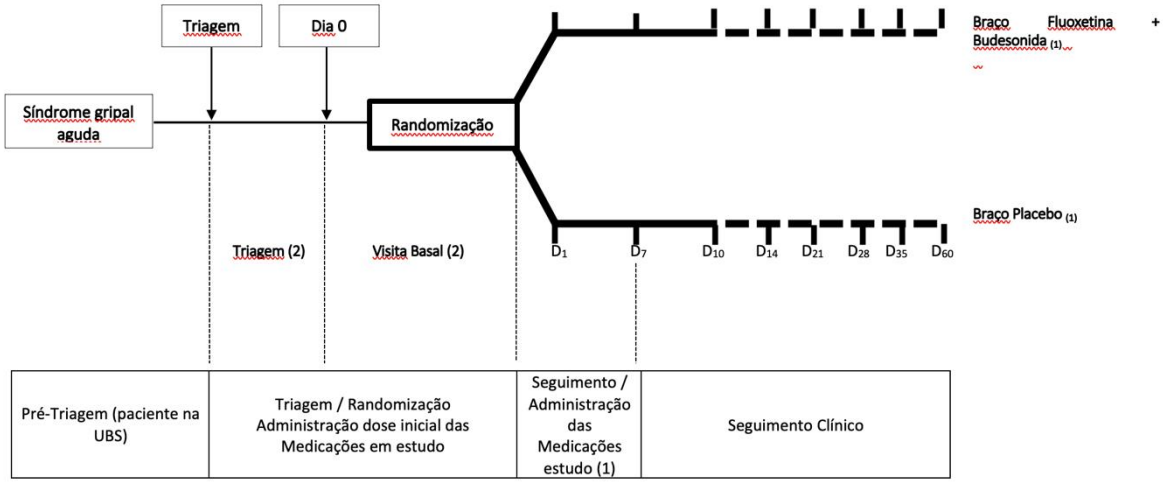


Figure 4 - Flow chart of the research: fluvoxamine, pegylated interferon lambda and fluvoxamine + budesonide combination

Fluxograma da Pesquisa - 2
Braços combinação de fluoxetina + budesonida e correspondente placebo



1. Tratamento: Combinação de Fluoxetina + budesonida e correspondente placebo em grupos paralelos pelo período planejado. Posologia das medicações varia conforme a alocação do paciente em um braço do estudo (combinação de fluoxetina + budesonida e correspondente placebo ; 07 dias. Medicações serão interrompidas a qualquer momento se houver evidência de reação adversa, a critério do sujeito da pesquisa ou por recomendação do DSMB (eficácia, futilidade ou segurança do participante).
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_1 a D_7, D_{10}, D_{24}, D_{21}, D_{28}, D_{35} e D_{60} serão realizadas através de contato telefônico, entretanto com possibilidade de visitas presenciais, caso necessário. Em qualquer momento visitas extras de segurança poderão ser realizadas, inclusive presenciais. A visita D_{35} e D_{60} é considerada visita pós-estudo, para acompanhamento de eventuais complicações tardias/ persistência de sintomas relacionados ao COVID-19 e também para avaliação eventual de reações adversas tardias aos medicamentos da pesquisa. Esta será realizada através de contato telefônico. Não há previsão de visitas presenciais regulares 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, inclusive presenciais, caso seja identificado alguma complicação e/ou evolução do COVID-19 que possa justificar nossa ida ao domicílio para avaliação do paciente.
4. Contato diário por telefone serão realizados entre os Dias 1 a 21 após randomização para identificação de sintomas de alarme. Outros contatos telefônicos poderão ser realizados, independentemente dos programados acima, tanto a pedido do paciente ou por nossa avaliação, visando a segurança do sujeito da pesquisa.

Figure 5 - Flowchart of research-2 (partnership with the ANTICOV research group)

3.2 Justification of the study design

The Study Steering Committee for COVID19_MG_AMB_2 periodically reviews current literature data regarding the potential efficacy treatments of the drugs proposed in this trial. The proposed drugs were listed based on the current literature on treatments in outpatient, symptomatic COVID-19, as well as pre-clinical studies with robust data on the potential of the study drugs and justification for their adoption in a clinical trial.

Considering the recently published results of the fluvoxamine arm, the steering committee has requested an opinion from the independent data safety committee on the insertion of a fluvoxamine + budesonide combination arm, as there are now PHASE III studies confirming the superiority of both drugs in patients with outpatient COVID-19 and symptoms less than 7 days old. We also request an opinion about the possible establishment of an academic-scientific collaborative partnership between this research program and the ANTICOV Consortium, an adaptive platform that is evaluating various drugs in patients with outpatient COVID-

19 and less than 7 days of symptom onset, linked to the World Health Organization. After presenting our proposal to insert an arm of the ANTICOV study (combination of fluoxetine + budesonide) and justifying the importance of verifying if fluoxetine has the same clinical profile of benefit, considering that this is a medication considered essential by the World Health Organization, lower cost and safety profile considered better than fluvoxamine. The DSMB was in favor of the principle of collaborative academic-scientific partnership and shared data analysis, especially considering the possibility of obtaining consistent results in a shorter time, which is an advantage in this pandemic. The DSMB then identified no ethical-regulatory and administrative obstacles to this partnership.

3.3 Rationale for the use of fluvoxamine

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) and an SR receptor$_1$ agonist[84]. 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[85]. 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 production[86]. 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[87]. 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 sub-lethal 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"[88,89]. 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[90,91]. Additional Nsp6 has been shown to physically associate with$_1$ SR[92]. Critically,$_1$ SR not only drives early-stage autophagy via the IRE/$_1$ UPR pathway but is also essential for lysosomal fusion and to complete autophagy, likely accompanying components of the SNARE[93] complex. 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[94,95].

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[96]. In the case of COVID-19, this may increase the effects of the treatment on the airway epithelium[97]. At high doses (10 uM), 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[98,99].

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[100,101,102]. 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[103,104].

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[105,106].

3.3.5 Elevation of melatonin levels in the body

The SARS-CoV2 virus can activate the NLRP3 inflammasome, which may contribute to the cytokine storm[107,108]. Melatonin may act on this NLRP3 pathway to reduce inflammation[109,110]. Fluvoxamine inhibits melatonin metabolism, so it may increase the level of melatonin in the body, which may be beneficial in COVID-19[111].

A summary of the potential benefits of using fluvoxamine in COVID was described by one of the researchers associated with this arm and can be summarized in the figure below[112].

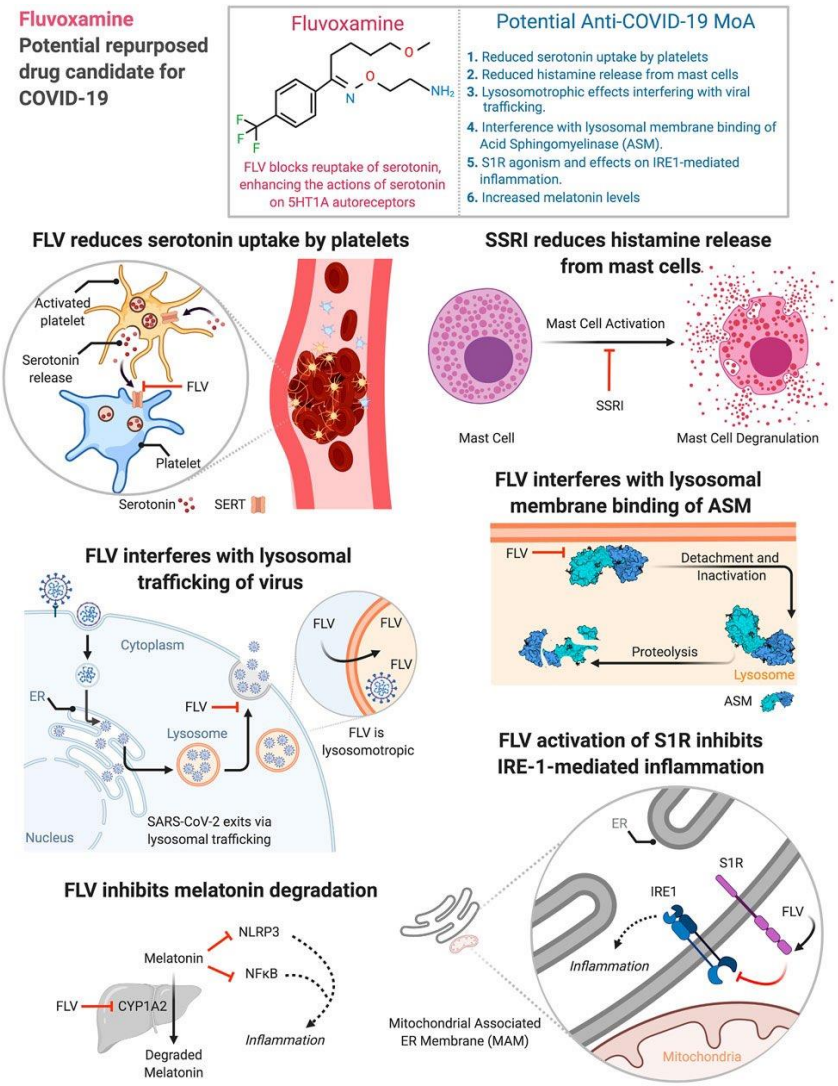


Figure 6 - Potential mechanisms of benefit from the use of fluvoxamine in patients with a COVID-19 condition[112]

3.3.6 Fluvoxamine studies in COVID-19

Considering the robust potential of fluvoxamine to act by modulating the inflammatory and immune response through various mechanisms already demonstrated in preclinical studies conducted before the pandemic and in preclinical studies using the novel coronavirus, clinical trials in patients with COVID-19 have suggested the potential of fluvoxamine to reduce complications in patients with COVID-19.

In a double-blind, randomized, preliminary study with a small number of adult outpatients with symptomatic COVID-19 and using indirect clinical outcome, 80 patients treated with VLF, compared with 72 treated with placebo, had a lower

probability of clinical deterioration over 15 days[113]. Patients were randomized within 07 days of symptom onset. These phase II data are provocative since none of the fluvoxamine-treated patients experienced clinical deterioration while 8.3% of patients in the control group experienced such complications.

In the original version of this research protocol, we proposed the evaluation of ivermectin, metformin and fluvoxamine in a phase III research protocol aiming to evaluate the effect of fluvoxamine in reducing well-defined clinical outcomes (hospitalization or emergency unit care with extended observation period > 06 hours). In this initial version, fluvoxamine was one of the drugs studied, and recruitment began on January 20, 2010. Since the start of recruitment, several interim analyses have been performed. At the time of the 4th interim analysis, the independent data and safety monitoring committee recommended discontinuation of the fluvoxamine arm due to it achieving superiority over the placebo treatment, as per the statistical analysis plan performed previously. We received formal communication from the DSMB on August 5 with the recommendation to discontinue this arm of the ongoing trial. In the final data analysis, we recruited 1,497 patients, with 741 in the fluvoxamine arm and 756 in the placebo arm. The median age was 50 years (18-102), and the mean time to symptom onset was 3.4 days.

The proportion of patients with the primary study outcomes was lower for the fluvoxamine group compared with the placebo group (79 [11%] of 741 vs 119 [16%] of 756); relative risk [RR] 0.68; 95% confidence interval Bayesian analysis [95% BCI]: 0 - 52-0.88), with a probability of superiority of 99.8%, exceeding the prespecified superiority threshold of 97.6% (risk difference: 5.0%). Considering the composite clinical outcome, 87% of the events were hospitalizations and 12% were emergency room visits and observation >6 hours associated with SpO2 < 94%, clinically important dyspnea, or hypotension due to dehydration, criteria that define severe COVID-19 according to the Center of Disease and Control, USA. The calculations for the primary outcome of the study were similar in the modified intention-to-treat (RR 0.69, 95% CI: BCI 0.53 - 0.90) and higher in the per-protocol analysis (RR: 0.34; 95% BCI: 0.21 - 0.54). There were 17 deaths in the fluvoxamine group and 25 deaths in the placebo group in the primary intention-to-treat analysis (odds ratio [OR] 0.68; 95% CI: 0.36 - 1.27). In the per-protocol analysis, considering only patients who were adherent to both arms for at least 7 days, we found 1 death in the fluvoxamine group and 12 deaths in the placebo group (OR 0.09; 95% BCI: 0.01 - 0.47). We found no significant differences in the number of clinically significant adverse events in the two arms evaluated. Thus, we identified that fluvoxamine is

useful in reducing hospitalizations or emergency room visits where there is a clinical decision to keep the patient in a prolonged observation bed (> 06 hours), and the final data from this arm of the study were recently published in The Lancet Global Health[114].

One of the criticisms of our clinical trial is the difficulty for our fellow first-world scientists to understand the dynamics of an emergency room in Brazil. Had we not reached technical occupancy of all available beds for COVID 19 for several weeks during the recruitment phase, all patients with moderate to severe COVID-19 and no evidence of acute respiratory failure would normally have been transferred to a tertiary hospital if bed overcrowding had not been a problem. For months the Belo Horizonte metropolitan region was faced with a virtual absence of ICU beds and ward beds for COVID-19. Entire wards were opened, ORs from reference hospitals were transformed into ICUs (Hospital Odilon Behrens, Belo Horizonte). This was the reason why we had to implement a composite clinical endpoint; otherwise, we would have several patients who simply would not be considered as the endpoint of the study, since although they were considered moderate/severe (by CDC criteria, adopted in our clinical trial), they would not be considered. It is equally difficult for colleagues who do not know to understand the dimension of our "Sistema Único de Saúde" (SUS), which is currently responsible for 80% of all care to the Brazilian population at no cost to them.

Despite the planning developed by the public health authorities to fight COVID-19, we observed in the period from the end of March to mid-July the technical exhaustion of observation beds, wards, and intensive care centers dedicated to the treatment of patients with COVID-19 in the participating cities. Fortunately, this exhaustion did not cause sad situations and lamentable scenes as it occurred in other regions of our country, where the capacity of the public and the private health system was not sufficient to receive the thousands of people who demanded hospitalization.

In the state of Minas Gerais, we did not face situations as dramatic as these, but we worked with more than 09% of the available beds allocated in COVID-19 occupied during almost the entire research period. Frontline physicians in emergency settings were overwhelmed with hundreds of patients with acute flu-like syndrome on a daily basis, and the emergency rooms were fully staffed. These healthcare professionals had to choose which patients were relatively stable enough to receive stabilization fluid therapy due to severe dehydration, hypotension, IV steroid therapy and massive inhalation therapy for respiratory stabilization as well.

Day to day, several patients were discharged home with clinically moderate to severe COVID-19. Only patients with significant dyspnea, hypotension associated with the flu-like syndrome and patients with SpO_2 between 85-90% were admitted to observation beds, intensively medicated with IV corticosteroids (dexamethasone), bronchodilators, and if they needed to be stable after 06-12 hours of observation were released to home. These patients would certainly be admitted to hospital beds if they were available. This was the "real world" context during the second peak of the pandemic in the state of Minas Gerais, and as we anticipated, we chose to introduce this criterion since all these patients met the moderate / severe COVID-19 clinical picture according to the criteria established by the CDC.

Aiming to provide a definitive answer as to whether fluvoxamine contributes to event reduction in this contingent of patients, which is significant in the emergency care units of the public health system (SUS), we chose to introduce this arm to specifically evaluate this population of individuals with COVID-19, who present clinical evidence of moderate disease, but not enough to motivate their admission to hospitalization by decision of the medical care teams responsible for conducting cases of COVID-19 in the emergency care units in the participating municipalities.

3.4 Rationale for the use of fluoxetine

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) that was discovered in 1972 and began use in humans in 1986. It is now considered an essential drug and is on the World Health115 Organization's list of essential drugs.

Fluoxetine is used to treat major depressive disorder, obsessive-compulsive disorder (OCD), bulimia nervosa, panic disorder, and premenstrual dysphoric disorder. It is approved for use in adolescents and children 8 years of age and older. Fluoxetine was approved by the US FDA in December 1987. However, due to another mechanism of action, it is considered to have antiviral and anti-inflammatory properties that make it an attractive option for patients with COVID-19, as described below. Because it distributes readily in the CNS, this activity can also be seen as useful for treating CNS-related symptoms and possibly preventing some of the symptoms of the post-COVID[116] condition.

Fluoxetine structure
Mw: 309.3

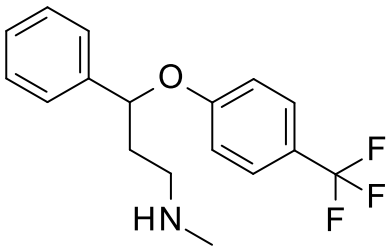


Figure 7 - Molecular structure of fluoxetine

Fluoxetine at usual doses has demonstrated agonistic action on Sigma-1 receptors, with its affinity being about 11 times lower than the affinity of fluvoxamine[117,118]. These effects are obtained at doses clinically used for the treatment of depression. The stimulation of these receptors has been consistently shown to be related to the modulation of several cytokines, reducing the activity of pro-inflammatory cytokines and potentiating the activity of anti-inflammatory cytokines.

Table 1. Affinity of antidepressants for sigma-1 receptor chaperone.

Drugs	Ki (nM)	Pharmacology at sigma-1 receptor
Fluvoxamine (SSRI)	17.0	Agonist
Sertraline (SSRI)	31.6	Antagonist?
Fluoxetine (SSRI)	191.2	Agonist
Escitalopram (SSRI)	288.3	Agonist
Citalopram (SSRI)	403.8	Agonist
Paroxetine (SSRI)	2041	
Duoxetine (SNRI)	3533	
Venlafaxine (SNRI)	>10,000	
Milnacipran (SNRI)	>10,000	
Mirtazapine (NaSSA)	>10,000	

Table 5 - Antidepressants and affinity for Sigma-1 receptors

3.4.1 The Ceramide/Acid Sphingomyelinase System

Surface ceramide is generated by acid sphingomyelinase (SMA), which is a lysosomal protein that catalyzes the conversion of sphingomyelin to ceramide. Since lysosomes are constantly recycled to the plasma membrane, SMA can also be found on the cell surface and binds to the outer leaflet of the plasma[119,120] membrane. Surface SMA acts as a signaling molecule and generates ceramide on the outer leaflet of the cell[121] membrane. Ceramide molecules are very hydrophobic and spontaneously associate with each other to form small ceramide-enriched membrane domains that fuse together to form large, highly hydrophobic, tightly packed, gel-like ceramide-enriched membrane domains called "platforms"[122,123]. Thus, the generation of ceramide by SMA dramatically alters the biophysical properties of the plasma membrane. These wide and distinct ceramide-enriched membrane domains serve to cluster, aggregate and rearrange activated receptor molecules, such as CD95, CD40, DR5 or integrin β1, to name a few[124,125,126,127]. Ceramide-rich platforms have also been shown to mediate a variety of stress stimuli, such as γ-irradiation[128,129] or ultraviolet light[130], as well as infection of cells with at least some pathogenic bacteria and viruses[131]. The high density of activated receptors after capture and clustering in ceramide-enriched membrane domains and the proximity to signaling molecules facilitate and amplify signaling through the specific receptor, as shown for CD95[132].

3.4.2 Functional SMA inhibitors (FIASMAs)

Since the 1970s, it has been shown that weak organic bases, such as desipramine, have the potential to inhibit SMA activity[133,134,135]. It has been suggested that SMA is bound to intralysosomal membranes and thus protected from proteolytic inactivation. Weak bases diffuse into lysosomes and are trapped after protonation. This leads to an intralysosomal accumulation of up to 1000-fold of weakly basic[136] substances. The weak bases also localize in other acidic subcompartments of the cell membrane and thus inhibit SMA not only in the lysosomes, but also in certain domains of the cell membrane. Functional inhibition of SMA requires only a few structural conditions; the molecules need to contain a lipophilic organic ring that integrates with the inner lysosomal membrane, a short spacer, and a charged tertiary amine group that displaces SMA from the inner lysosomal membrane, which results in proteolysis of the enzyme in the lysosomal[137] lumen. Therefore, weak bases do not directly inhibit SMA but lead to functional inhibition of SMA. The acronym FIASMA (functional inhibitor of acid

sphingomyelinase) was then proposed for a compound in this large drug[138] group. FIASMAs include mono-, bi-, tri- and tetracyclic compounds. All FIASMAs identified so far have at least one basic nitrogen atom, have a medium to high logP value, and most of them have a molecular weight below 500. FIASMAs more often violate Lipinski's Rule of Five than compounds that have no effect on SMA and FIASMAs appear to have good permeability across the blood-brain barrier. On the other hand, not all lipophilic weak bases are FIASMAs. This is explained below using the example of chloroquine. We have identified several new FIASMAs (e.g., fluoxetine, fluvoxamine, maprotiline, nortriptyline, orphenadrine, sertraline, dextromethorphan, emetine, and trifluprom azine)[139], most of which are known bioactive compounds approved by the US Food and Drug Administration (FDA), probably minimally toxic and potentially available for new clinical applications.

3.4.3 The SMA/ Ceramide system and SARS-CoV-2

3.4.3.1 Pre-clinical evidence

Infection of epithelial cells with SARS-CoV-2 is initiated by binding of the virus S protein to ACE2. Binding is followed by fusion of the viral and cell membrane, which requires activation of the spike by cellular proteases that cleave the spike into the S1 and S2subunits[140]. Cleavage of the spike protein is mediated by TMPRSS2, but also by cathepsin B and L[141]. Ceramide may have several functions in SARS-CoV-2 infection: Ceramide-enriched membrane domains bind and cluster ACE2 after cellular infection with SARS-CoV-2, which is most likely a prerequisite for signaling via this receptor and thus a prerequisite for infection[142]. It is possible that ceramide-mediated clustering of ACE2 in large membrane domains amplifies signaling via ACE2 and is therefore necessary for the internalization of ACE2 and SARS-CoV-2 into endosomes. However, it may also be possible that ceramide generated within endosomes or on the outer leaflet of the cell membrane after infection with SARS-CoV-2 binds to cathepsins on endosomes and thus triggers spike protein activation and membrane fusion. Previous studies using TNF have already demonstrated activation of cathepsins by ceramide[143]. In line with direct ceramide-protein interaction, it may also be possible that ceramide directly binds to and activates TMPRSS2 and thus facilitates membrane fusion. Alternatively, ceramide-enriched membrane domains may capture ACE2 and TMPRSS2 within a small and distinct area of the plasma membrane, resulting in a high concentration of

TMPRSS2 and thus S-protein initiation, membrane fusion, and infection. Importantly, all of these events are inhibited by fluoxetine or other FIASMAs, since the drugs induce long-lasting protein degradation in lysosomes.

Fluoxetine also prevents the efflux of cholesterol from endosomes and lysosomes. As a result, less cholesterol is available for the plasma membrane and other cellular functions. Cholesterol is particularly important for enveloped viruses as they form their envelopes from the host membrane. This mechanism is exhibited in the influenza virus via enveloped viruses with lower cholesterol content (crucial for viral survival) and less viral release. In fact, 10 μM of fluoxetine, when used in a model cell culture of COVID-19, significantly reduced viral load and the inhibitory effect was observed to be dose-related[144]. Similarly, experimental studies have suggested that fluoxetine at doses commonly used for the treatment of depression can inhibit SARS-CoV2 infection[145].

3.4.3.2 Clinical evidence: fluoxetine and COVID-19

Two observational studies suggest that patients hospitalized with a COVID-19 condition and on chronic fluoxetine use have a lower complication rate. Hoertel et al. performed a multicenter retrospective analysis in 23 Parisian[146] hospitals. In this observational study, 7,230 inpatients with COVID-19 confirmed by RT-PCR examination were included. It was observed that patients on chronic use of fluoxetine at a mean dose of 21.6 mg/day were significantly associated with a reduced risk of intubation or death from complications arising from COVID-19, even when adjusting variables considering co-morbidities (HR 0.56; 95% CI: 0.43-0.73; p<0.001). The exploratory analyses performed suggest that this effect may be of the entire class of serotonin-receptor inhibitors, not just fluoxetine.

Oskotsky et al. evaluated hospitalizations for COVID-19 in 87 US hospitals from January to September 2021[147] Of the 83,574 patients hospitalized for COVID-19 complications, 3401 adult patients were on serotonin reuptake inhibitors. When compared with the control group (80,173 adult patients) it was noted that mortality was significantly reduced in the group of patients taking fluoxetine (46 of 470 [9.8%] vs 937 of 7,050 [13.3%]; RR, 0.72 [95% CI, 0.54-0.97]; *P* = .03 after adjustment). Similarly, lower mortality was also evidenced in patients who were on chronic use of fluvoxamine.

Such evidence shows the need to study whether fluoxetine can indeed reduce clinical events in patients with COVID-19 and early-stage disease.

3.5 Rationale for the use of budesonide

Budesonide is a second-generation, non-halogenated synthetic corticosteroid with potent glucocorticoid activity and weak mineralocorticoid activity. Initially patented in 1.973 and used in humans since 1.981, it is currently on the list of essential drugs of the World Health[115] Organization. It has been approved by ANVISA for several years for the long-term treatment of bronchial asthma and chronic obstructive pulmonary disease.

The medication has an excellent anti-inflammatory activity when administered inhaled and a low systemic activity, which provides greater efficacy and less risk of adverse reactions resulting from the use of glucocorticoids. Its action is in several points of the inflammatory cascade, from inhibiting the formation of specific antibodies; preventing the formation, storage, and release of chemical mediators by mast cells; interfering in bronchoconstriction, inflammatory edema, and also in the mucous secretion resulting from the inflammatory148 process.

Budesonide, which is of intermediate lipophilicity, is retained longer in the airways. It has been suggested that the esterification of budesonide contributes to its prolonged anti-inflammatory action and may explain why budesonide is so effective when in similar doses of another corticosteroid[149] ester formation.

Pharmacology data and drug package inserts can be found on the ANVISA[150] website and in this research dossier.

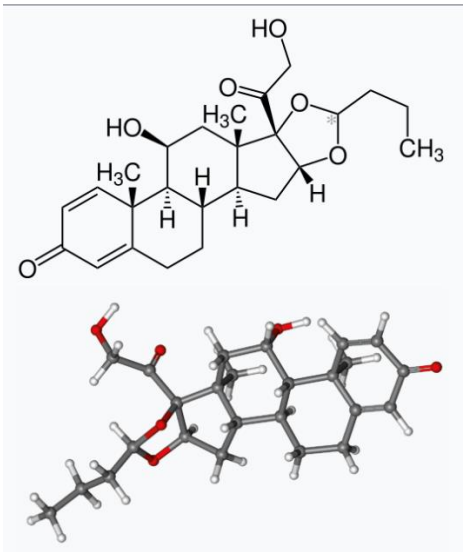


Figure 8 - Budesonide - molecular structure

Inhaled glucocorticosteroids are considered standard therapy for inflammatory diseases of the airway mucosa, such as allergic rhinitis, chronic rhinosinusitis, or bronchial asthma[151]. These clinical conditions are among the most common inflammatory diseases, and chronicity is often associated with epithelial damage and tissue destruction that can promote viral[152] infections.

Bronchial asthma is an important comorbidity associated with allergic rhinitis and chronic rhinosinusitis, and inadequate control of these conditions are clearly associated with asthmatic decompensations[153,154,155].

Approximately 75% of episodes of decompensation of chronic obstructive pulmonary disease are secondary to acute viral airway infections. Similarly, viral infections have been considered an important cause of episodes of asthma decompensation in susceptible individuals. There is no evidence that the use of inhaled corticotherapy is a predisposing factor for complications in patients with established asthma decompensation, and it is considered an important therapeutic weapon in cases of persistent symptoms, considering its beneficial role in curbing the triggered inflammatory process. Topical or inhaled corticotherapy is then considered the standard treatment in these conditions and is recommended in virtually all the consensus and position statements of known allergy and pulmonology societies.

COVID-19 causes severe bronchial mucosal involvement leading to intense inflammation, with consequent bronchospasm. To date, there is no evidence to link the use of inhaled or nasal glucocorticoids with an increased risk of SARS-CoV-2 infection or a more severe course of COVID-19 disease. These medications are expected to exert effective anti-inflammatory control of the upper and lower airways being a good protection against virus-triggered exacerbations for these patients. From today's perspective, there is sufficient data that patients with chronic inflammatory airway disease should receive guideline-based pharmacological treatment in the context of pandemic COVID-19, including glucocorticoids[156,157.]

Inhaled corticosteroids are widely available, inexpensive, and their safety is widely known. Due to their anti-inflammatory effects observed in episodes of decompensation of bronchial asthma and chronic obstructive pulmonary disease, where usually one of the frequent causes of decompensation is a viral infection[158,159]. In experimental and clinical studies, a reduction in the expression of ACE-2 and TMPRSS[160,161] has been observed, both relevant in the internalization process of the SARS-CoV-2 virus in airway epithelial cells[162]. Moreover, inhaled corticotherapy also reduces the expression of these proteins in cell cultures[163]. Epidemiological data

suggest that patients with COVID-19 and using corticotherapy have a lower complication rate, considering the small number of patients with bronchial asthma and chronic obstructive pulmonary disease hospitalized with complications of COVID-19.[158,159]. In fact, while some studies suggest a reduction in events and hospitalizations in patients with COVID-19, others do not confirm this finding[164,165,166].

3.5.1 Clinical Studies of inhaled budesonide in COVID-19

Ramakrishnan et al. evaluated the use of 400 µg of inhaled budesonide twice daily in patients with a clinical picture of COVID-19 and mild symptoms within 7 days of symptom onset in a united[167] kingdom community. The primary endpoint criterion of the study was emergency department visit due to COVID-19 symptoms after randomization and hospitalization. Important secondary endpoints were time to resolution of flu-like symptoms and assessments by flu-like symptoms outcome questionnaires (FLUPro, CCQ), SpO_2 and viral load assessment. A total of 167 participants were recruited in the period July-December 2020, with 73 patients randomized to budesonide and 73 patients randomized to conventional treatment. In the "per protocol" analysis, primary outcomes were observed in ten (14%) of 70 participants in the usual care group and one (1%) of 69 participants in the budesonide group (difference in proportions 0.131; 95% CI: 0.043 to 0.218; p = 0.004). In the "intention-to-treat" analysis the primary outcome occurred in 11 (15%) participants in the usual care group and two (3%) participants in the budesonide group (difference in proportions 0,123; 95% CI: 0.033 to 0.213 ; p = 0.09). Thus the number needed to treat with budesonide to achieve a reduction in a primary event was 8 participants. Although not statistically significant, recovery in the budesonide-treated group was faster (01 day) compared with the usual treatment group (median 7 days [95% CI 6 to 9] in the budesonide group vs 8 days [7 to 11] in the usual treatment group; log-rank test p = 0.07).

These data supported the conduct of a phase III trial using budesonide at a dose of 800 µg twice daily for 14 days in patients with COVID-19 and mild symptoms conducted by Yu et al. from the group of Prof. Christopher Butler at the University of Oxford and coordinator of the adaptive COVID research platform called PRINCIPLE. Eligible participants were either over 65 years of age or over 50 years of age-associated with some co-morbidity and symptom onset within 14 days but not admitted to hospital treatment.[168] The primary endpoint of the study was time to symptom recovery and hospital admission or death associated with COVID-19 within

28 days of randomization. From November 27, 2020 to March 31, 2021 4,700 participants were randomized to the budesonide group (n=1,073) or usual treatment (1,988) or other treatment (n=1,639). The primary analysis model included 2,530 SARS-CoV-2 positive participants, with 787 in the budesonide group, 1,069 in the usual treatment group and 974 receiving other treatments.

A greater recovery of flu symptoms of 2.44 days (95% Bayesian credible interval [BCI] 1.19 to 5.12) was observed in the budesonide-treated group versus the usual treatment group (11.8 days [95% BCI 10.0 to 14.1] vs 14.7 days [12.3 to 18.0]; RR 1.21 [95% BCI 1.08 to 1.36]), with a probability of superiority greater than 0.999, meeting the pre-specified superiority threshold of 0.99. For hospital admission or death outcome, the estimated rate was 6.8% (95%; BCI 4.1 to 10.2) in the budesonide group versus 8.8% (5.5 to 12.7) in the usual care group (estimated absolute difference 2.0% [95% BCI -0.2 to 4.5]; "odds ratio" 0.75 [95% BCI 0.55 to 1.03]), with a probability of superiority 0.963, below the pre-specified superiority threshold of 0.975.

3.6 Rationale for using fluvoxamine + budesonide combination and fluoxetine + budesonide combination

Fluvoxamine and Budesonide have been approved for clinical use in specific medical situations for more than 30 years. To date, there are no reports of pharmacological interactions between the combination of these SSRIs with Budesonide or any other inhaled glucocorticoid. Similarly, on the FDA website (www.fda.gov), there are no restrictions or safety guidelines regarding the possibility of using these two pharmacological classes in combination, nor these drugs with budesonide.

Fluvoxamine and fluoxetine have a well-defined action concerning oxidative stress and modulation in the production of pro-inflammatory cytokines, reducing these and thus avoiding the triggers that trigger the massive production of these cytokines, known as cytokine storm. The effects on the ceramide system modulating this production are important in reducing the expression of pro-inflammatory cytokines. Furthermore, fluvoxamine has an excellent agonist activity of the Sigma-1 receptor, which is an important point in the modulation of the inflammatory response and production of pro-inflammatory cytokines, its action being via activation of the IRE-1.

Fluvoxamine has extensive preclinical evaluation (in animals and cell cultures), demonstrating its anti-inflammatory and possibly antiviral potential, including the novel coronavirus. There is clinically noticeable regulation of intracellular stress and consequently of the inflammatory process. IRE-1 mediated activity demonstrated at doses approved for clinical use can modulate the production of pro-inflammatory cytokines, and such an effect has been evidenced in experimental models of sepsis, including LPS mediated and fecal peritonitis induced sepsis. This class has been shown to induce phagosome-mediated autophagy via the IRE pathway, which is stimulated by the activation of S1 receptors. It is possible that through activation of Nsp6 via sigma-1 receptors may allow the elimination of the new coronavirus.

Fluvoxamine and fluoxetine have a high concentration in lung tissues, something important regarding the possibility of therapeutic effects against viral pneumonia arising from COVID-19. Experimental studies of sepsis have shown a longer survival of animals pretreated with fluvoxamine. Finally, fluvoxamine has a known antiplatelet activity which may contribute by antagonizing in part the intense pro-thrombotic state observed in patients with novel coronavirus infection and thus reducing acute thrombosis in this disease. By inhibiting melatonin metabolism, SSRIs may reduce the activation of inflammasomes via NLRP343 and thus reduce cytokine and ceramide production.

Fluvoxamine and fluoxetine have a relevant functional acid sphingomyelinase inhibition activity (FIASMA), and this activity has been relevant as a potential reduction of ceramide production and as an important pathway for TMPRSS2 and ACE2 activity inhibition. Finally, experimental trials have shown a reduction in viral load with fluvoxamine.

To date, there are no published studies on the association between SSRIs and inhaled glucocorticoids for the treatment of patients with initial and outpatient COVID-19. Considering the potentially additive rationale of both pharmacological classes, we are therefore proposing the evaluation of these two pharmacological classes using fluvoxamine, a drug studied by this research program in previous stages, which has shown an expressive action in the improvement of the clinical picture of patients, with a lower rate of hospitalization, clinical worsening and mortality, and with an important FIASMA action, which can also contribute to its benefit. We chose to choose budesonide because there were two clinical trials; one of them was a large one, which demonstrated the benefit of using this drug in this phase of the disease caused by the new coronavirus.

Fluoxetine has a more exuberant FIASMA activity than fluvoxamine, and this activity is also responsible for a modulation of the ceramide/cytokine system, important in the inflammatory process associated with COVID-19. Fluoxetine is a medication considered essential by the World Health Organization, and in the face of phase II clinical trials suggesting a benefit from this medication, then we also propose this arm of research in our clinical trial.

3.7 Rationale for the use of pegylated interferon lambda 1A

The cornerstone of the innate antiviral immune response is the interferon (IFN) system. Detection of viral infection leads to the production of Type I (alpha, beta) and Type III (lambda) IFNs, which drive a potent antiviral response by inducing a wide range of genes, collectively known as IFN-stimulated genes (ISGs)[169]. Both Type I and Type III IFNs signal through the JAK-STAT pathway to drive the induction of ISGs with comparable antiviral activity, but their systemic effects differ markedly due to their use of distinct receptors with different tissue distributions (figure9)[169]. The Type I IFN receptor is highly expressed in all cells of the body, whereas the IFN- (lambda) receptor is mainly expressed in epithelial cells with high expression in the lung, intestine and liver and very limited expression in the hematopoietic and central170 nervous system cells.

As a result, production or treatment with Type I IFNs can lead to significant off-target effects, which may limit the safety, tolerability, and ultimately the clinical use of this class of agents. Interferon-alpha was used with some evidence of clinical efficacy in a pilot trial during the first SARS outbreak[171]; however, concerns were raised about the toxicity of a Type I IFN to COVID. IFN- was developed as a therapeutic agent to overcome the toxicity seen with IFN alpha and beta. The conjugation of IFN- to polyethylene glycol increases the half-life and allows once-weekly dosing. Peginterferon-lambda has been studied in phase 1, 2 and 3 clinical trials in over 3000 patients for the treatment of hepatitis C[172] virus, hepatitis B[173] virus and, more recently, hepatitis delta[174] virus infections, showing antiviral activity comparable to IFN-, but with much better safety and tolerability profile.

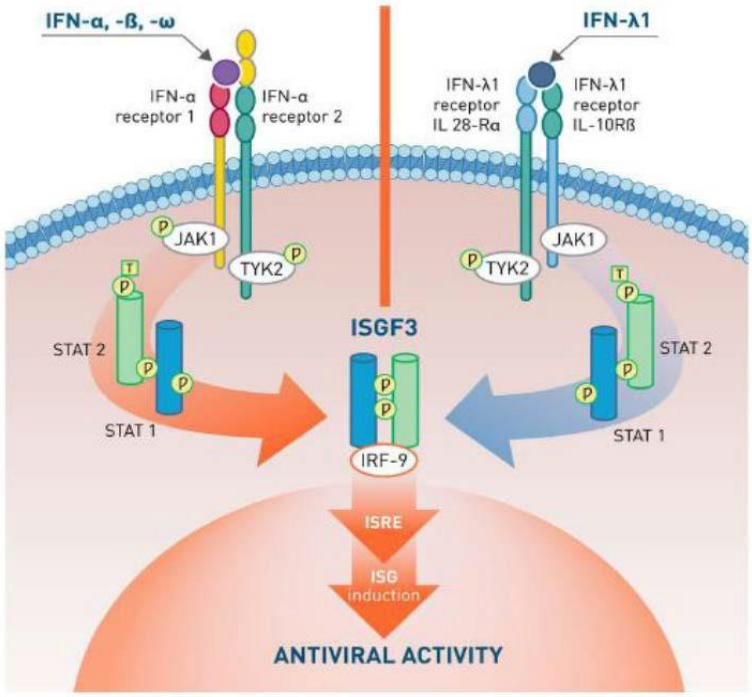


Figure 9: Mechanism of action: IFN lambda and IFN signaling via the JAK-STAT transduction signaling pathway

3.7.1 Pharmacokinetics and metabolism

The single-dose PK of lambda was evaluated in 4 Phase 1 studies in healthy subjects and in 2 Phase 2 studies in subjects with Hepatitis virus

	PK Parameters			
Dosage Group	**Cmax (ng/mL) Geometric Mean [n] (%CV)**	**AUC(INF) (ng-h/mL) Geometric Mean [n] (%CV)**	**Tmax (h) Median [n] (Min, Max)**	**T1/2 (h) Mean [n] (SD)**
526H04/AI452004 [EMERGE Phase 2a, Part 1] (HCV subjects)				
80 mcg	0.39 [12] (82.4)	84.84 [11] (46.4)	25.1 [11] (12.0, 49.8)	84.84 [11] (46.4)
120 mcg	0.78 [11] (46.8)	70.2 [11] (50.6)	12.0 [11] (8.0, 48.0)	70.2 [11] (50.6)
180 mcg	1.06 [11] (102)	116.9 [11] (73.1)	24.0 [11] (8.1, 73.1)	116.9 [11] (73.1)
240 mcg	1.77 [11] (106.5)	145.4 [7] (59.3)	24.0 [11] (4.0, 72.0)	145.4 [7] (59.3)

Table -6 PK parameters after a single dose of pegylated interferon lambda

In these studies, interferon lambda exhibited a dose-proportional pharmacokinetic profile in the 80 to 240 µg range. Both C_{max} and AUC increased in approximate proportion with increasing doses of lambda following both single and multiple-dose administration at a dose range of 80 to 240 µg. In these studies, the dose of 180 µg administered SC weekly was shown to have an adequate pharmacological effect profile with no increase in adverse reactions and is currently recommended for use.

Bioavailability

Administration of interferon lambda in humans has been via the subcutaneous route. Following single-dose administration of lambda in healthy subjects and in subjects with HCV, median T_{max} ranged from 8.00 to 25.1 hours, with individual T_{max} values ranging from 1 to 120 hours. The geometric mean Cmax (%CV) ranged from 1.06 (102%) to 2.41 ng/mL (177%) after single-dose administration of 180 mcg solution formulation to healthy subjects or subjects with HCV. Similarly, after multiple-dose administration of lambda to individuals with HCV, the median T_{max} ranged from 12.0 to 25.1 hours, with individual values ranging from 4 to 95.5 hours. After administration of multiple doses of 180 µg to subjects with HCV, the geometric mean C_{max} (%CV) was 1.54 ng/mL (86.0%), demonstrating a modest accumulation of lambda. The AUC_{inf} (%CV) after a single dose administration of lambda 180 mcg for healthy subjects and subjects with HCV ranged from 116.9 (73.1%) to 221 ngh/mL (59%). After a single dose of lambda 180 mcg for subjects with HCV, the geometric mean Vz/F was approximately 105 L.

After single-dose administration of lambda to healthy subjects, the mean (SD) T½ estimates ranged from 51.10 (13.723) to 81.0 (27.4) hours over the 80-mcg to 240-mcg dose range. The mean estimates were similar in healthy Western subjects, healthy Chinese subjects in Hong Kong, and healthy Japanese subjects. The mean (SD) T½ estimates following single and multiple doses in HCV subjects ranged from 36.30 (16.1) to 52.04 (22.3) hours. Following single and multiple-dose administration of the 180 mcg clinical dose to healthy subjects and subjects with HCV, the mean (SD) T½ ranged from 50.43 (20.47) to 74.0 (42.7) hours.

Drug-Drug Interactions

The effect of a single dose of peginterferon lambda on a cocktail of CYP substrates was evaluated in healthy subjects. The activity of selected CYP enzymes was assessed using the following probe substrates: caffeine (CYP1A2), warfarin (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6) and midazolam (CYP3A4). Subjects received the cocktail on day 1 followed by PK sampling for 5 days; subjects then received a single dose of peginterferon lambda 180 µg on day 8, followed by a second dose of the cocktail on day 15 with subsequent PK sampling for 5 days. Peginterferon lambda increased the AUC of the probe drugs as follows: caffeine ~73%, warfarin ~40%, omeprazole ~2-fold, dextromethorphan ~2-fold, and midazolam ~75%. These results suggest that following a single 180 µg dose of peginterferon lambda is a mild inhibitor of CYP1A2, CYP2C9 and CYP3A4 and a moderate inhibitor of CYP2C19 and CYP2D6. Since the effects on these sensitive CYP substrates are mild or moderate, dose adjustments for other concomitant CYP substrates may not be necessary, but such agents should be used with caution. Given that only one dose will be used in this trial, the concern for drug interactions is limited compared to other settings in which peginterferon lambda is administered weekly for extended periods of time.

Further details on the full safety profile, pharmacokinetics, pharmacodynamics, metabolism, excretion and use of peginterferon lambda can be found in the clinical development brochure for the molecule attached to this submission dossier.

3.7.2 Clinical Trial Data

Clinical activity in chronic HCV and HBV infection

The clinical activity of peginterferon lambda in combination with direct-acting antiviral agents is summarized in section 5 of the investigator's brochure attached to this research protocol. The antiviral activity of lambda against HCV was demonstrated in 2 Phase 2 studies in treatment for chronic HCV. The regimens included peginterferon lambda/ribavirin (RBV) in EMERGE Phase 2a/2b (526H04, N = 624) and peginterferon lambda/RBV/DCV (daclatasvir) and lambda/RBV/ASV (asunaprevir) in D-LITE (AI452008, N = 140). The initial doses tested in the Phase 2a/2b EMERGE study were 80, 120, 180, or 240 µg per week for 24 weeks (GT 2/4) or 48 weeks (GT 1/4).

Pharmacodynamic modeling to derive the optimal dose and duration of treatment with peginterferon lambda for Phase 3 studies have been described in 2

publications (Wang 2014, Hruska 2014). Wang et al. (2014) derived a population model of peginterferon lambda exposure, adapting a previously published dynamic viral model for peginterferon lambda treatment and host genotype and using it to simulate sustained virologic responses (SVR). The pharmacokinetics of the peginterferon lambda population was described by a one-compartment model with first-order absorption and 33.0 L per day release with 47% inter-individual variability (36% intra-individual). Weight explained an insignificant proportion of the variability.

Based on SVR predictions, the optimal treatment durations were 48 weeks for HCV genotypes 1 or 4 (SVR estimates for 120, 180, and 240 µg peginterferon lambda: 58%, 54%, 47%, respectively) and 24 weeks for genotypes 2 or 3 (75%, 72%, 67%). SVR predictions for 240 mg were lower due to dropout predictions. The SVR model established the optimal treatment duration for Phase 3 studies but did not differentiate between 120 and 180 mg dosing. Hruska et al. (2014) described the derivation of regression models for 12 weeks of virologic response on treatment and safety outcomes on 120, 180 and 240 µg peginterferon lambda with ribavirin.

In patients with HCV genotypes 1 or 4, there was a significant relationship (P=0.024) between undetectable HCV-RNA at Week 4 and exposure to peginterferon lambda (AUC or Cmax), with the largest difference between adjacent dose levels between the 180 and 120 µg exposure ranges. The risk of aminotransferase levels 3-4 or bilirubin elevations relative to a peginterferon alfa-2a/ribavirin control were related to peginterferon lambda exposure for all patients and the largest increase between adjacent dose levels was seen for 240 versus 180 µg. Anemia and neutropenia events were lower than control at all doses and exposures.

Thus, Phase 3 studies for HCV were designed to evaluate fixed doses of 180 µg peginterferon lambda in combination with ribavirin and a direct-acting antiviral for 24-48 weeks in HCV genotypes 1 or 4 or 12-24 weeks in HCV genotypes 2 or 3.

3.7.3 Rationale for the use of interferon lambda in patients with COVID-19

IFN- is particularly attractive for acute respiratory diseases because of the high expression of the IFN- receptor in lung epithelia (figure10). In vitro and mouse studies have shown that IFN- is strongly induced in infections by influenza, SARS-CoV-1 and other respiratory viruses, but induction is limited by SARS-CO-V-2[175] infection. IFN- treatment has been shown to be highly effective in a mouse model of severe influenza A infection. In influenza A-infected mice, pretreatment with IFN-ß

or IFN- prevented mortality[176]. However, when IFNs were given after infection, IFN-ß worsened outcome, whereas IFN- treatment improved survival[176]. IFN- is particularly attractive as a treatment strategy for SARS-CoV-2 infection because, in addition to its anticipated effect on the lung, the IFN- receptor is highly expressed in the intestine and liver[177], which would address the intestinal and hepatic involvement documented in patients with COVID-19[178]. In addition, the lack of the lambda receptor in hematopoietic cells limits concerns about the potential for worsening cytokine[179] storm syndrome.

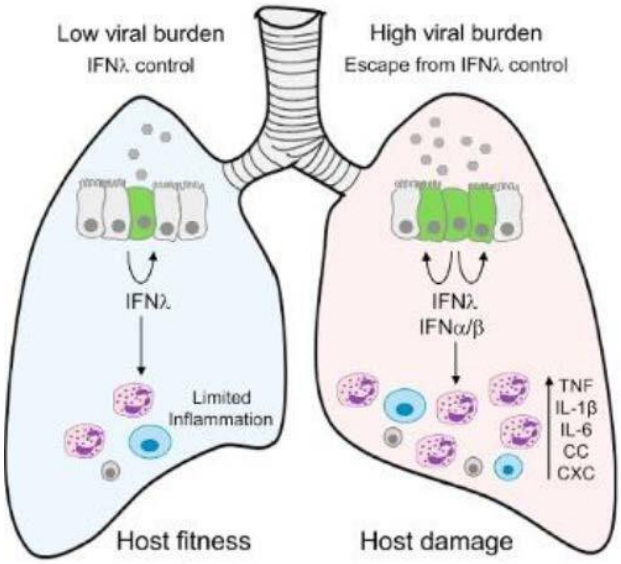


Figure 10: IFN-lambda reduces viral load and inflammation in lung tissue

To test this effect clinically, trials of peginterferon lambda were conducted to treat COVID-19. Recently, we completed a trial showing that treatment with peginterferon lambda in outpatients with mild to moderate COVID-19 accelerated viral decline and was very well tolerated[180]. In this placebo-controlled study, 60 outpatients with COVID-19 were randomized to a single dose of peginterferon lambda 180 µg SC or placebo in 0.9% saline. Treatment with peginterferon lambda accelerated viral decline compared to placebo. After controlling for baseline viral load, those who received peginterferon lambda had a 4.12 (95%CI 1.15-16.7, p=0.029) higher probability of viral decline by day 7 compared to those who received placebo. The probability of viral load decline by day 7 was higher the higher the degree of viral load was before the start of treatment.

Stratification of the population by those with a baseline viral load above or below $10E^6$ copies/mL showed that the benefit of peginterferon lambda treatment

was most evident in those with a high baseline viral load. Of those with a baseline viral load above 10 ^{6}copies/mL (58% of the study population), 79% of those treated with peginterferon lambda had the virus eliminated by day 7, compared to 38% in the placebo arm (p=0.038). The mean log decline in SARS-CoV-2 RNA was greater with peginterferon lambda than with placebo from day 3, with more pronounced differences seen in those with a high baseline viral load. The mean time to release of SARS-CoV-2 RNA was 7 days in the peginterferon lambda group compared with 10 days in the placebo group, among those with a high baseline[191] viral load.

In those subjects with low viral loads (below 10E ^{6}copies/mL), clearance was rapid in all, with no clear difference between those treated with peginterferon lambda or placebo. It is notable that 25% of participants had undetectable viral loads at the time of study entry, despite having a positive nasopharyngeal swab at the time of initial testing. Peginterferon lambda was well tolerated with a side effect profile similar to placebo. Treatment led to a higher rate of transient aminotransferase elevations, as previously reported, but was not associated with any other notable adverse laboratory events. There was a trend toward clinical improvement with peginterferon therapy with fewer emergency room visits (1 vs 4) and faster improvement in respiratory symptoms (p=0.06) compared to placebo[117].

A similar clinical study was conducted by Jagannathan *et al.* in 120 outpatients with mild[181] COVID-19 at Stanford University. In this phase II-III study, the single dose of peginterferon lambda of 180 µg in a single dose was used. While the study did not confirm a significant antiviral effect of peginterferon lambda, likely due to recruiting participants late in the course of their infection (median Ct at baseline of 30), they documented a very similar safety profile with no safety signal. Enriching the population for those with high viral loads and at higher risk of severe COVID-19 would be helpful in targeting therapy to those most likely to benefit.

Additional studies with peginterferon lambda are currently underway to evaluate its role in hospitalized patients with moderate to severe form COVID-19 and also as post-exposure prophylaxis in household contacts of individuals with mild COVID-19.

3.7.4 Pegylated interferon lambda

Pegylated interferon lambda 1A (peginterferon lambda) is a sterile, nonpyrogenic solution delivered in pre-mounted glass syringes for immediate intramuscular or subcutaneous use (0.4 mg/mL), and the solution is clear and/or

opalescent, usually colorless but may be pale yellow in color and essentially particulate free. The drug is supplied in a 1-mL maximum volume Type I glass syringe (0.18 mg/per syringe) with a 29-gauge, 1/2-inch, thin-walled needle. The syringe has a rigid needle guard and is capped with a plunger stopper. The syringes are pre-filled with a solution of peginterferon lambda, mannitol, L-histidine, polysorbate 80, hydrochloric acid, and water for injection; they are intended for single use in adjustable doses. The syringe is marked with dose indicator lines, which are used as a reference point to administer the correct dose. Peginterferon lambda injection should be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) and protected from prolonged exposure (> 24 hours) to light. Peginterferon lambda injection must not be frozen.

Peginterferon lambda is a medication in clinical development currently approved by the Food and Drug Administration for use in phase III clinical trials in multiple sclerosis, viral hepatitis and in COVID-19. The manufacturer (Eiger BioPharmaceuticals, Inc.) will supply the drug for the purpose of this research, free of charge and without direct or indirect interference, as this is an academic clinical study with no commercial interest.

Mechanism of action

Peginterferon lambda is a covalent conjugate of IFN lambda (IFN L) and a 20-kDa linear PEG chain. Peginterferon lambda binds to the interferon lambda receptor expressed on epithelial cells in the lung, intestine, liver, and skin and activates a signaling pathway that leads to the production of a variety of genes with antiviral and anti-proliferative effects, collectively known as interferon-stimulated genes (ISGs; see Figure X).

3.7.5 Usage

As of January 26, 2021, approximately 3,959 individuals (including 248 healthy individuals; 3,275 individuals with HCV; 197 individuals with HBV; and 59 individuals with HDV) have received peginterferon lambda or comparator in 19 phase 1, 2, or 3 studies. One hundred and eighty patients with COVID-19 have received pegylated interferon lambda in phase II and III clinical trials.

3.7.6 Summary

In general, peginterferon lambda was well tolerated at single doses of up to 5 µg/kg and at multiple doses of up to 180 SC µg administered weekly for 48 weeks in diverse acute and chronic viral syndromes. The main safety finding observed was a dose-dependent and reversible elevation in serum transaminases, with most events observed in studies in the highest dose group (240 µg), which were accompanied in some cases by increases in total and conjugated (direct) bilirubin. The 240 µg dose was discontinued from further development. Increases in total and direct bilirubin have also been observed with doses of 180 µg, which may be accompanied by mild increases in transaminases. These increases were not accompanied by evidence of loss of liver function and were readily reversible with withholding and/or dose reduction.

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

3.8.1 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[182]. Considering contacts made with the researchers of the STOP COVID trial, we chose to adopt a dosage of (100 mg twice a day), which is different from the initial study, which adopted a 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.

3.8.2 Budesonide

In the regulatory approval dossier for budesonide, there is a description of two studies performed to evaluate the systemic absorption. In the first study D5896C00010, an open-label, randomized, single-dose study conducted in 29 adult patients with bronchial asthma divided into 4 groups:

- Budesonide 1920 µg / formoterol 54 µg administered in 12 inhalations of Symbicort pMDI (160 / 4.5)
- Budesonide 1920 µg administered in 12 inhalations of budesonide pMDI (160 µg)
- Budesonide 2400 µg delivered per 12 inhalations of Pulmicort Turbuhaler (200 µg)
- Formoterol 54 µg delivered per 12 inhalations of Oxis Turbuhaler (4.5 µg)

The mean budesonide normalized dose AUC0-inf and Cmax after 12 inhalations of Symbicort pMDI (160/4.5) in adults was 9.68 pM-h/µg and 2.35 pM/µg, respectively.

The second study D5896C00013 was an open, randomized, single-dose, two-way crossover study in 24 children with asthma. The two single-dose treatments were:

- Budesonide 640 µg / formoterol 18 µg administered by 4 inhalations of Symbicort pMDI (160 / 4.5)
- Budesonide 800 µg / formoterol 18µg administered by 4 inhalations of Pulmicort Turbuhaler (200 µg).

The mean budesonide normalized dose AUC0-inf and Cmax after 4 inhalations of Symbicort pMDI (160 / 4.5) in children were 6.59 pM-h/µg and 2.13 pM/µg, respectively (Table below).

Table 1.1 Comparison of Budesonide $AUC_{0\text{-}inf}$ and C_{max} following Single Dose Administration of Symbicort pMDI in Children and Adults

Population	Single Dose of Budesonide	Nominal[1]		Dose Normalized[1]	
		$AUC_{0\text{-}inf}$ (pM·h)	C_{max} (pM)	$AUC_{0\text{-}inf}$ (pM·h/µg)	C_{max} (pM/µg)
Adults (N=28)[2]	1920 µg	18594 (36%)	4512 (51%)	9.68 (36%)	2.35 (51%)
Children (N=24)[3]	640 µg	4221 (55%)	1361 (100%)	6.59 (55%)	2.13 (100%)

[1] geometric mean (CV%)
[2] from CSR d5896c00010, page 92, Table ST2
[3] from CSR d5896c00013, page 74, Table ST2

The normalized dose systemic exposure of budesonide (AUC0-inf and Cmax) in children was numerically lower than that of adults after single-dose inhalation with the Symbicort pMDI device and considered very low[183].

The dose of budesonide approved for use in patients with bronchial asthma by ANVISA is 1,000 µg to 2,000 µg as the first dose, followed by a maintenance dose which can vary from 500 µg to 4,000 µg daily depending on the therapeutic response.

In this research program, we will use the dose of 400 µg in two daily doses, with the following posology:

- Fluvoxamine and budesonide combination: budesonide 400 µg administered via turbinhaler every 12 hours for 10 days

We adopted 10 days as the endpoint following the dosing regimen used by this research program to study fluvoxamine (we then propose the addition of budesonide while maintaining the same 10-day period).

3.8.3 Peginterferon lambda

In this clinical trial, we are planning to use the peginterferon lambda dose of 180 µg in a single dose to be administered on the day of randomization. This dose has been used in two phase II clinical trials in COVID-19 and without evidence of significant adverse reactions. Another 03 clinical trials are in planning for the use of interferon lambda at the same dose as proposed in this clinical trial.

For more information on the clinical development, pharmacokinetics, pharmacodynamics, tolerability, safety, and efficacy of peginterferon lambda, please refer to the investigator's brochure, which covers the entire clinical development of the drug to date, attached to this regulatory filing.

Clinical activity in chronic HCV and HBV infection

The antiviral activity of peginterferon lambda against HCV was demonstrated in 2 Phase 2 studies investigating peginterferon lambda regimens in treatment-naive individuals with chronic HCV. In these two studies, approximately 700 patients used the drug for up to 12 months. The SVR model established the optimal treatment duration for Phase 3 studies but did not differentiate between 120 and 180 mg dosing. Hruska et al. (2014) described the derivation of regression models for 12 weeks of virologic response on treatment and safety outcomes on 120, 180 and 240 µg peginterferon lambda with ribavirin. In patients with HCV genotypes 1 or 4, there was a significant relationship (P=0.024) between undetectable HCV-RNA at Week 4 and peginterferon lambda exposure (AUC or Cmax), with the largest difference between adjacent dose levels between the 180 and 120 µg exposure ranges. The risk of aminotransferase levels 3-4 or bilirubin elevations relative to a peginterferon alfa-2a/ribavirin control were related to peginterferon lambda exposure for all patients and the largest increase between adjacent dose levels was seen for 240 versus 180 µg. Anemia and neutropenia events were lower than control at all doses and exposures.

Based on these findings, Phase 3 studies for HCV were designed to evaluate fixed doses of 180 µg peginterferon lambda in combination with ribavirin and a direct-acting antiviral for 24-48 weeks in HCV genotypes 1 or 4 or 12-24 weeks in HCV genotypes 2 or 3.

Taking these clinical trials as a reference, as well as the two clinical trials already conducted and published on the use of this drug in patients with COVID-19, we have chosen to propose a dose of 180 µg as a single subcutaneous dose at the time of randomization.

3.8.4 Fluoxetine

Fluoxetine is a medication approved by ANVISA for use in several psychiatric conditions in doses ranging from 20 to 80 mg/day. In experimental models, the FIASMA activity of fluoxetine is already measured in cell cultures infected with the SARS-CoV-2 virus after 30 minutes of exposure to the drug, preventing/reducing the generation of ceramide and altering the biophysical properties of the plasma membrane, making viral[184] internalization more difficult. In "*in vitro"* studies*,* fluoxetine inhibits SARS-CoV-2 viral replication in the µM range: EC_{50} 0.69 µM (Vero E6), 0.82 µM (Calu-3). Fluoxetine remains effective against SARS-CoV-2

pseudoviruses with N501Y, K417N, and E484K peak mutations, and SARS-CoV-2[185] variants B.1.1.7 (alpha) and B.1.351 (beta). This activity was confirmed in experimental studies with human lung tissue infected with SARS-CoV-2, with a 2-3 log reduction in the existing viral load after 3 days of exposure to 5.2 µM fluoxetine[186]. Furthermore, Sigma-1 receptor agonists (of which fluoxetine is one of the most important) reduce inflammatory mediators associated with severe COVID-19, including IL-6, IL-10, TNF-α, and CCL-2.

Pharmacokinetic studies with Fluoxetine in patients affected with the new coronavirus show through modeling that with a daily dose of 40 mg/day, 90% of the population reach the C_{90} through antiviral EC target in the lung by day 4, and 92% are above this mean by day 7, and there is a prolonged effect, which extends up to 16 days due to the observed activity with the metabolite desmethyl fluoxetine[187].

In observational studies with fluoxetine, the usual doses of 20-40 mg/day have shown an association between reduced risk of death and intubation in patients hospitalized for COVID-19[146,147]. Considering this information, the ANTICOV Consortium opted for the fluoxetine regimen of 40 mg administered in a single dose in the morning for 07 consecutive days, and so we will adopt the same posology.

3.9 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[188].

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[189]. Many of these studies brought important information that impacted the way in which COVID-19 is approached, causing changes in care in several countries.

Although the decline in brazil is consistent, there is epidemiological evidence that a new wave may arrive in brazil in the coming weeks if the viral epidemiology

follows the same scenario as at the end of last year, where the united states and Europe were hit by a wave of COVID. Currently, the same situation is occurring, and therefore it is possible that we will have a new wave of new coronavirus infections starting in December 2021.

Today, from January 02, 2022, the pandemic shows signs not only of persistence but also of a rise in cases, possibly reflecting the new wave of COVID-19 associated with the Omicron variant (Figure 11 and 12).

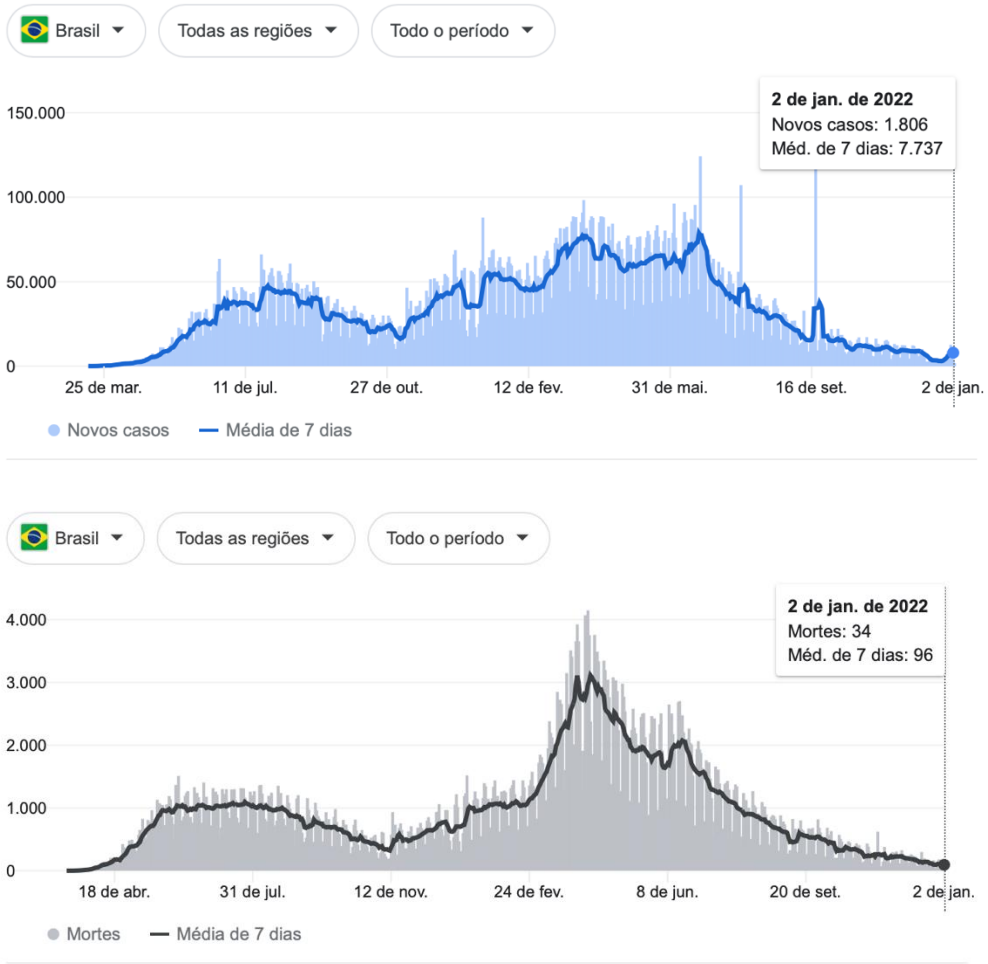


Figure 11 and 12 - Number of cases (Blue) and deaths (Black) diaries associated with COVID-19. Source: Johns Hopkins University Data Center (02/20/2022)

There is, therefore, the need to remain vigilant in relation to this pandemic and especially to maintain research to verify real therapeutic options for people who develop COVID-19, even in the scenario of increasing vaccination, since the adequate containment of the new omicron variant has been evidenced the need for

antibodies in titers above those needed for the containment of other variants of concern.

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

The need to offer a rapid response to an epidemic that has been ravaging our country since March 2020, coupled with the exuberance of recent 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 behaviors, 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.

The following visit design will be performed for the lambda pegylated interferon arm (single-dose treatment), fluvoxamine (10-day treatment) and combination of fluvoxamine + budesonide (10-day treatment) respective placebo (single dose administered subcutaneously at the randomization visit or 10-day treatment):

- V1 (D_0) - Screening visit
- V2 (D_0) - Baseline Visit + Randomization (Start of treatment phase; single dose if treated subcutaneously)
- V3 to V7(D_1 to D_5) - Telephone Contact from Day 1 to 5 (+ 1 day)
- V8 (D_7) - Day 7 Telephone Contact (+ 1 day)
- V9 (D_{10}) - Day 10 Telephone Contact (±days2; End of treatment phase with oral and/or inhaled medications)
- V10 (D_{14}) - Day 14 Telephone Contact (±days2)
- V11 (D_{28}) - Day 28 Telephone Contact (±days3)
- V12 (D_{60}) - Telephone Contact of the Day (60±5 days)

The following visit design will be performed for the fluoxetine + budesonide combination arm (07 days of treatment):

- V1 (D_0) - Screening visit
- V2 (D_0) - Baseline Visit + Randomization (Start of treatment phase)
- V3 - V22 ($_1$ From D_{20}) - Day 1 to Day 20 (+ 1 day; D_{07} final stage of treatment) Telephone Contact
- V23 (D_{21}) - Telephone Contact of the Day (21±2 days)
- V24 - V25 (D_{28}, D_{35}) - Phone Contact from Day 28 and Day 35 (±3 days)
- V26 (D_{60}) - Day 60 (±5 days) Telephone Contact

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 will be performed. As proposed in this amendment, patients who tested negative for COVID-19 will be offered participation in a pilot study on the use of interferon lambda 1A to evaluate the safety and tolerability of the medication in patients with acute influenza syndrome caused by other viruses

Participants who already have a positive RT-PCR test for SARS-CoV2 at the time of screening and meet all the criteria for inclusion in the trial 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 will then be randomized to one of the five research arms using the following sequencing:

1) **Randomization to the fluvoxamine arm:** Patients with criteria of moderate/important condition and decision by the care team (not involved with the research) to keep the patient on home outpatient treatment. These will be randomized on a 1:1 regimen to fluvoxamine or corresponding placebo.

2) **Randomization in the (a) pegylated interferon lambda or (b) fluvoxamine + budesonide combination arms:** Patients with mild COVID-19 and comorbid criteria as per protocol. These will be randomized in a 1:1:1 ratio, considering the corresponding placebo.
3) **Randomization in the combination arm between fluoxetine + budesonide:** patients without having been exposed to COVID-19 vaccines and with mild or moderate COVID-19 and protocol comorbidity criteria, where the care team (not involved with the research) has made the clinical decision for their outpatient follow-up. These will be randomized in a 1:1 ratio, considering the corresponding placebo.

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 a way that does not allow the identification of the medication being studied by any individual.

Participants will start their assigned treatments (pegylated interferon lambda, fluvoxamine, combination of fluvoxamine + budesonide, and combination of fluoxetine + budesonide) or corresponding placebo.

4.2 Duration of participation in the study

Participation of each eligible research subject includes a screening visit (D_0), followed by the treatment phase, which can be for one day (in the case of subcutaneously administered medications, for days 07 and 10 in the case of medications administered for days 07 and 10, respectively. In all situations, the first day of drug administration is at the time of randomization (D_0). The study will continue in a follow-up phase after completion of the investigational product, with telephone contacts expected at various times after randomization, the last being days60 after the randomization date.

For verification of the primary endpoint, a follow-up of up to 28 days 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 prematurely discontinue the investigational product will remain in the study for the data collection on the events of the composite endpoint and will receive the usual care for treatment and follow-up of COVID-19.

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

A - Inclusion criteria for the injectable medication arms (single dose at randomization), fluvoxamine, fluvoxamine + budesonide combination (10-day treatment):

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 full days of the randomization date;
3 Patients over the age of 18 and with at least ONE of the following criteria:
    a) Age 50≥ years (you don't need any of the other criteria),
    b) *Diabetes mellitus* requiring oral medication or insulin,
    c) Hypertension requiring at least 01 oral medication for treatment,
    d) Known cardiovascular diseases (heart failure, congenital heart disease, valve disease, coronary artery disease, myocardiopathy under treatment, clinically manifest heart diseases with clinical repercussions),
    e) Lung disease that is symptomatic and/or being treated (emphysema, fibrosing diseases),
    f) Patients with symptomatic asthma requiring chronic use of agents for symptom control,
    g) Obesity, defined as BMI > 30 kg/m^2 on weight and height information provided by the patient,
    h) Transplant patients,
    i) Patient with stage IV chronic kidney disease or on dialysis,

j) Patient with fever measured at screening > 38º C (criterion limited to 25% of randomizations)

k) Patients with at least one of the following symptoms: cough, dyspnea, ventilator-dependent chest pain, or myalgias with limitation of daily activities (Criteria limited to 25% of randomizations),

l) Immunosuppressed patients/on corticotherapy (maximum 10 mg prednisone equivalent per day) and/or immunosuppressive therapy if injectable arm or 40 mg/day prednisone equivalent in the medication arms for 10 days)),

m) Patients with a history of Cancer in the last 05 years or in current oncological treatment;

4 Patient with a positive rapid test for SARS-CoV2 antigen performed at the time of screening or patient with positive SARS-CoV2 diagnostic test within 07 days of symptom onset (antigen test or RT-PCR);

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

6 Signing the Informed Consent Form prior to any research procedures;

7 Specific inclusion criteria for the fluvoxamine arm:

8 Present significant dyspnea, hypotension, severe dehydration, or SpO2 between 85 and 93% on admission and be released home later, with an observation period of no more than 12 hours.

B - Inclusion criteria for the Fluoxetine + Budesonide combination arm (07-day treatment):

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;

3 Patients over 18 years of age and a history of at least ONE of the following criteria:

a) Diabetes mellitus, heart disease, chronic kidney disease, chronic obstructive pulmonary disease, cerebrovascular disease, or patients considered underweight or overweight as judged by the investigator (BMI ≤ 16 or BMI > 25);

OR

b) Individuals aged ≥ 60 years without co-morbidities

4 COVID-19 confirmed by molecular or antigenic testing for SARS-CoV-2 within 24 hours prior to screening and no later than 2 days after sample collection;
5 Viral syndrome with or without pneumonia and Arterial O_2 saturation > 94%;
6 Signing the Informed Consent Form prior to any research procedures;
7 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. Negative diagnostic test for SARS-CoV2 associated with acute influenza symptoms (patient with a negative test taken early and becomes positive a few days later is eligible, provided he/she is < 07 days from the onset of influenza symptoms);
2. Patients with an acute respiratory condition compatible with COVID-19 seen in the primary care network and with a decision to hospitalize;
3. Patients with an acute respiratory condition due to other causes;
4. Dyspnea secondary to other acute and chronic respiratory causes or infections (e.g., decompensated COPD, acute bronchitis, pneumonia other than viral, primary pulmonary arterial hypertension);
5. Patients with a need for hospitalization due to COVID-19 or SpO_2 ≤ 93%.

NOTE: Patients allocated to the fluvoxamine arm alone may be included if the SpO_2 is between 85-93%, with no evidence of respiratory failure, provided the attending physician decides to discharge them from the unit and continue treatment on an outpatient basis

6. Exclusion criteria applicable to injectable medication arms:

a) Patients in chronic use of prednisone, prednisolone or another corticosteroid, with doses > 10 mg/day prednisone equivalent,

7. Exclusion criteria applicable to the 07-day treatment arms:
    a) Abnormal findings on physical examination: respiratory rate ≥ 25 systolic; blood pressure < 90/ 60 mmHg or > 160/ 100 mmHg; Weight < 45 kg; recent episodes of vomiting in the past 24 hours, recurrent diarrhea; serum potassium below 3.5 mEq/L,
    b) Severe organ damage requiring resuscitation and ongoing treatment,
    c) Use of corticotherapy chronically with equivalent doses of prednisone of > 40 mg/day,
    d) Ongoing immunosuppressive treatment,
    e) History of known pulmonary arterial hypertension,
    f) Patients who have received a previous dose of the SARS-CoV-2 vaccine.
    g) Use of serotonin reuptake inhibitors
8. Exclusion criteria applicable to 10-day treatment arms:
    a) Chronic use of serotonin reuptake inhibitors with the exception of sertraline,
    b) Use of corticotherapy chronically with equivalent doses of prednisone of > 40 mg/day
9. Continued use of monoamine oxidase inhibitors (MAOI): Phenelzine, Tranylcypromine, Selegiline, Isocarboxazid, moclobemide;
10. Patients with severe psychiatric disorders - schizophrenia, uncontrolled bipolar disorder, major depression with suicidal ideation.
11. Pregnant or nursing patients;
12. History of severe ventricular cardiac arrhythmia (ventricular tachycardia, recovered ventricular fibrillation patients) or Long QT Syndrome;
13. Known history of decompensated heart failure (NYHA III or IV), recent myocardial infarction (event < 90 days from screening), unstable angina, recent coronary by-pass surgery (procedure < 90 days from screening), recent stroke (event < 90 days from screening), symptomatic carotid disease, or mitral or aortic stenosis of moderate to severe intensity;
14. Surgical procedure or hospitalization planned (for other indications) to occur during treatment or up to 05 days after the last dose of study medication;

15. Current daily and/or uncontrolled alcoholism, which in the view of the investigator could compromise participation in the study;
16. History of seizures in the last month or an uncontrolled seizure condition;
17. Clinical history of moderate to severe liver impairment or cirrhosis of the liver with a Child-Pugh C classification;
18. Patients with known severe degenerative neurological diseases and/or severe mental illnesses as assessed by the investigator;
19. Inability of the patient or representative to give consent or adhere to the procedures proposed in the protocol;
20. Any medical conditions, including psychiatric conditions, which in the investigator's view would preclude the use of the investigational medicinal products
21. Hypersensitivity and/or known intolerance to fluvoxamine, budesonide or pegylated interferon lambda and fluoxetine;
22. Use of drugs that have a known interaction with fluvoxamine, budesonide or pegylated interferon lambda and fluoxetine;
23. Inability to use the drugs and formulations provided in this research;

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 good 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 suspended by the investigator

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 Budesonide

It will be provided to the participant in the form of capsules for inhalation + "turbinhaler" and the capsules containing 400 µg budesonide.

6.2.3 Pegylated interferon lambda

It will be provided to the participant in the form of a pre-filled injection, ready for immediate administration, at a dose of 180 µg for single-dose administration at the time of randomization.

All investigational products will be supplied to patients from pharmaceutical companies approved by ANVISA and certified to produce them or from companies with GMP certification and with authorization for use in clinical research issued by the Food and Drug Administration and imported through an import license issued by ANVISA for clinical use specifically in this research.

6.2.4 Fluoxetine

Will be provided to the participant in the form of 20 mg tablets for oral use.

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.

- **Budesonide:**

  Capsules containing budesonide 400 µg budesonide powder for inhalation. Doses should be administered via "turbinhaler" every 12 hours according to the randomization regimen.

- **Pegylated interferon lambda:**

  Pre-filled syringe containing 180 µg of the drug for single-dose administration at the time of randomization.

- **Fluoxetine:**

  Dose 20 mg twice a day, always at 7 am and 7 pm, for a period of 07 days.

6.3.2 Active Control Group paracetamol (fluoxetine + budesonide arm)

- **Paracetamol:**

  A dose of 500 mg twice a day over a period of 07 days, always taken at 7 a.m. and 7 p.m.

6.3.3 Dosage and administration guidelines

6.3.3.1 Fluvoxamine

The dose on the day of randomization will be 100 mg to be taken at the end of the visit and before the patient leaves the unit where he was randomized, followed by 100 mg every 12 hours until completing 10 days of treatment (If the randomization is with an interval of less than 06 hours from the subsequent dose it 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)

6.3.3.2 Budesonide

The dose on the day of randomization will be 400 µg to be administered by turbinhaler at the end of the visit and before the patient leaves the unit where he was randomized, followed by 400 µg (01 inhalation) every 12 hours until completing 07 or 10 days of treatment (according to the randomization allocation). If the randomization is with an interval of less than 06 hours from the subsequent dose, the same dose will not be administered. Example: A 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)

6.3.3.3 Pegylated interferon lambda

On the day of randomization, after completion of all the procedures planned for the visit, if the patient is allocated to receive injectable medication, the nurse will provide the medication and administer it subcutaneously (180 µg or corresponding placebo).

The patient will remain for 30 minutes under observation in the health care unit for possible observations of adverse events arising after the immediate application of the investigational drug.

After this point, the patient will be released home with no additional medication to administer (single dose).

6.3.3.4 Fluoxetine

The dose as established in the ANTICOV study is 20 mg to be always started in the morning and then daily at 7 a.m. and 7 p.m. until the completion of the 07 days treatment (If randomization is before mid-day, the dose can be administered at randomization).

6.3.3.4 Paracetamol (active control fluoxetine + budesonide arm)

The dose as established in the ANTICOV study is 500 mg every 12 hours, always at 7 am and 7 pm, starting in the morning and then daily, always at 7 am and 7 pm until 7 days of treatment are completed.

6.4 Packaging and labeling

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 medications delivered.

The study medication used will come from pharmaceutical plants with commercial authorization for their production, already approved by ANVISA or through importation authorized by ANVISA for use specifically in this research protocol.

6.5 Study treatment allocation

Each eligible participant will be allocated to 1 of the treatment groups5 via an internet-accessible remote randomization system (IWRS), namely:

- Fluvoxamine
- Combination of fluvoxamine + budesonide
- Fluoxetine + budesonide combination
- Pegylated Interferon lambda
- Matching placebo (or paracetamol in the case of active control of fluoxetine + budesonide, as per ANTICOV protocol)

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 will 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_{10}. 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 telephone safety 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 Oxidase Inhibitors (MAOI): Phenelzine, Tranylcypromine, Selegiline, Isocarboxazid, moclobemide;
- Selective Serotonin Reuptake Inhibitors (except sertraline)

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 is not on the list of prohibited medications or does 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 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 Budesonide

Most adverse reactions reported in clinical studies conducted are self-limiting and are resolved with medication discontinuation or non-pharmacological measures.

Common reactions to the use of inhaled budesonide are nausea, headache, dysphonia, respiratory tract infection and sinusitis, palpitations, syncope, tachycardia, weight gain, abdominal pain, oral candidiasis, dyspepsia, vomiting, xerostomia, diffuse myalgias, asthenia, somnolence, insomnia, migraine, cataract,

glaucoma, cough, epistaxis, nasal congestion, nasal irritation. Rare reactions are dermatitis, urticaria, Cushing's syndrome, hypoglycemia, dyslipidemia, anxiety, depression, irritability, behavior problems, psychosis (psychiatric disease), bronchospasm, and throat irritation.

7.2.3 Pegylated interferon lambda

Most adverse reactions reported in clinical studies conducted are self-limiting and are resolved with nonpharmacological or anti-inflammatory measures. Mild flu-like symptoms (chills, myalgias, fever) can occur in up to20 % of patients, and the same statistic is true for gastrointestinal symptoms (nausea, vomiting). Injection site reactions (pain, local erythema, edema and pruritus) can occur in up to 30% of patients. Other common symptoms are headache and nausea, usually within 24 hours of drug administration. Elevations of liver enzymes (> 3x normal value) and hematological enzymes occur in respectively1 % and 4% of patients with repeated use of peginterferon lambda. Less than 1% of treated patients experience urticaria and angioedema, which are reversed with corticotherapy and antihistamines. Depression and suicidal ideation can occur in up to2 % of patients and appear after repeated and prolonged administration of the drug.

7.2.4 Fluoxetine

Most adverse reactions reported in clinical studies conducted with fluoxetine are related to the digestive system, usually mild gastrointestinal symptoms. Common reactions to fluoxetine: diarrhea, nausea, fatigue (including asthenia), headache and insomnia, palpitations, blurred vision, dry mouth, dyspepsia, vomiting, chills, feeling shaky, weight loss. Uncommon reactions: QT interval prolongation (QTcF ≥ 450 msec), anorexia, attention disturbance, dizziness, loss of libido, frequent urination, bleeding, rash, urticaria,

7.2.5 Paracetamol

Adverse effects related to paracetamol are rare; however, hypersensitivity including rash may occur. There have been reports of blood dyscrasias, including thrombocytopenia, neutropenia, pancytopenia, leukopenia, and agranulocytosis, but these were not necessarily causally related to paracetamol. Very rare cases of

severe skin reactions have been reported. There are no reports of elevations of liver enzymes in the literature with the doses recommended in this clinical trial

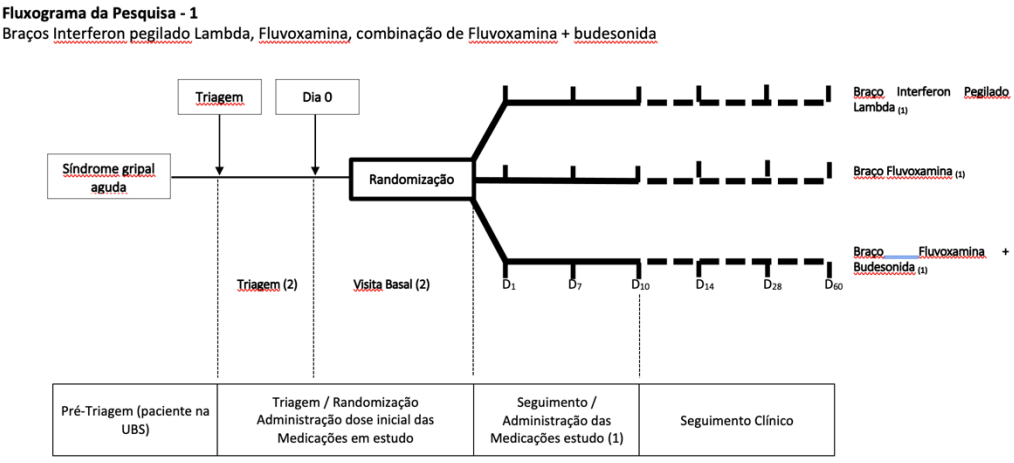
8 STUDY PROCEDURES

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

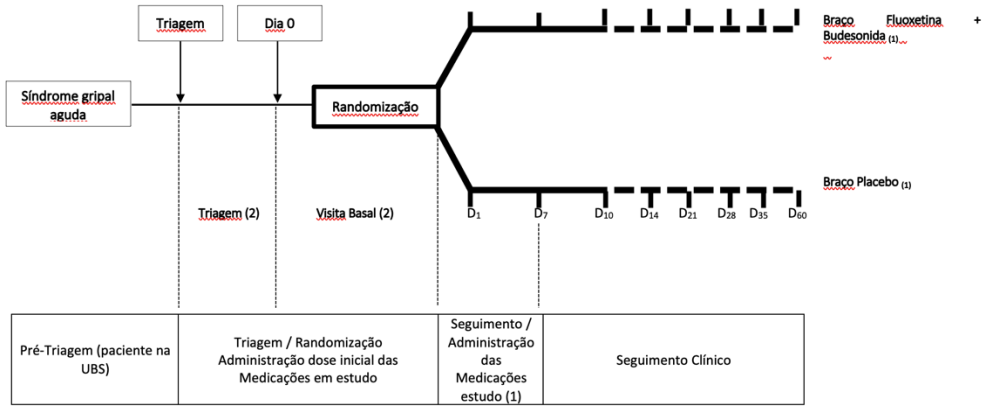
Before any specific procedure of the study, the participant will receive an explanation of all the procedures of the study and must date and sign an informed consent form (ICF) approved by a Research Ethics Committee (REC). The screening visit will be performed (1) in Basic Health Units / Outpatient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



1. Tratamento: Interferon Pegilado Lambda, Fluvoxamina e combinação de Fluvoxamina + Budesonida em grupos paralelos pelo período planejado. Posologia das medicações varia conforme a alocação do paciente em um braço do estudo (interferon pegilado lambda: dose única; fluvoxamina: 10 dias; combinado de fluvoxamina + budesonida: 10 dias). Para cada braço há o correspondente placebo, na mesma formulação e posologia. Medicações serão interrompidas a qualquer momento se houver evidência de reação adversa, a critério do sujeito da pesquisa ou por recomendação do DSMB (eficácia, futilidade ou segurança do participante).
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_1 a D_7, D_{10}, D_{14}, D_{28}, D_{60} serão realizadas através de contato telefônico, entretanto com possibilidade de visitas presenciais, caso necessário. Em qualquer momento visitas extras de segurança poderão ser realizadas, inclusive presenciais. A visita D_{28} é considerada a visita de desfecho para a pesquisa. A visita D_{60} é considerada visita pós-estudo, para acompanhamento de eventuais complicações tardias/ persistência de sintomas relacionados ao COVID-19 e também para avaliação eventual de reações adversas tardias aos medicamentos da pesquisa. Esta será realizada através de contato telefônico. Não há previsão de visitas presenciais regulares 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, inclusive presenciais, caso seja identificado alguma complicação e/ou evolução do COVID-19 que possa justificar nossa ida ao domicílio para avaliação do paciente.
4. Contato diário por telefone serão realizados entre os Dias 1 a 10 de tratamento, incluindo para sintomas clínicos de alarme. Outros contatos telefônicos poderão ser realizados, independentemente dos programados acima, tanto a pedido do paciente ou por nossa avaliação, visando a segurança do sujeito da pesquisa.

Table 4 - Flow chart of study 1: fluvoxamine, pegylated interferon lambda and combination of fluvoxamine + budesonide

Fluxograma da Pesquisa - 2
Braços combinação de fluoxetina + budesonida e correspondente placebo



1. Tratamento: Combinação de Fluoxetina + budesonida e correspondente placebo em grupos paralelos pelo período planejado. Posologia das medicações varia conforme a alocação do paciente em um braço do estudo (combinação de fluoxetina + budesonida e correspondente placebo : 07 dias. Medicações serão interrompidas a qualquer momento se houver evidência de reação adversa, a critério do sujeito da pesquisa ou por recomendação do DSMB (eficácia, futilidade ou segurança do participante).
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_1 a D_7, D_{10}, D_{24}, D_{21}, D_{28}, D_{35} e D_{60} serão realizadas através de contato telefônico, entretanto com possibilidade de visitas presenciais, caso necessário. Em qualquer momento visitas extras de segurança poderão ser realizadas, inclusive presenciais. A visita D_{35} e D_{60} é considerada visita pós-estudo, para acompanhamento de eventuais complicações tardias/ persistência de sintomas relacionados ao COVID-19 e também para avaliação eventual de reações adversas tardias aos medicamentos da pesquisa. Esta será realizada através de contato telefônico. Não há previsão de visitas presenciais regulares 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, inclusive presenciais, caso seja identificado alguma complicação e/ou evolução do COVID-19 que possa justificar nossa ida ao domicílio para avaliação do paciente.
4. Contato diário por telefone serão realizados entre os Dias 1 a 21 após randomização para identificação de sintomas de alarme. Outros contatos telefônicos poderão ser realizados, independentemente dos programados acima, tanto a pedido do paciente ou por nossa avaliação, visando a segurança do sujeito da pesquisa.

Table 5 - Flowchart of research 2 (collaborative partnership with "ANTICOV consortium")

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 (for patients with acute influenza syndrome without a positive test for SARS-CoV-2 within 7 days of symptom onset).

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 a confirmatory test for COVID-19, randomization can be performed, provided that it occurs within 7 full days of the onset of acute flu symptoms.

The following procedures will be performed in this visit

- IWRS Registration
- Review of eligibility criteria
- Medical History
- Weight (informed by the patient)
- Height (informed by the patient)
- ECG (Kardiamobile, 01 or 06 leads) for measurement of Heart Rate and QT interval.
- Adverse Events if applicable
- Concomitant medications
- WHO Flu Syndrome Questionnaire and WURSS-21
- Alarm Symptoms Questionnaire
- Blood pressure measurement and delivery of automatic blood pressure measuring device (for patients allocated to 14 days of treatment)
- Baseline pulse oximetry measurement
- Randomization
- Delivery of medications and orientation regarding the same
- Orientation regarding daily telephone contacts and subsequent visits
- Guidelines for post-randomization visits.
- 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. In patients allocated to treatment with oral medications or a combination of medications, the same will be delivered according to randomization and offered the global orientations referring to the treatment group (if for medications for 7 days or for 10 days of treatment). If the patient is allocated to treatment with injectable medications, the same will be administered in a single dose, at the end of the randomization procedures and before the patient leaves for home. Patients allocated to a single dose will receive nasopharyngeal SWAB kits for sputum/saliva collection to check the viral load on day 3 and day 7 after randomization. All patients will receive orientation regarding daily telephone contacts and the procedures associated with the upcoming 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 a priority after randomization. If face-to-face care is required, the research team will arrange a home visit, preferably.

8.2.1 Daily telephone contacts

The patient will be contacted daily, either by phone. 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, WURSS-21 and Alarm Symptoms Questionnaire.
- Whenever possible and available, the patient should report the SpO_2

Patients allocated to take medication under investigation for 07 or 10 days will be contacted by phone and/or social media app as described in section 4.1 of this protocol.

All patients allocated to a single dose of subcutaneous medication will be tested for viral load. The patient 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 telephone contact on D_7, the participant will be instructed 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

In the group allocated to use the investigational medicinal product for 07 and 10 days, RT-PCR will not be collected since, in previous steps of this research, the viral load in a subgroup of patients has already been evaluated.

8.2.2 Visit 3 to V25: D_1 to D_{60}

The flowchart of these visits is variable, depending on the patient's allocation (01, 07 or 10-day treatment arm). If for single-dose or 10-day treatment, the patient will make daily telephone contacts until D_5 and then D_7, D_{10} D_{14}, D_{28} and D_{60}. All patients allocated to single-dose subcutaneous will have nasopharyngeal and/or sputum SWAB self-collection.

For patients allocated to the 07-day treatment arm, there will be daily telephone contact until D_{21} post randomization. Thereafter there will be telephone contact at D_{28}, D_{35} and D_{60}.

In addition, the following procedures can be checked in these visits:

- Adverse Events
- Concomitant Medications
- Clinical alarm symptoms questionnaire
- WURSS- Questionnaire21
- Respiratory Symptoms
- Clinical outcomes
- SpO_2 (if the patient has an oximeter or if it is measured during a medical appointment)
- Remote Product Accounting under Investigation

- WHO ordinal scale of clinical improvement

8.2.3 D_{14}, D_{28}, D_{35} and D_{60} visits (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 at the initiative of the participant). The following procedures will be verified in these visits:

- IWRS Registration
- Evaluation of adverse events
- Evaluation of clinical outcomes
- Collection of the research medication KIT's for accounting.
- Guidelines on Ending the Treatment Period
- Follow-up phone contact guidelines
- Registration of drugs and concomitant procedures
- Guidance about the end of contacts and termination of the research (D_{60})
- PROMIS V10 Questionnaire (D_{28})
- WURSS- Questionnaire21
- Alarm Symptoms Questionnaire (D_{21})
- WHO ordinal Clinical Improvement Scale

At the visit D_{28}, the patient will also answer the TICS-M questionnaire to assess any memory changes.

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 (Visit8).

On an unscheduled visit during any phase of the study, the following activities will be performed:

- IWRS Registration
- Blood pressure measurement when applicable.
- AE assessment/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 as 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_{60} 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 visit$_{28}$.

9 STUDY EVALUATIONS

9.1 Laboratory examinations

In this clinical research protocol, there is no provision for laboratory tests, with the exception of the rapid test for COVID-19 and the RT-PCR tests, both using nasopharyngeal secretion/saliva 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.
- Weight and height (informed by the patient)

9.2.1 Heart and respiratory rate

For patients allocated to the 3- and 10-day treatment arms, 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, for these groups of patients, except in situations where the research team identifies the need to know the blood pressure levels for immediate action.

Respiration rate will be measured by digital oximetry.

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 (PROMIS-10, WURSS-12, alarm symptom questionnaire, and WHO influenza 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. Progressive values of the scale indicate greater severity of the COVID-19 condition.

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)[190]. 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 of 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 originally formulated questions. Progressive values indicate improved patient well-being.

TICS-M Questionnaire

We will assess eventual memory deficits using a known standardized questionnaire that can be applied via telephone contact (TICSM). The items on this scale assess the general domains of memory. Progressive values indicate greater memory impairment.

WURSS-12 Questionnaire

The Wisconsin Upper Respiratory Symptom Survey (WURSS) is a flu symptom assessment tool developed by Barrett et al.[191,192] is a disease-specific questionnaire instrument that assesses URTIs emphasizing patient-oriented outcomes. The WURSS has versions in different languages, including English, Spanish, French, German, Korean, etc., whose reliability and validity have been tested in previous studies. WURSS-24 is a version intended for evaluation in influenza-like illnesses and has been used for an extensive evaluation of SVI patients in clinical practice, including COVID-19, as it allows estimation of myalgia and associated headache.

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 medications can cause neurological withdrawal symptoms in newborns of mothers taking fluvoxamine. Budesonide has no specific actions of concern in pregnancy and is considered a "B" risk medication.

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[193]. 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, 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 EAGs occurring after the reporting period specified in the protocol if, according to the investigator's judgment, there is a reasonable possibility that the EAG 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 AS 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 their 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 EAG, 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 EAGs).

10.4.2 Causality and reporting

The investigator will provide a causality assessment for all AEs using his/her 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 EAG is reported as recovered/resolved with sequelae, the investigator should specify the type of sequelae on the EAG form. If the outcome of an EAG is reported as unknown, the investigator should specify (on the EAG 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/EAGs 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 EAG.

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 of 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 of 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 potential adverse reactions are expected to be already described in the RSI of the medications under investigation (ANVISA Drug Dossier, Drug Package Insert registered with 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 EAG is defined as any unfavorable 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 EAGs
- 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 EAG criteria should be considered an EAG, 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 EAGs:

- 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 EAG reporting period begins at the time the TCLE is signed by the participant. The EAG reporting period ends at visit D_{28} in the single-dose treatment arms or the 10-day treatment arms. For the 07-day treatment arm, there will be monitoring for pregnancy and/or EAGs, which must be reported.

The occurrence of an EAG must be reported immediately to the research coordinating committee within 24 hours of its notification by fax, e-mail or telephone. This includes all EAGs (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 (D_{60}), whether considered treatment-related or not, must be reported to the study's follow-up committee.

Any EAG 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 EAG 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 EAG, a new EAG should be recorded. The resolution date of the original AE should be the same as the start date of the EAG. However, when the EAG 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 EAG 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 EAG report form and verify the accuracy of the information recorded on the EAG pages with the source documents. The sponsor's EAG 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 (follow-up) EAG report 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 EAG 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 EAG 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 EAGs, some of the information in the list above may be generated by the electronic system. Since EAGs are also

AEs, the information for the AE clinical record and the EAG form should be consistent.

Follow-up information should be handled in the same manner and reported at the same time interval as the initial EAG 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 report 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 EAGs, 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 EoS8 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:

- Viral load change on day 03 and 07 after randomization (first 600 patients, as per approved protocol version 2.0);

- 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 time to 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 EAGs, but will not be reported individually on an immediate basis. Although these EAGs 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 the basis of a single case 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.

The sponsor or investigator will notify the ethics committee and regulatory authorities of all SUSARs and other types of EAGs (if applicable) in accordance with local safety requirements.

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 EAG, 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 allows us to conclude that this medication should not be prescribed to pregnant patients without a careful evaluation of the risks and benefits of its use during this phase. Therefore, pregnancy is not expected 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 EAG, it must be reported within 24 hours of its notification by the participant. Complications of pregnancy are reported as AEs or EAGs (if applicable). Any pregnancy will be followed up until delivery to note any EAGs. Deaths, spontaneous or elective abortion, congenital abnormalities/congenital defects, and AEs/EAGs occurring in newborns should be reported as EAGs. Newborns potentially exposed to the study drug through maternal or paternal sources who present with an EAG 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).

Patients tested NEGATIVE for COVID-19 and participating in the pilot substudy of pegylated interferon lambda will be followed using the same criteria as above.

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: the internal pilot phase and the main clinical trial.

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 need 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.
iv) Associate with other study platforms in order to study arms of common interest, with the goal of getting answers in less time compared to conducting them alone.

12.2 Randomization

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

1. Fluvoxamine
2. Combination of fluvoxamine + budesonide
3. Pegylated interferon lambda
4. Combination of fluoxetine + budesonide
5. Placebo (or active control paracetamol for the fluoxetine + budesonide arm)

We will use a computer-generated, centralized random allocation schedule implemented using a remote access online system. Randomization will be stratified by participating primary care facility. The randomization system will use an allocation ratio of 1:1 in the case of fluvoxamine alone versus placebo (patients with moderate disease); 1:1:1:1 in the case of pegylated Interferon lambda, the combination of fluvoxamine + budesonide, the combination of fluvoxamine + budesonide and placebo, which will be blocked using variable patient set sizes.

For each active drug arm, there will be a placebo arm, including for the different research formulations and dosages. E.g. if a patient is allocated to a single dose subcutaneous treatment, he/she may receive either active medication or subcutaneous injection of a corresponding placebo. The same is true for 07- and 10-day treatments.

For each arm of the research, there will be the equivalent counterpart in placebo.

The pilot substudy of pegylated interferon lambda in patients with acute influenza syndrome and tested NEGATIVE for SARS-CoV-2 will have a placebo control on a double-blind basis, similar to the pegylated interferon lambda arm in patients with COVID-19. For these, there will be a specific placebo group of patients tested negative for COVID-19 with random allocation in a 1:1 ratio.

12.3 Sample calculation

The sample size calculation is based on the test for the hypothesis that each of the treatments: i) fluvoxamine; ii) combined fluvoxamine + budesonide, iii) pegylated interferon lambda, and iv) combined fluoxetine + budesonide) will be better than placebo in reducing the risk of hospitalization and/or emergency room care with a stay longer than 6 hours 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 from patients infected with COVID on December 10th, 2020, confirmed prospectively at the time of analysis of the placebo arm corresponding to the fluvoxamine and ivermectin arms, as well as real-time analysis of epidemiological data of patients with COVID-19 and similar co-morbidities available in the coronavirus database of the municipal health secretariats of the participating cities, data from the state health secretariat of Minas Gerais, and data from the ministry of health for Brazil and the state of Minas Gerais. It is important to note that this is an evolving situation. Therefore, we calculated the sample size table showing the sensitivity of the sample size estimates based on different baseline risks for hospitalization and expected treatment effects (see Table below15).

As there are interim analyses, the non-blinded statistician who advises the DSMB will do an analysis of the global event data and compare it with the epidemiological data from Brazil and the State of Minas Gerais. These data are checked against the actual global numbers of events that have occurred and also considering the current epidemiology in the regions where the study is taking place. This is necessary because depending on the predominant variant in a region, the expected complication rate may fluctuate.

On the occasion of the 4ª interim review that took place on August 05, 2021, and after blindly analyzing the data recommended:

(1) The Ivermectin arm was discontinued due to futility compared to the placebo group;
(2) The suspension of the fluvoxamine arm for superiority over the placebo group;
(3) The maintenance of the pegylated interferon lambda arm without modification;

(4) The definitive suspension of the pegylated interferon lambda arm considering that the sponsor has withdrawn the proposal to sponsor the drug, thus making it unfeasible to perform this arm;

(5) The conduct of a specific interim analysis to evaluate adverse events associated with the doxazosin arm, since there will be a projection of at least 125 patients included in the doxazosin arm (considering 1:1 randomization), to be scheduled by September 15.

On September 12, 2012, the 5th interim analysis was conducted specifically to assess adverse events regarding the doxazosin arm, and the trial's independent data and safety review committee recommended discontinuation of the 14-day treatment arms.

On December 16, 2021, the research protocol has registered the randomization of patients3.584

Considering (1) the discontinuation of the fluvoxamine, ivermectin arms as described above, (2) the discontinuation of the doxazosin arm due to undesirable adverse reactions, (3) the maintenance of the pegylated interferon arm and (4) the proposed initiation of the following arms: fluvoxamine, the combination of fluvoxamine + budesonide and combination of fluoxetine + budesonide, 6,246 patients necessary for us to reach the threshold needed for validation of clinical outcomes data (the randomization of 2,662 additional patients).

Table 7- Sample calculation using paired samples versus the control group. For these calculations, we focused on a paired comparison between Treatment 1 and Treatment 2 (fluvoxamine, fluvoxamine + budesonide combination and pegylated interferon lambda). Treatment group proportions were estimated by 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.

An exploratory analysis will be adopted in the same way for the pilot substudy of patients tested NEGATIVE for COVID-19.

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) Competing risk analysis: this analysis will adjust for death as a competitive increase for any binary outcome;

iii) missing data analysis: This analysis will assess the impact of missing data on key findings.

iv) Bayesian analysis: We will also perform sensitivity analyses using Bayesian methods to assess the impact of including data in other studies as before.

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:

c) Age - assumption that younger patients will benefit more than older patients

d) Gender - we think that women will benefit more than men.

e) 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 co-morbidities 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 comorbidities under baseline conditions. The subgroup effects will be evaluated by including an interaction term between the treatment group and the subgroup

variables. These interaction effects will be exploratory in nature and will be evaluated using alpha = 0.05.

12.9 Lost data

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

12.10 Combined studies analysis policy

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

12.11 - Summary Table of Events

Outcome	Hypothesis	Outcome Measurement	Statistical Analysis Method
1) **Primary** a) Emergency room attendance and observation time > 06 hours b) Hospitalization for complications of COVID-19 2) Co-Primary	Treatment with medications will be better than placebo	Hospitalization due to COVID-19 or related complications Mortality due to complications of COVID-19	Cox Regression/Logistic Regression
2) **Secondary** Negative/viral load reduction on days 03 and 07 (150 patients per stratum)	Negative viral load treatment with medications	Negative/viral load reduction	Descriptive Analysis
Time to clinical improvement (28 days)	Treatment will shorten time to clinical improvement	Interval of days between randomization and clinical improvement (scales used in the research)	Cox Regression/Logistic Regression
Number of times health care resources were used for treatment/evaluation of COVID-19	The more health care services you use, the more severe the flu syndrome	Number of times patient consults with health care professionals due to COVID-19	Cox Regression/Logistic Regression
Time to SpO2 < 94% associated with symptoms (up to 28 days)	Treatment will reduce the number of pacs with this change	Interval of days between randomization and obtaining SpO2 < 94%.	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, Fluvoxamine + budesonide, fluoxetine + budesonide and pegylated interferon	Drugs are safe in patients with COVID-19	Measurement of adverse events in the treatment groups	Descriptive Analysis

lambda in patients with COVID-19			
Cardiovascular mortality	Treatment will prevent cardiovascular mortality	Measurement of cardiovascular deaths in the groups	Cox Regression/Logistic Regression
Mortality from any cause	Treatment will prevent global mortality	Measurement of deaths in the groups	Cox Regression/Logistic Regression
3) **Subgroup Analysis:** i) age (young vs. old) ii) Sex (male vs. woman) iii) Diabetes iv) Hypertension v) Chronic kidney disease KDIGO IV or hemodialysis vi) Chronic lung disease vii) Solid-organ transplantation viii) Heart Failure	Elderly have a higher risk of complications Men have a higher risk Diabetes has a higher risk Hypertensives have a higher risk Kidney disease carries a higher risk Lung disease has a higher risk Transplantation has a higher risk Heart Failure carries a higher risk	Risk Measurement	Regression methods with appropriate interaction terms.
4) **Sensitivity Analysis**	Results remain robust	Primary and co-primary outcome	

IMPORTANT REMARKS:

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

13 ETHICAL CONSIDERATIONS OF THE STUDY

13.1 Ethical conduct of the study

The study will be conducted in accordance with the principles of the World[194] Medical Association's Declaration of Helsinki, and the International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, as amended.[193]as amended.

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 REC

All investigators participating in this study must be governed by an appropriate REC. The REC/ 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 REC approval annually or more frequently in accordance with regulatory requirements and established REC policies and procedures. Copies of the investigator's annual report and other reports are required to be submitted to the REC, and copies of continuing REC approval must be provided to the Steering Committee. The investigator must also inform the REC of any changes or amendments to the protocol, expedited EAG reports submitted to regulatory authorities, and other significant safety concerns in accordance with REC policy. Written documentation of approval of protocol amendments by the REC must be received prior to implementation. Upon completion or termination of the trial, investigators should notify their RECs. The investigator will be in compliance with the REC 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 REC, 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

14.1 Quality 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 that 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 must be consistent with the source documents, or discrepancies must be explained. An explanation should be provided for all 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 change or correction 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 REC 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 PROCEDURE 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/REC should review and approve the amendments prior to their implementation. Regulatory authority/REC 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 being 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 prior approval from the steering committee. The confidentiality agreement to be established with the participating research centers will establish the publication policy.

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

18 BIBLIOGRAPHIC REFERENCES

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

2 ZHOU P, YANG XL, WANG, XG, HU B, ZHANG L, ZHANG W, et al. Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin. bioRxiv. 2020; doi: https://doi.org/10.1101/2020.01.22.914952

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

18 Siddiqi, H. K. & Mehra, M. R. COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal. *The Journal of Heart and Lung Transplantation* S105324982031473X (2020) doi:10.1016/j.healun.2020.03.012.

19 Li, G. *et al.* Coronavirus infections and immune responses. *J Med Virol***92** , 424-432 (2020).

20 Konig, M. F. *et al.* Preventing cytokine storm syndrome in COVID-19 using α-1 adrenergic receptor antagonists. *J. Clin. Invest.* (2020) doi:10.1172/JCI139642.

21 Siddiqi, H. K. & Mehra, M. R. COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal. *The Journal of Heart and Lung Transplantation* S105324982031473X (2020) doi:10.1016/j.healun.2020.03.012.

22 Mehta, P. *et al.* COVID-19: consider cytokine storm syndromes and immunosuppression. *The Lancet* S0140673620306280 (2020) doi:10.1016/S0140- 6736(20)30628-0.

23 McGonagle, D., Sharif, K., O'Regan, A. & Bridgewood, C. The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. *Autoimmunity Reviews* 102537 (2020) doi:10.1016/j.autrev.2020.102537.

24 Arentz, M. *et al.* Characteristics and Outcomes of 21 Critically Ill Patients With COVID- 19 in Washington State. *JAMA* (2020) doi:10.1001/jama.2020.4326.

25 Vital Surveys: The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) - China, 2020. http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51 (2020).

26 Xu, X. *et al.* Effective treatment of severe COVID-19 patients with tocilizumab. *PNAS* (2020) doi:10.1073/pnas.2005615117.

27 Cavalli, G. *et al.* Interleukin-1 blockade with high-dose anakinra in patients with COVID- 19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *The Lancet Rheumatology* S2665991320301272 (2020) doi:10.1016/S2665-9913(20)30127- 2.

28 Zhou, F. *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet*

S0140673620305663 (2020) doi:10.1016/S0140-6736(20)30566-3.

29 Guan, W.-J. *et al.* Clinical Characteristics of Coronavirus Disease 2019 in China. *N. Engl. J. Med.* (2020) doi:10.1056/NEJMoa2002032.

30 Chen, T. *et al.* Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ***368** , m1091 (2020).

31 Qin, C. *et al.* Dysregulation of immune response in patients with COVID-19 in Wuhan, China.
Clinical Infectious Diseases ciaa248 (2020) doi:10.1093/cid/ciaa248.

32 Wan, S. *et al*. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). *medRxiv* 2020.02.10.20021832 (2020) doi:10.1101/2020.02.10.20021832.

33 Wu, C. *et al.* Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* (2020) doi:10.1001/jamainternmed.2020.0994

34 Liu, J. *et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients.* http://medrxiv.org/lookup/doi/10.1101/2020.02.16.20023671 (2020) doi:10.1101/2020.02.16.20023671.

35 Chen, G. *et al.* Clinical and immunologic features in severe and moderate Coronavirus Disease 2019. *J. Clin. Invest.* (2020) doi:10.1172/JCI137244.

36 Chen, X. *et al.* Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely associated with dramatically elevated interleukin (6IL-6) level in critically ill COVID-19 patients. *medRxiv* 2020.02.29.20029520 (2020) doi:10.1101/2020.02.29.20029520.

37 Liu, T. *et al. The potential role of IL-6 in monitoring severe cases of coronavirus disease 2019.* http://medrxiv.org/lookup/doi/10.1101/2020.03.01.20029769 (2020) doi:10.1101/2020.03.01.20029769.

38 Mehta, P. *et al.* COVID-19: consider cytokine storm syndromes and immunosuppression. *The Lancet* S0140673620306280 (2020) doi:10.1016/S0140- 6736(20)30628-0.

39 Channappanavar, R. & Perlman, S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol***39** , 529- 539 (2017).

40 Wong, C. K. *et al.* Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin. Exp. Immunol.* **136**, 95-103 (2004).

41 Mahallawi, W. H., Khabour, O. F., Zhang, Q., Makhdoum, H. M. & Suliman, B. A. MERS- CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile. *Cytokine***104** , 8-13 (2018).

42 Cai, X. *An Insight of comparison between COVID-19 (2019-nCoV disease) and SARS in pathology and pathogenesis.* https://osf.io/hw34x (2020) doi:10.31219/osf.io/hw34x.

43 Kim, E. S. *et al.* Clinical Progression and Cytokine Profiles of Middle East Respiratory Syndrome Coronavirus Infection. *J Korean Med Sci* **31**, 1717 (2016).

44 Lew, T. W. K. Acute Respiratory Distress Syndrome in Critically Ill Patients With Severe Acute Respiratory Syndrome. *JAMA***290** , 374 (2003).

45 McGonagle, D., Sharif, K., O'Regan, A. & Bridgewood, C. The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. *Autoimmunity Reviews* 102537 (2020)

46 Ramos-Casals, M., Brito-Zerón, P., López-Guillermo, A., Khamashta, M. A. & Bosch, X. Adult haemophagocytic syndrome. *Lancet* **383**, 1503-1516 (2014).

47 Karakike, E. & Giamarellos-Bourboulis, E. J. Macrophage Activation-Like Syndrome: A Distinct Entity Leading to Early Death in Sepsis. *Front Immunol***10** , (552019).

48 Crayne, C. B., Albeituni, S., Nichols, K. E. & Cron, R. Q. The Immunology of Macrophage Activation Syndrome. *Front. Immunol.* **10**, 119 (2019).

49 Brudno, J. N. & Kochenderfer, J. N. Toxicities of chimeric antigen receptor T cells: recognition and management. *Blood* **127**, 3321-3330 (2016).

50 Hay, K. A. *et al.* Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor-modified T-cell therapy. *Blood* **130**, 2295-2306 (2017).

51 Neelapu, S. S. *et al.* Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol***15** , 47-62 (2018).

52 Moore, J. B. & June, C. H. Cytokine release syndrome in severe COVID-19. *Science* **368**, 473-474 (2020).

53 Gritti, G. *et al. Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support.* http://medrxiv.org/lookup/doi/10.1101/2020.04.01.20048561 (2020) doi:10.1101/2020.04.01.20048561.

54 Sanofi: Press Releases, Monday, April 27, 2020. *https://www.sanofi.com/en/media- room/press-releases/2020/2020-04-27-12-58-00* https://www.sanofi.com/media-room/press- releases/2020/2020-04-27 12-58-00 2022288.

55 Perricone, C. *et al.* The anti-viral facet of anti-rheumatic drugs: lessons from COVID-19. *J Autoimmun* (2020) doi:10.1016/j.jaut.2020.102468.

56 Dienz, O. *et al.* Essential role of IL-6 in protection against H1N1 influenza virus by promoting neutrophil survival in the lung. *Mucosal Immunol* **5**, 258-266 (2012).

57 Karnowski, A. et *al.* B and T cells collaborate in antiviral responses via IL-6, IL-21, and transcriptional activator and coactivator, Oct2 and OBF-1. *J Exp Med***209** , 2049-2064 (2012).

58 Rose-John, S., Winthrop, K. & Calabrese, L. The role of IL-6 in host defense against infections: immunobiology and clinical implications. *Nat Rev Rheumatol***13** , 399-409 (2017).

59 Ruan, Q., Yang, K., Wang, W., Jiang, L. & Song, J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* (2020) doi:10.1007/s00134-020-05991-x.

60 Ritchie, A. I. & Singanayagam, A. Immunosuppression for hyperinflammation in COVID- 19: a double-edged sword? *The Lancet* S0140673620306917 (2020) doi:10.1016/S0140- 6736(20)30691-7.

61 Schett, G., Sticherling, M. & Neurath, M. F. COVID-19: risk for cytokine targeting in chronic inflammatory diseases? *Nat Rev Immunol* **20**, 271-272 (2020).

62 Emanuel, E. J. *et al.* Fair Allocation of Scarce Medical Resources in the Time of Covid- 19. *N Engl J Med* NEJMsb2005114 (2020) doi:10.1056/NEJMsb2005114.

63 Truog, R. D., Mitchell, C. & Daley, G. Q. The Toughest Triage - Allocating Ventilators in a Pandemic. *N Engl J Med* NEJMp2005689 (2020) doi:10.1056/NEJMp2005689.

64 Zumla, A., Hui, D. S., Azhar, E. I., Memish, Z. A. & Maeurer, M. Reducing mortality from 2019-nCoV: host-directed therapies should be an option. *The Lancet***395** , e35-e36 (2020).

65 Konig, M. F. *et al.* Preventing cytokine storm syndrome in COVID-19 using α-1 adrenergic receptor antagonists. *J. Clin. Invest.* (2020) doi:10.1172/JCI139642.

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

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

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

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

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

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

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

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

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

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

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

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

78 Park JJH, Mogg R, Smith GE, Nakimuli-Mpungu E, Jehan F, Rayner CR, Condo J, Decloedt EH, Nachega JB, Reis G, Mills EJ. How COVID-19 has fundamentally changed clinical research in global health. Lancet Glob Health. 2021 May;9(5):e711-e720. doi: 10.1016/S2214-109X(20)30542-8.

79 Woodcock, J. & LaVange, L. M. Master protocols to study multiple therapies, multiple diseases, or both. *N. Engl. J. Med.* **377**, 62-70 (2017).

80 Morris, Z. S., Wooding, S. & Grant, J. The answer is 17 years, what is the question: understanding time lags in translational research. *J. R. Soc. Med.* **104**, 510-520 (2011).

81 Institute of Medicine (US) Committee on Quality of Health Care in America. *Crossing the Quality Chasm: A New Health System for the 21st Century*. (National Academies Press, 2001).

82 Adaptive Platform Trials Coalition. Adaptive platform trials: definition, design, conduct and reporting considerations. Nat Rev Drug Discov. 2019 Oct;18(10):797-807. doi: 10.1038/s41573-019-0034-3.

83 Rayner CR, Dron L, Park JJH, Decloedt EH, Cotton MF, Niranjan V, Smith PF, Dodds MG, Brown F, Reis G, Wesche D, Mills EJ. Accelerating Clinical Evaluation of Repurposed Combination Therapies for COVID-19. Am J Trop Med Hyg. 2020 Oct;103(4):1364-1366. doi: 10.4269/ajtmh.20-0995

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

112 Sukhatme VP, Reiersen AM, Vayttaden SJ, Sukhatme VV. Fluvoxamine: A Review of Its Mechanism of Action and Its Role in COVID-19. Front Pharmacol. 2021 Apr 20;12:652688. doi: 10.3389/fphar.2021.652688.

113 Lenze EJ, Mattar C, Zorumski CF, Stevens A, Schweiger J, Nicol GE, Miller JP, Yang L, Yingling M, Avidan MS, Reiersen AM. Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19: A Randomized Clinical Trial. JAMA. 2020 Dec 8;324(22):2292-2300. doi: 10.1001/jama.2020.22760.

114 Reis G, Dos Santos Moreira-Silva EA, Silva DCM, Thabane L, Milagres AC, Ferreira TS, Dos Santos CVQ, de Souza Campos VH, Nogueira AMR, de Almeida APFG, Callegari ED, de Figueiredo Neto AD, Savassi LCM, Simplicio MIC, Ribeiro LB, Oliveira R, Harari O, Forrest JI, Ruton H, Sprague S, McKay P, Glushchenko AV, Rayner CR, Lenze EJ, Reiersen AM, Guyatt GH, Mills EJ; TOGETHER investigators. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. Lancet Glob Health. 2021 Oct 27:S2214-109X(21)00448-4. doi: 10.1016/S2214-109X(21)00448-4.

115 WHO Essential Medicines list. Accessible at https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2021.02, access ralyzed on November 16, 2021

116 Meinhardt, J., Radke, J., Dittmayer, C. et al. Olfactory transmucosal invasion of SARS-CoV-2 as a central nervous system port of entry in individuals with COVID-19. Nat Neurosci 24, 168-175 (2021). https://doi.org/10.1038/s41593-020-00758-5.

117 Narita N, Hashimoto K, Tomitaka S, Minabe Y. Interactions of selective serotonin reuptake inhibitors with subtypes of sigma receptors in rat brain. Eur J Pharmacol. 1996 Jun 20;307(1):117-9. doi: 10.1016/0014-2999(96)00254-3.

118 T. Ishima, Y. Fujita, K. Hashimoto
Interaction of new antidepressants with sigma-1 receptor chaperones and their potentiation of neurite outgrowth in PC12 cells
Eur J Pharmacol, 727 (2014), pp. 167-173

119 Grassmé H, Jekle A, Riehle A, Schwarz H, Berger J, Sandhoff K, et al. CD95 signaling via ceramide-rich membrane rafts. J Biol Chem. 2001;276:20589-96.

120 Schissel SL, Jiang X, Tweedie-Hardman J, Jeong T, Camejo EH, Najib J, et al. Secretory sphingomyelinase, a product of the acid sphingomyelinase gene, can hydrolyze atherogenic lipoproteins at neutral pH. Implications for atherosclerotic lesion development. J Biol Chem. 1998;273:2738-46.

121 Ferranti CS, Cheng J, Thompson C, Zhang J, Rotolo JA, Buddaseth S, et al. Fusion of lysosomes to plasma membrane initiates radiation-induced apoptosis. J Cell Biol. 2020;219:e201903176.

122 Kolesnick RN, Goni FM, Alonso A. Compartmentalization of ceramide signaling: physical foundations and biological effects. J Cell Physiol. 2000;184:285-300.

123 Nurminen TA, Holopainen JM, Zhao H, Kinnunen PKJ. Observation of topical catalysis by sphingomyelinase coupled to microspheres. J Am Chem Soc. 2002;124:12129-34.

124 Grassmé H, Bock J, Kun J, Gulbins E. Clustering of CD40 ligand is required to form a functional contact with CD40. J Biol Chem. 2002;277:30289-99.

125 Grassmé H, Henry B, Ziobro R, Becker KA, Riethmüller J, Gardner A, et al. β1-Integrin accumulates in cystic fibrosis luminal airway epithelial membranes and decreases sphingosine, promoting bacterial infections. Cell Host Microbe. 2017;21:707-18.

126 Dumitru CA, Gulbins E. TRAIL activates acid sphingomyelinase via a redox mechanism and releases ceramide to trigger apoptosis. Oncogene. 2006;25:5612-25.

127 Carpenter A, Becker KA, Japtok L, Hessler G, Keitsch S, Pozgajova M, et al. Regulation of hematogenous tumor metastasis by acid sphingomyelinase. EMBO Mol Med. 2015;7:714-34.

128 Ferranti CS, Cheng J, Thompson C, Zhang J, Rotolo JA, Buddaseth S, et al. Fusion of lysosomes to plasma membrane initiates radiation-induced apoptosis. J Cell Biol. 2020;219:e201903176.

129 Rotolo J, Stancevic B, Zhang J, Hua G, Fuller J, Yin X, et al. Anti-ceramide antibody prevents the radiation gastrointestinal syndrome in mice. J Clin Invest. 2012;122:1786-90.

130 Charruyer A, Grazide S, Bezombes C, Müller S, Laurent G, Jaffrézou JP. UV-C light induces raft-associated acid sphingomyelinase and JNK activation and

translocation independently on a nuclear signal. J Biol Chem. 2005;280:19196-204.

131 Grassmé H, Riehle A, Wilker B, Gulbins E. Rhinoviruses infect human epithelial cells via ceramide-enriched membrane platforms. J Biol Chem. 2005;280:26256-62.

132 Gulbins E, Kolesnick R. Raft ceramide in molecular medicine. Oncogene. 2003;22:7070-7.

133 Sakuragawa N, Sakuragawa M, Kuwabara T, Pentchev PG, Barranger JA, Brady RO. Niemann-Pick disease experimental model: sphingomyelinase reduction induced by AY-9944. Science. 1977;196:317-9.

134 Yoshida Y, Arimoto K, Sato M, Sakuragawa N, Arima M, Satoyoshi E. Reduction of acid sphingomyelinase activity in human fibroblasts induced by AY-9944 and other cationic amphiphilic drugs. J Biochem. 1985;98:1669-79.

135 Kornhuber J, Tripal P, Reichel M, Terfloth L, Bleich S, Wiltfang J, et al. Identification of new functional inhibitors of acid sphingomyelinase using a structure-property-activity relation model. J Med Chem. 2008;51:219-37.

136 Trapp S, Rosania GR, Horobin RW, Kornhuber J. Quantitative modeling of selective lysosomal targeting for drug design. Eur Biophys J. 2008;37:1317-28.

137 Kölzer M, Werth N, Sandhoff K. Interactions of acid sphingomyelinase and lipid bilayers in the presence of the tricyclic antidepressant desipramine. FEBS Lett. 2004;559:96-8.

138 Kornhuber J, Tripal P, Reichel M, Mühle C, Rhein C, Muehlbacher M, et al. Functional inhibitors of acid sphingomyelinase (FIASMAs): a novel pharmacological group of drugs with broad clinical applications. Cell Physiol Biochem. 2010;26:9-20.

139 Kornhuber J, Muehlbacher M, Trapp S, Pechmann S, Friedl A, Reichel M, et al. Identification of novel functional inhibitors of acid sphingomyelinase. PLoS ONE. 2011;6:e23852.

140 Matsuyama S, Nagata N, Shirato K, Kawase M, Takeda M, Taguchi F. Efficient activation of the severe acute respiratory syndrome coronavirus spike protein by the transmembrane protease TMPRSS2. J Virol. 2010;84:12658-64.

141 Matsuyama S, Nagata N, Shirato K, Kawase M, Takeda M, Taguchi F. Efficient activation of the severe acute respiratory syndrome coronavirus spike protein by the transmembrane protease TMPRSS2. J Virol. 2010;84:12658-64.

142 Carpenter A, Gripp B, Hoffmann M, Pohlmann S, Hoertel N, Edwards MJ, et al. Inhibition of acid sphingomyelinase by ambroxol prevents SARS-CoV-2 entry into epithelial cells. J Biol Chem. 2021;296:1-12.

143 Heinrich M, Wickel M, Schneider-Brachert W, Sandberg C, Gahr J, Schwandner R, et al. Cathepsin D targeted by acid sphingomyelinase-derived ceramide. EMBO J. 1999;18:5252-63.

144 Schloer S., Brunotte L., Goretzko J., Mecate-Zambrano A., Korthals N., Gerke V., Ludwig S., Rescher U. Targeting the endolysosomal host-SARS-CoV-2 interface by clinically licensed functional inhibitors of acid sphingomyelinase (FIASMA) including the antidepressant fluoxetine. *Emerg. Microbes Infect.* 2020;9(1):2245-2255

145 A.R. Eugene, Fluoxetine pharmacokinetics and tissue distribution suggest a possible role in reducing SARS-CoV-2 titers. medRxiv 2020

146 Hoertel N, Sánchez-Rico M, Vernet R, Beeker N, Jannot AS, Neuraz A, Salamanca E, Paris N, Daniel C, Gramfort A, Lemaitre G, Bernaux M, Bellamine A, Lemogne C, Airagnes G, Burgun A, Limosin F; AP-HP / Universities / INSERM COVID-19 Research Collaboration and AP-HP COVID CDR Initiative. Association between antidepressant use and reduced risk of intubation or death in hospitalized patients with COVID-19: results from an observational study. Mol Psychiatry. 2021 Sep;26(9):5199-5212. doi: 10.1038/s41380-021-01021-4

147 Oskotsky T, Maric I, Tang A, Oskotsky B, Wong RJ, Aghaeepour N, Sirota M, Stevenson DK. Mortality Risk Among Patients With COVID-19 Prescribed Selective Serotonin Reuptake Inhibitor Antidepressants. JAMA Netw Open. 2021 Nov 1;4(11):e2133090. doi: 10.1001/jamanetworkopen.2021.33090. PMID: 34779847.

148 Silva P, Farmacologia. 8. ed. Brazil: Guanabara Koogan; 2010.

149 Brett E, Stanaland MD. Once-Daily Budesonide Aqueous Nasal Spray for Allergic Rhinitis: A Review. Florida. Clin Ther. 2004; 26(4):473-92.

150 Approved formulations of Budesonide in Brazil - ANVISA. Accessed at: https://consultas.anvisa.gov.br/#/medicamentos/q/?substancia=1491&monodroga=S&situacaoRegistro=V access date: 16/ 11/ 2021.

151 Klimek L, Becker S, Buhl R, Chaker AM, Huppertz T, Hoffmann TK, Dazert S, Deitmer T, Förster-Ruhrmann U, Olze H, Hagemann J, Plontke SK, Wrede H, Schlenter W, Welkoborsky HJ, Wollenberg B, Beule AG, Rudack C, Strieth S, Mösges R, Bachert C, Stöver T, Matthias C, Dietz A. Positionspapier: Empfehlungen zur Behandlung der chronischen Rhinosinusitis während der COVID-19-Pandemie im deutschen Gesundheitssystem - Empfehlungen des

Ärzteverbandes Deutscher Allergologen (AeDA) und der Deutschen Gesellschaft für HNO-Heilkunde, Kopf- und Halschirurgie (DGHNO-KHC) - Diese Empfehlungen basieren auf dem EAACI Positionspapier "Treatment of chronic RhinoSinusitis with nasal polyps (CRSwNP) in the COVID-19 pandemics - An EAACI Position Paper", Allergy, 2020 und wurden auf die Situation im deutschen Gesundheitswesen angepasst. Laryngorhinootologie. 2020 Jun;99(6):356-364. German. doi: 10.1055/a-1164-9696.

152 Klimek L, Förster-Ruhrmann U, Becker S, et al. Stellungnahme zur Anwendung von Glukokortikosteroiden bei entzündlichen Erkrankungen der oberen Atemwege (u. a. allergische Rhinitis/chronische Rhinosinusitis) während der aktuellen COVID-19-Pandemie - Empfehlungen des Ärzteverbandes Deutscher Allergologen (AeDA), des Deutschen Berufsverbandes der HNO-Ärzte (BVHNO) und der AGs Klinische Immunologie, Allergologie und Umweltmedizin und Rhinologie und Rhinochirurgie der Deutschen Gesellschaft für HNO-Heilkunde, Kopf- und Halschirurgie (DGHNO-KHC) *Laryngorhinootologie.* 2020;99:280-281. doi: 10.1055/a-1148-3553

153 Bölke G, Church MK, Bergmann K-C. Comparison of extended intervals and dose reduction of omalizumab for asthma control. *Allergo J Int.* 2019;28:1-4. doi: 10.1007/s40629-018-0087-6.

154 Hamelmann E. Long-acting muscarinic antagonists for the treatment of asthma in children-a new kid in town. *Allergo J Int.* 2018;27:220-227. doi: 10.1007/s40629-018-0066-y.

155 Rothe T. A Century of "intrinsic asthma"-a view on the development of phenotyping in asthma in the last 100 years. *Allergo J Int.* 2018;27:215-219. doi: 10.1007/s40629-018-0051-5.

156 Bousquet J, Akdis C, Jutel M, et al. Intranasal corticosteroids in allergic rhinitis in COVID-19 infected patients: an ARIA-EAACI statement. *Allergy.* 2020 doi: 10.1111/all.14302.

157 Bousquet J, Jutel M, Akdis CA, et al. ARIA-EAACI statement on asthma and COVID-19. *Allergy.* 2020;76:689-697. doi: 10.1111/all.14471.

158 Nicolau DV, Bafadhel M. Inhaled corticosteroids in virus pandemics: a treatment for COVID-19? *Lancet Respir Med.* 2020;**8**:846-847.

159 Halpin DMG, Faner R, Sibila O, Badia JR, Agusti A. Do chronic respiratory diseases or their treatment affect the risk of SARS-CoV-2 infection? *Lancet Respir Med.* 2020;**8**:436-438.

160 Finney LJ, Glanville N, Farne H. Inhaled corticosteroids downregulate the SARS-CoV-2 receptor ACE2 in COPD through suppression of type I interferon. *J Allergy Clin Immunol.* 2021;**147**:510-519.e5.

161 Peters MC, Sajuthi S, Deford P. COVID-19-related genes in sputum cells in asthma. Relationship to demographic features and corticosteroids. *Am J Respir Crit Care Med.* 2020;**202**:83-90.

162 Hoffmann M, Kleine-Weber H, Schroeder S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell.* 2020;**181**:271-280.e8.

163 Matsuyama S, Kawase M, Nao N. The inhaled steroid ciclesonide blocks SARS-CoV-2 RNA replication by targeting the viral replication-transcription complex in cultured cells. *J Virol.* 2020;**95**:e01620-e01648.

164 Horby P, Lim WS, Emberson JR. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med.* 2021;**384**:693-704.

165 WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group. Sterne JAC, Murthy S. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA.* 2020;**324**:1330-1341

166 Welte T. SARS-CoV-2-triggered immune reaction: for COVID-19, nothing is as old as yesterday's knowledge. *Am J Respir Crit Care Med.* 2021;**203**:156.

167 Ramakrishnan S, Nicolau DV Jr, Langford B, Mahdi M, Jeffers H, Mwasuku C, Krassowska K, Fox R, Binnian I, Glover V, Bright S, Butler C, Cane JL, Halner A, Matthews PC, Donnelly LE, Simpson JL, Baker JR, Fadai NT, Peterson S, Bengtsson T, Barnes PJ, Russell REK, Bafadhel M. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. Lancet Respir Med. 2021 Jul;9(7):763-772. doi: 10.1016/S2213-2600(21)00160-0. Epub 2021 Apr 9. Erratum in: Lancet Respir Med. 2021 Jun;9(6):e55.

168 Yu LM, Bafadhel M, Dorward J, Hayward G, Saville BR, Gbinigie O, Van Hecke O, Ogburn E, Evans PH, Thomas NPB, Patel MG, Richards D, Berry N, Detry MA, Saunders C, Fitzgerald M, Harris V, Shanyinde M, de Lusignan S, Andersson MI, Barnes PJ, Russell REK, Nicolau DV Jr, Ramakrishnan S, Hobbs FDR, Butler CC; PRINCIPLE Trial Collaborative Group. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet. 2021 Sep 4;398(10303):843-855. doi: 10.1016/S0140-6736(21)01744-X.

169 Hermant P, Michiels T. Interferon-λ in the context of viral infections: production, response and therapeutic implications. *J Innate Immun.* 2014;6(5):563-74. doi:10.1159/000360084

170 Syedbasha M, Egli A. Interferon Lambda: Modulating Immunity in Infectious Diseases. *Front Immunol*. 2017;8:119. doi:10.3389/fimmu.2017.00119

171 Loutfy MR, Blatt LM, Siminovitch KA, et al. Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: a preliminary study. *JAMA*. Dec 2003;290(24):3222-8. doi:10.1001/jama.290.24.3222

172 Muir AJ, Arora S, Everson G, et al. A randomized phase 2b study of peginterferon lambda-1a for the treatment of chronic HCV infection. *J Hepatol*. Dec 2014;61(6):1238-46. doi:10.1016/j.jhep.2014.07.022

173 Chan HLY, Ahn SH, Chang TT, et al. Peginterferon lambda for the treatment of HBeAg-positive chronic hepatitis B: A randomized phase 2b study (LIRA-B). *J Hepatol*. May 2016;64(5):1011-1019. doi:10.1016/j.jhep.2015.12.018

174 Etzion O, Hamid S, Lurie Y, et al. End of study results from LIMT HDV study: 36% durable virologic response at 24 weeks post-treatment with pegylated interferon lambda monotherapy in patients with chronic hepatitis delta virus infection. presented at: International Liver Congress 2019; 2019; Vienna, Austria.

175 Crotta S, Davidson S, Mahlakoiv T, et al. Type I and type III interferons drive redundant amplification loops to induce a transcriptional signature in influenza-infected airway epithelia. *PLoS Pathog*. 2013;9(11):e1003773. doi:10.1371/journal.ppat.1003773

176 Davidson S, McCabe TM, Crotta S, et al. IFNλ is a potent anti-influenza therapeutic without the inflammatory side effects of IFNα treatment. *EMBO Mol Med*. 09 2016;8(9):1099-112. doi:10.15252/emmm.201606413

177 Mordstein M, Neugebauer E, Ditt V, et al. Lambda interferon renders epithelial cells of the respiratory and gastrointestinal tracts resistant to viral infections. *J Virol*. Jun 2010;84(11):5670-7. doi:10.1128/JVI.00272-10

178 Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut*. Mar 2020;doi:10.1136/gutjnl-2020-320926

179 Zhang W, Du RH, Li B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. *Emerg Microbes Infect*. 2020;9(1):386-389. doi:10.1080/22221751.2020.1729071

180 Feld JJ, Kandel C, Biondi MJ, et al. Peginterferon lambda for the treatment of outpatients with COVID-19: a phase 2, placebo-controlled randomised trial. Lancet Respir Med. 2021, May;9(5): 498-510. doi: 10.1016/S2213-2600(20)30566-X.

181 P J, Andrews J, Bonilla H, et al. Peginterferon Lambda-1a for treatment of outpatients with uncomplicated COVID-19: a randomized placebo-controlled trial. *MedRxiv*. 2020;

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

183 Investigator's brochure - Budesonide (Symbicort). Available at: https://www.fda.gov/media/103870/download and accessed on November 17, 2.021

184 Carpenter, A. et al. Pharmacological Inhibition of Acid Sphingomyelinase Prevents Uptake of SARS-CoV-2 by Epithelial Cells. *Cell Rep. Med.* 1*(*2020)100142

185 Senem Merve Fred, Suvi Kuivanen, Hasan Ugurlu, et al. Antidepressant and antipsychotic drugs reduce viral infection by SARS-CoV-2 and fluoxetine show antiviral activity against the novel variants *in vitro*. *bioRxiv* 2021.03.22.43637. doi.org/10.1101/2021.03.22.436379.

186 Melissa Zimniak, Luiza Kirshner, Helen Hilpert et al. The serotonin reuptake inhibitor Fluoxetine inhibits SARS-CoV-2 in human lung tissue. *Sci. Rep.* 11(2021)5890doi
.org/10.1038/s41598-021-85049-0

187 Eugene AR. Fluoxetine pharmacokinetics and tissue distribution suggest a possible role in reducing SARS-CoV-2 titers [version 1; peer review: 2 approved with reservations]. *F1000Research* 10(2021)477. doi.org/10.12688/f1000research.53275.1

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

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

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

191 Barrett B, Brown R, Mundt M, et al. The Wisconsin Upper Respiratory Symptom Survey is responsive, reliable, and valid. J Clin Epidemiol 2005;58:609-17. doi:10.1016/j.jclinepi.2004.11.019

192 Barrett B, Brown R, Mundt M, et al. Validation of a short form Wisconsin upper respiratory symptom survey (WURSS-21). Health Qual Life Outcomes 2009;7:76. doi:10.1186/1477-7525-7-76

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

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