Clinical Trial Protocol

COVID19_AMB_Brazil_2

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

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ADR	Adverse drug reaction
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
CEP	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
ZIP CODE	Research Ethics Committee
IWRS	Interactive Internet response system
EAG	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 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 trial component 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	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 fluvoxamine, ivermectin, doxazosin, interferon pegylated beta 1A, and interferon pegylated lambda on reducing hospitalization in patients with mild COVID-19 and high risk for complications**
Short Title:	Repositioning of available and in-development medications for outpatient treatment of patients with COVI-19 and mild symptoms.
Product under Investigation:	Fluvoxamine, Ivermectin, Doxazosin, Interferon pegylated beta 1A, Interferon pegylated lambda
Indication:	COVID-19 Infection in Outpatients
Phase:	PHASE III - New indication
Sponsor	CARDRESEARCH - Cardiology Care and Research LTDA
Study code	COVID19_AMB_2
Coordinating Researchers:	Gilmar Reis, Eduardo Augusto dos Santos Moreira Silva, Daniela Carla Medeiros Silva, Edward J Mills, Lehana Thabane, Gordon H Guyatt
Proposing Institutions:	Cardresearch - Cardiology Care and Research LTDA
Researchers / Collaborating Institutions	Ed. J Mills PhD Lehana Thabane PhD Gordon H Guyatt MD McMaster University, Hamilton, Canada
Objectives:	Primary Objective(s) • To evaluate the effect of fluvoxamine, ivermectin doxazosin, pegylated interferon beta 1A and pegylated interferon lambda in reducing the need for urgent care AND observation for longer than 06h due to worsening COVID-19; • To evaluate the effect of fluvoxamine, ivermectin doxazosin, interferon pegylated beta 1A and interferon pegylated lambda in reducing the need for Hospitalization due to COVID-19 related complications Co-primary Objective: To evaluate the effect of Fluvoxamine, Ivermectin, Doxazosin, Interferon Pegylated Beta 1A and Interferon Pegylated Lambda in reducing mortality associated with COVID-19 up to 28 days from randomization. Secondary objective(s) • To evaluate, in comparison with placebo, the effect of fluvoxamine, ivermectin and doxazosin, pegylated interferon beta 1A and pegylated interferon lambda on the following parameters: o Reduction in viral load after randomization (D_3 and D_7) (injectable medication arm only, first 400 patients); o Time to clinical improvement (up to 28 days from randomization), defined as greater than 50% improvement in reference to symptoms at the time of randomization; o 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. o Number of days with respiratory symptoms after randomization; o Number of days in Intensive Care Center o Number of days on invasive mechanical ventilation

	○ Number of days of hospitalization ○ Serious adverse events after randomization; ○ 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 (randomization up to 28 days). ○ Adverse reactions associated with the proposed treatment regimens
Design:	Multicenter, double-blind, adaptive, prospective, randomized, parallel-group, placebo-controlled, 8-week follow-up after randomization.
Treatment:	**Table 1 - Study treatment regimen**

	Treatment Scheme				
Visit Clinic	**Fluvoxamine**	**Ivermectin**	**Doxazosin**	**Pegylated interferon beta 1A**	**lambda pegylated interferon**
$_{0}$. DRand.	**100 mg**	**See Table 2**	**See Table and 34**	**125µg SC dose (single dose)**	**180µg SC dose (single dose)**
D_1 to D_2	**100 mg BID**	**See Table 2**	**See Table and 34**	**No medication**	**No medication**
D_3	**100 mg BID**	**See Table 2**	**See Table and 34**	**No medication**	**No medication**
D_4 to D_9	**100 mg BID**	**No medication**	**See Table and 34**	**No medication**	**No medication**
D_{10} to D_{13}	**No medication**	**No medication**	**See Table and 34**	**No medication**	**No medication**

SC - subcutaneous injection

Table 2 - Dosage Ivermectin

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

Tabela 2 – Posologia considerando comprimidos de ivermectina 06 mg

Treatment (continued):

Table 3- Doxazosin dosage if BP < 120 mmHg at baseline visit

Doxazosin*	Drug	Dose	Total daily dose
Day 1-2	**Doxazosin 2 mg**	0,5 tablet	1 mg
Day 3-4	**Doxazosin 2 mg**	1 tablet	2 mg
Day 5-7	**Doxazosin 2 mg**	2 tablets	4 mg
Day 8-10	**Doxazosin 2 mg**	3 pills	6 mg
Day 11-14	**Doxazosin 2 mg**	4 pills	8 mg

Table 4- Doxazosin dosage if BP > 120 mmHg at baseline visit

Doxazosin*	Drug	Dose	Total daily dose
Day 1-2	**Doxazosin 2 mg**	1 tablet	2 mg
Day 3-4	**Doxazosin 2 mg**	2 pill	4 mg
Day 5-7	**Doxazosin 2 mg**	3 pills	6 mg
Day 8-14	**Doxazosin 2 mg**	4 pills	8 mg

For each active treatment arm with oral medication, there will be a placebo control arm with bottles containing an equal number of tablets. For the injectable medication treatment arms, there will be a placebo control arm of subcutaneous injection of 0.9% saline.

Considering results from previous studies of the effects of medications in reducing viral load and in current studies in patients with COVID-19, where there are indications of benefits (non-randomized studies, or open randomized or randomized and not placebo-controlled) and the current situation of the virtual absence of effective treatment associated, The placebo arm will be re-evaluated through an interim blinded analysis, by a committee independent from the research, which will be performed when we reach 25, 50, and 75% of the initially projected sample of participants. On the recommendation of the Data Safety Review Committee, a specific interim analysis for the proposed subcutaneous medication arms is planned when there are 120 patients randomized and adequately followed up for at least 14 days, in order to assess the safety and adverse events (interferon pegylated beta 1A and interferon pegylated lambda). This analysis will also evaluate the primary clinical outcomes and adverse event data obtained in the oral treatment arms in patients randomized and followed up for at least 14 days (fluvoxamine, ivermectin and doxazosin). With the proposed addition of the interferon pegylated beta 1A and interferon pegylated lambda arms, the interim analyses that will occur after this safety analysis will include analysis of the primary study endpoints.

	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) Ivermectin; (3) Doxazosin (4) Pegylated Interferon beta 1A; (5) Pegylated Interferon lambda and (6)Placebo, with doses as provided in the clinical protocol (table 1). 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 research arms until D_{14}. All patients will undergo a rapid test for confirmation of COVID-19 at the time of screening. The viral load will be evaluated in 400 patients randomized to receive subcutaneous injectable medication through nasopharyngeal/oral samples, which will be collected immediately before randomization on D_3 and D_7 for RT-PCR.
Inclusion Criteria Inclusion Criteria (Continued)	1. Patients over 18 years of age with the capacity to provide informed consent 2. Patients seen at a Primary Care Unit of the Brazilian National Health System (SUS) or patients seen at SUS or supplementary care units with an acute clinical picture compatible with COVID 19 and symptoms beginning within 7 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
Exclusion Criteria:	1. negative diagnostic test for SARS-CoV2 associated with acute influenza symptoms (patient with a negative test taken early and becomes positive a few days later is eligible, provided he/she is < 07 days from the onset of influenza symptoms); 2. Patients with an acute respiratory condition compatible with COVID-19 seen in the primary care network and with a decision to hospitalize; 3. Patients with an acute respiratory condition due to other causes; 4. Patients who received the first dose of the SARS-CoV-2 vaccine more than 14 days from the screening date. 5. Dyspnea secondary to other acute and chronic respiratory causes or infections (e.g., decompensated COPD, acute bronchitis, pneumonia, primary pulmonary arterial hypertension); 6. Patients requiring hospitalization due to COVID-19 7. Patients taking serotonin reuptake inhibitors (Donepezil, Sertraline); 8. Exclusion criteria valid only for the oral medication administration arms: a. Continued use of monoamine oxidase inhibitors (MAOI): Phenelzine, Tranylcypromine, Selegiline, Isocarboxazid, moclobemide; b. Use of Antiretroviral Agents (Treatment of Acquired Immune Deficiency Syndrome - AIDS) c. use of alpha-1 adrenergic receptor antagonists, combined alpha-1/beta adrenergic receptor antagonists, sotalol, clonidine, phosphodiesterase type 5 inhibitors, nitrates, asenapine, alpha-methyldopa d. history of hypersensitivity or serious adverse reactions to the use of quinazolines (Prazosin, Doxazosin or Terazosin); 9. Patients with severe psychiatric disorders - schizophrenia, uncontrolled bipolar disorder, major depression with suicidal ideation. 10. Pregnant or nursing patients; 11. History of severe ventricular cardiac arrhythmia (ventricular tachycardia, recovered ventricular fibrillation patients) or Long QT Syndrome; 12. Known history of orthostatic hypotension, unexplained history of syncope, postural orthostatic tachycardia syndrome (POTS), neurally mediated hypotension (within the past year), heart failure (NYHA III or IV), myocardial infarction (within months3 of screening), stable or unstable angina, coronary bypass surgery (within months3 of screening), stroke (within months3 of screening), symptomatic carotid disease, or moderate to severe mitral or aortic stenosis; 13. Surgical or contrast use planned to occur during treatment or within 5 days of the last dose of study medication;

Criteria for Exclusion (cont...)	14. Current daily and/or uncontrolled alcoholism, which in the view of the investigator could compromise participation in the study; 15. History of seizures in the last month or an uncontrolled seizure condition; 16. Clinical history of moderate to severe liver impairment or cirrhosis of the liver with a Child-Pugh C classification; 17. Patients with known severe degenerative neurological diseases and/or severe mental illness; 18. Inability of the patient or representative to give consent or adhere to the procedures proposed in the protocol; 19. Any medical conditions, including psychiatric conditions, which in the investigator's view would preclude the use of the investigational medicinal products 20. Hypersensitivity and/or known intolerance to Fluvoxamine, Doxazosin, Ivermectin, Pegylated Interferon beta 1A or Pegylated Interferon Lambda 21. Inability to take oral medications;
Primary and Secondary Outcomes:	<u>Primary endpoint:</u> o To evaluate the effect of fluvoxamine, doxazosin interferon beta 1A, interferon lambda in reducing the need for urgent care associated with observation for longer than 06h due to worsening COVID-19; o To evaluate the effect of fluvoxamine, ivermectin and doxazosin, interferon beta 1A, interferon lambda in reducing the need for Hospitalization due to complications and/or worsening of COVID-19. <u>Co-primary Outcome:</u> To evaluate the effect of Fluvoxamine, Ivermectin and Doxazosin, Pegylated Interferon beta 1A and Pegylated Interferon lambda in reducing mortality associated with COVID-19 up to 28 days from randomization. <u>Secondary outcomes:</u> The secondary endpoints will assess, relative to the placebo group: o Viral load change at randomization, Day 03 and Day 07 after randomization (only for 400 patients who will receive investigational medical product subcutaneously); o Time to clinical improvement (within 28 days of randomization), defined as greater than 50% improvement in reference to symptoms at the time of randomization (WHO 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 Number of days with respiratory symptoms since randomization o Hospitalization for any cause o Hospitalization due to progression of COVID-19

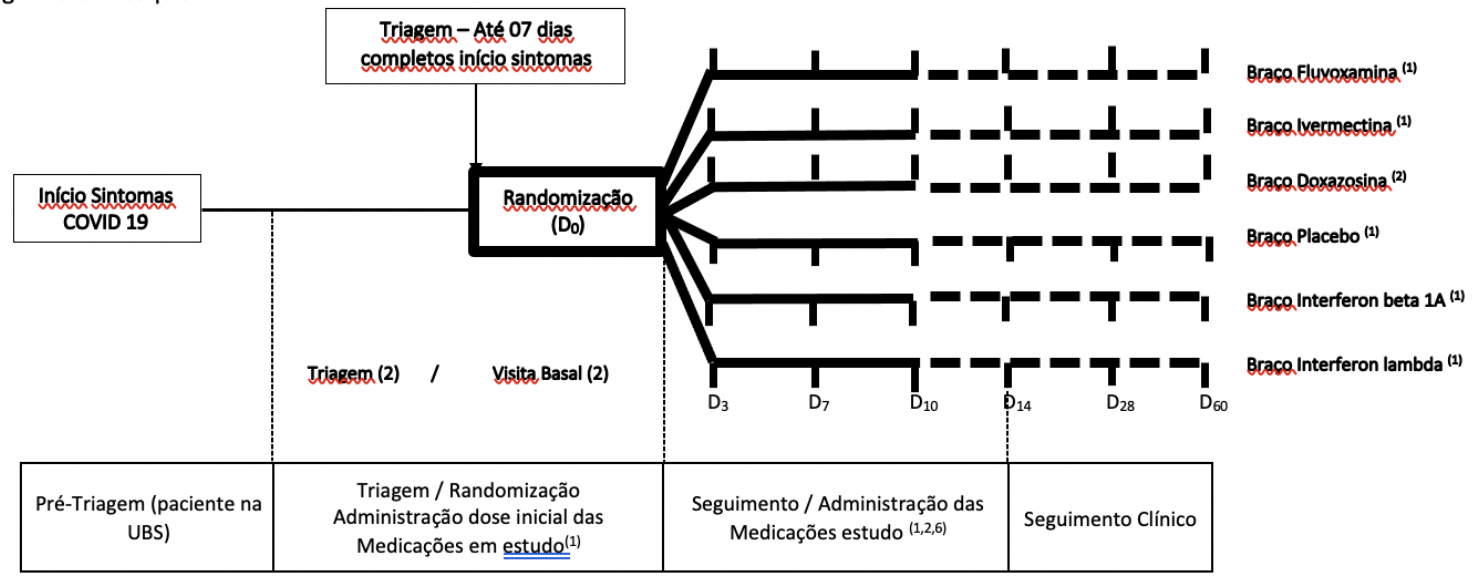
Primary and Secondary Outcomes:	○ Mortality due to pulmonary complications ○ Cardiovascular mortality ○ Mortality from any cause ○ Adverse events (up to 28 days); ○ COVID-19 symptom scale assessment (D_1 to D_{28}) ○ WHO Clinical Worsening Scale Assessment (D_1 to D_{10}) ○ Assessment of the PROMIS Global Health Scale ("Global-10") days 14 and after28 randomization. ○ TICSM scale assessment on day 28 after randomization. ○ Mortality rate of patients by day 14 and 28 after randomization; ○ Proportion of non-adherent patients with the product under investigation; ○ Specific adverse reactions to the study medications: fluvoxamine, doxazosin, pegylated interferon beta 1A and pegylated interferon lambda.
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 or patients seen in supplementary medicine emergency care units with clinical criteria for presumptive diagnosis of COVID-19, without fulfilling hospitalization indication criteria, will be invited to participate in this research. • obtaining the informed consent form (ICF) for potentially eligible subjects prior to any procedures related to this protocol. • checking the inclusion/exclusion criteria • 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> • 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 nos (to be performed on 400 initial patients allocated to receive investigational medical product subcutaneously); • urinary pregnancy test for women with at least one menstrual period in the last 12 months; • checking the inclusion/exclusion criteria • randomization in the IWRS system. • completion of the WHO acute influenza syndrome questionnaire • completion of the PROMIS-10 questionnaire • digital oximetry measurement. • blood pressure measurement
Procedures (continued)	

Procedures (continued)	• randomization and delivery of the investigational drug as allocated by IWRS. All patients will receive the standard treatment for COVID-19 as adopted by the health units to which they are linked, as defined by the local medical team. All patients will also receive 24-hour telephone contact, to be activated in case of need and will be instructed about the telephone contact as provided in the protocol, which will be carried out by the research team until D_{60}. Patients allocated to subcutaneous medication will have to self-collect nasal swab and/or saliva for RT-PCR at randomization, D_3, and D_7 treatment (only in the initial 400 patients). Patients will receive home visits for in-person evaluation at D_7 and D_{14}. During these visits, the samples and research materials will eventually be collected <u>Evaluations after randomization (fluvoxamine, ivermectin and corresponding placebo arm)</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 and following the guidelines of health authorities regarding recommendations for confinement and distancing from cases. • Daily telephone contact assessments: between D_1 and D_{07}, 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_{10} De D_{14} - telephone/video call contact for evaluation of the evolution of the clinical picture and verification of outcomes. • Evaluation of D_{28} - telephone/video call contact for evaluation of the evolution of the clinical picture and verification of in-person outcomes. Possible persistence of symptoms that appeared at the time of COVID-19 diagnosis will be evaluated. • Evaluation of the D_{60}- telephone/video call to evaluate the evolution of the clinical picture and verify the persistence of symptoms after 28 days. Possible late complications related to COVID-19 will also be evaluated. <u>Evaluations after randomization (doxazosin and doxazosin placebo arm)</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 and following the guidelines of health authorities regarding recommendations for confinement and distancing from cases. • Daily telephone contact assessments: Between D_1 and D_{14}, the patient will be monitored daily by telephone and/or video calls, which will preferably be made BEFORE taking daily medication. The patient's blood pressure will be checked by an automated blood pressure monitor provided to the patient, and the release of the doxazosin/ doxazosin placebo dose will follow a specific flow based on the patient's blood pressure and symptoms. The WHO Flu Syndrome Symptom Questionnaire will be administered. Further telephone contacts are planned according to the study flow chart. • Assessment of D_{14} - telephone contact/video call to assess the evolution of the clinical picture and verify outcomes. • Evaluation of D_{28} - telephone/video call contact for evaluation of the evolution of the clinical picture and verification of in-person outcomes. Possible persistence of symptoms that appeared at the time of COVID-19 diagnosis will be evaluated. • Evaluation of the D_{60}- telephone/video call to evaluate the evolution of the clinical picture and verify the persistence of symptoms after 28 days. Possible late complications related to COVID-19 will also be evaluated.

	Evaluations after randomization (subcutaneously administered medication arm: pegylated interferon beta 1A, pegylated interferon lambda, and interferon placebo) • Patient evaluations will be done by telephone, social media applications, video calls or telemedicine. There is a forecast of in-person visits on D-Day $_7$and D-Day$_{14}$, preferably home visits due to the fact that the virus is highly transmissible and following the guidelines of the health authorities regarding recommendations for confinement and distancing from cases. • Daily telephone contact assessments: between D $_1$and D_{14}, the patient will be monitored daily via telephone contact and/or video calls in order to identify adverse events, adverse reactions potentially related to interferon use and clinical assessment of symptoms and evolution of COVID-19. The WHO Flu Syndrome Symptom Questionnaire will be administered. Other telephone contacts may be made to assess subject safety or on-demand. • Assessment of D_{14} - telephone contact/video call to assess the evolution of the clinical picture and verify outcomes. • Evaluation of D_{28} - telephone/video call contact for evaluation of the evolution of the clinical picture and verification of in-person outcomes. Possible persistence of symptoms that appeared at the time of COVID-19 diagnosis will be evaluated. • Evaluation of the D $_{60}$- telephone/video call to evaluate the evolution of the clinical picture and verify the persistence of symptoms after 28 days. Possible late complications related to COVID-19 will also be evaluated. Research Monitoring Committee The research has a research adjudication committee that is responsible for ensuring that the source documents supporting the event 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, which has already conducted two interim reviews. This committee has a pre-defined plan for statistical data analysis and approved research safety analysis. The analyses follow the Good Clinical Practice and are conducted in a blinded manner, with the possible breaking of the blind with respect to the research arms if the pre-specified criteria for this are met (see committee composition in the document attached to the regulatory file). A research steering committee is in place 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 researchers 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 file). The endpoint monitoring committee will reassess identified clinical endpoints and ensure that they indeed fall within the intended endpoints of the trial, using predefined event classification criteria.
Sample Size	It is planned to randomize a total of patients3.645, considering 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 planned sample. Critical adjustments involve (a) withdrawing the placebo arm if there is great benefit from the others and (b) withdrawing any arm that does not show benefit or meets futility criteria, and (c) adding a new medication arm. 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-way alpha of 0.05 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 is reevaluated in the next interim analysis. As of May 20, 2020, the research protocol has recorded the randomization of 1602 patients. With the proposed introduction of two new arms of the trial, an additional 921 patients will need to be added in order for the current arms to reach the target of 681 participants per group. Thus the new sample of patients for the entire study, taking into account since the beginning of the clinical trial, will be increased to 3,645 patients. As planned, the Independent Data and Security Review Committee met recently and after blindly reviewing the data recommended: (1) maintaining the progress of the study as planned, without changes; the conduct of an interim safety analysis when 120 patients are included in the investigational product subcutaneous administration arms. This analysis will be restricted to evaluating adverse reactions potentially associated with the investigational products used and adverse events. (2) Evaluate possible outcomes in current arms of the study according to the statistical analysis plan; (3) Initially hold the next interim analysis as planned (50% of patients randomized and with complete D_{14})
Statistical Methods (cont.)	The protocol design will be adaptive, with provision for blinded interim analyses comprising 25, 50 and 75% of the initially projected sample of participants. The sample size will be revised based on the outcomes that occurred in the placebo group at the time of the interim analyses. Blinded outcome analysis will be performed with simulations to limit type I errors within the 5% tolerance range (97.5% or greater probability of superiority over the control group). Decisions may be made at this point to terminate arms of the study if there are not acceptable projections of benefit over futility.

Fluxograma da Pesquisa:



1. Tratamento: Fluvoxamina, Doxazosina, Interferon Pegilado Beta 1A e Interferon Pegilado Lambda em grupos paralelos pelo período planejado. Posologia das medicações varia conforme a alocação do paciente em um braço do estudo (Fluvoxamina: 10 dias; Ivermectina: 03 dias; Interferon pegilado beta 1A: dose única; interferon pegilado lambda: dose única. Para cada braço há o correspondente placebo, inclusive ajustado pelo pelo (braço ivermectina). Medicações serão interrompidas a qualquer momento se houver evidência de reação adversa ou a critério do sujeito da pesquisa.
2. Doxazosina com titulação crescente, a partir de 01 ou 2 mg até 08 mg/ dia. Dose pode ser reduzida em caso de sintomas clínicos e/ou níveis de pressão arterial conforme programa de medição da mesma durante a administração do medicamento.
3. Triagem e Randomização devem ser realizadas na mesma visita. Assegurar que o paciente seja randomizado por ocasião do atendimento.
4. As visitas subsequentes: D_3, D_7, D_{10}, D_{14}, D_{28}, D_{60} serão realizadas através de contato telefônico, entretanto com possibilidade de visitas presenciais em D_7 e D_{14}. Em qualquer momento visitas extras de segurança poderão ser realizadas. As visitas D_{14} e D_{28} são consideradas visitas de desfecho para a pesquisa. 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 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.
5. Contato diário por telefone (assinaladas acima) serão realizadas entre os Dias 1 a 7 de tratamento. 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.
6. Nos braços Doxazosina e de medicações administradas por via subcutânea o contato telefônico será realizado diariamente até o D_{14}.

Table 5. Procedure flowchart: fluvoxamine, ivermectin, pegylated interferon beta 1A, pegylated interferon lambda and corresponding placebo arm

FLOWCHART		STUDY VISIT SCHEDULE (Fluvoxamine, Ivermectin and corresponding placebo arm)						
	V1Triage (1)	V2Basal/ Randomization(2)	V3 Day	V4 Day 7	V5 Day 10	V6 Day 14	V7 Day 28	V8 Day 60 (EoS or Early Termination
			V3+1(3) day	V4+1(3) day	V5 ± 2 days	V6 (3) ±2 days	V7(3) ± 3 days	V8 ± 5 days
Free and Informed Consent	X							
Revision of Eligibility Criteria	X	X						
Demography	X							
Medical History		X						
Physical Exam		X						
Weight		X						
Height		X						
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)		
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	X13
TICSM Scale - memory assessment							X	
Rapid Test for SARS-CoV2	X(1)							
Patient ID Card / Phone Contact		X						

Table 6. Flow chart of procedures: doxazosin arm and corresponding placebo arm

FLOWCHART		STUDY VISIT SCHEDULE (Doxazosin or doxazosin placebo)				
	V1Triage [1]	V2Basal/ Randomization[2]	V3 to V15 Day 1 to 13	V16 Day 14	V17 Day 28	V18 Day 60 (EoS or Early Termination
			V3 - V15+1 [3] day	V16 [3] ± 2 days	V17[3] ± 3 days	V18 ± 5 days
Free and Informed Consent	X					
Revision of Eligibility Criteria	X	X				
Demography	X					
Medical History		X				
Physical Exam		X				
Weight		X				
Height		X				
ECG (QT measurement)		X				
Oximetry		X				
Blood Pressure Measurement		X	X	X		
Pregnancy Test	X[4]					
Adverse Events		X[5]	X	X	X	X
Previous concomitant medications		X	X			
WHO Clinical Worsening Scale	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]			
Verification of clinical outcomes		X[12]	X	X	X	X[13]
TICSM Scale - memory assessment						X
Rapid Test for SARS-CoV2	X[1]					
Patient ID Card/Telephone 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 of randomization (immediately after randomizing)
11 Maintain the administration of the product under investigation as scheduled. Discontinue it if adverse events prevent the continuation of the medication.
12 As soon as I start the product under investigation.
13 Evaluation of late complications associated with COVID-19.
14 The Patient will have their blood pressure checked on a device to be provided (automated blood pressure measuring device) BEFORE taking the medications: doxazosin or doxazosin placebo).

1 INTRODUCTION

1.1 Background

In December 2019, a series of cases of unknown etiology and with symptoms similar to 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, and 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[9,10,11] professionals.

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

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

1.3 Clinical Manifestations and Risk Profile

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

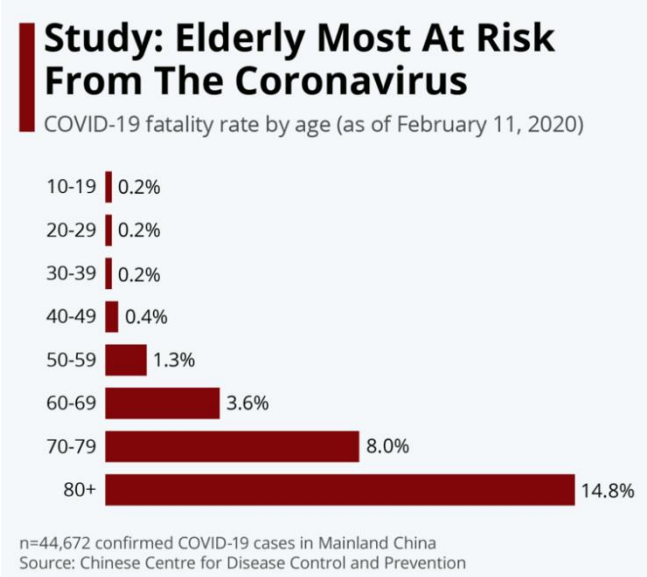


Figure 1 - Age-adjusted mortality rate

Mortality is also high in some disease strata, as initially suggested by early epidemiological studies 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].

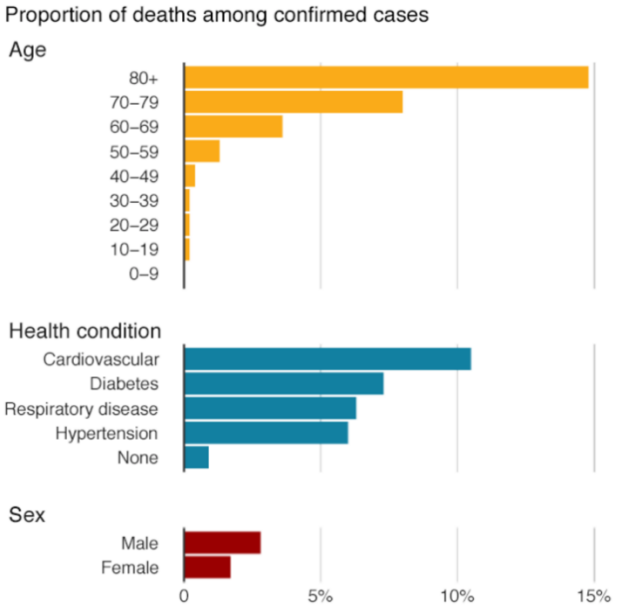


Figure 2 - Global Mortality by Age Group - COVID-19

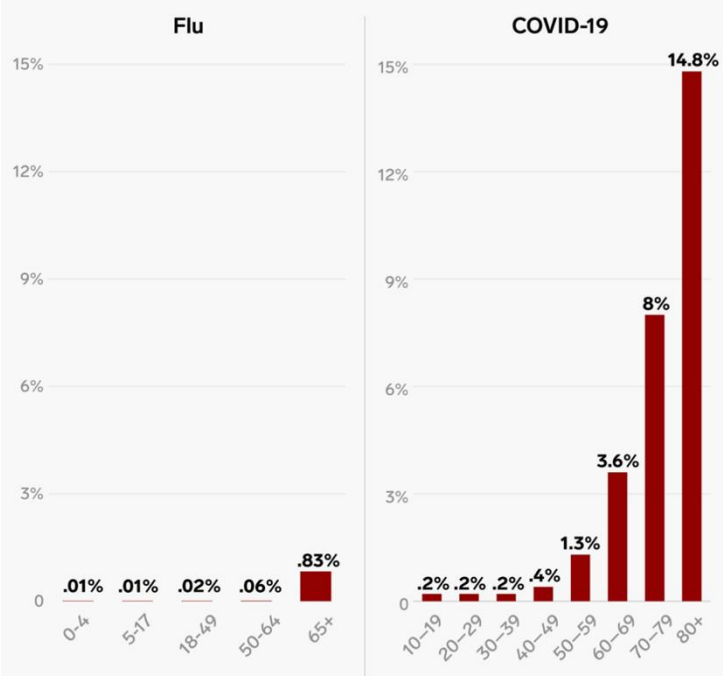


Figure 3 - Influenza and COVID-19 mortality

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[17] response. 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[18,19] coronavirus infections. 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 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[49,50,51,52] cell therapy.

In 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[55,56,57,58] reactivation or co-infection. 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-19[59,60,61] patient. In fact, the use of glucocorticoids in SARS and MERS was associated with delayed viral clearance and did not reduce mortality57-59.

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[62,63] pandemic. 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[64] therapies. 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 a 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[77] disease. 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 using Fluvoxamine, Ivermectin, Doxazosin, Pegylated Interferon Beta 1A, and Interferon Lambda 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 06 treatment arms (including placebo): (1) Fluvoxamine; (2) Ivermectin; (3) Doxazosin (4) Placebo, (5) Pegylated Interferon beta 1A and (6) Pegylated Interferon Lambda.

The research subject's participation in the protocol is for 60 days, with the first 14 days being the treatment phase and the remaining period for follow-up after the end of treatment.

2.1 Objectives/primary endpoint

- Reducing the need for emergency department visits due to clinical worsening of COVID-19 and keeping the participant under observation for > 06hours in acutely affected patients with evidence of high risk for complications 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 Fluvoxamine, Ivermectin, Doxazosin, Pegylated Interferon Beta 1A and Interferon Lambda 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 placebo, the effect of fluvoxamine, ivermectin, doxazosin, pegylated interferon beta and pegylated interferon gamma on the following parameters:

- Reduction in viral load after randomization (D_3 and D_7) (only arm injectable medications, 400 initial patients);
- Number of days with respiratory symptoms since randomization
- Serious adverse events after randomization;
- 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 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

3 INVESTIGATIONAL PLAN

3.1 Study design

This is a multicenter, adaptive, double-blind, randomized, placebo-controlled study to evaluate the effect of fluvoxamine, ivermectin, doxazosin, pegylated interferon beta 1A and pegylated interferon lambda in reducing hospitalization of patients with mild COVID-19 and high risk for complications.

The groups will be as follows:

1. Placebo
2. Fluvoxamine
3. Ivermectin
4. Doxazosin
5. Pegylated interferon beta 1A
6. Lambda interferon

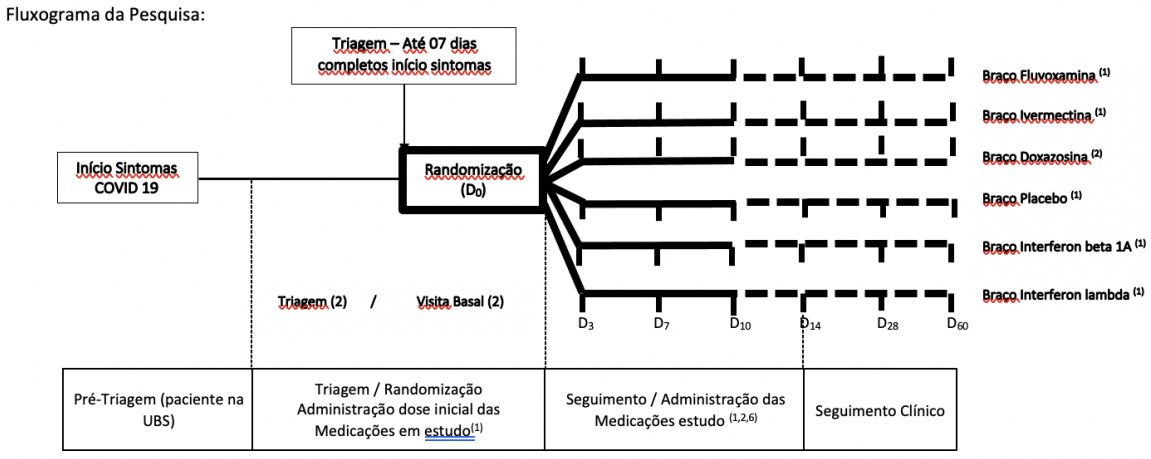
Patients will be randomized to one of the 4 study arms via an iterative automatic centralized randomization system (IVRS or IWRS). The protocol provides for an adaptive phase to accommodate any pre-specified modification needs.

The protocol is designed to reach 681 patients in each of the 5 above groups in a 1:1:1:1 randomization ratio (total: 2,724 patients). Considering from the start of the clinical trial and the withdrawals of one treatment arm (Metformin and Ivermectin), additional randomization of 921 patients will be required to reach the expected number of 681 patients in the current arms of the trial and the two proposed in this amendment, which will provide a total of 3,645 patients at the end of the trial as currently planned.

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 an 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.



1. Tratamento: Fluvoxamina, Doxazosina, Interferon Pegilado Beta 1A e Interferon Pegilado Lambda em grupos paralelos pelo período planejado. Posologia das medicações varia conforme a alocação do paciente em um braço do estudo (Fluvoxamina: 10 dias; Ivermectina: 03 dias; Interferon pegilado beta 1A: dose única; interferon pegilado lambda: dose única. Para cada braço há o correspondente placebo, inclusive ajustado pelo pelo (braço ivermectina). Medicações serão interrompidas a qualquer momento se houver evidência de reação adversa ou a critério do sujeito da pesquisa.
2. Doxazosina com titulação crescente, a partir de 01 ou 2 mg até 08 mg/ dia. Dose pode ser reduzida em caso de sintomas clínicos e/ou níveis de pressão arterial conforme programa de medição da mesma durante a administração do medicamento.
3. Triagem e Randomização devem ser realizadas na mesma visita. Assegurar que o paciente seja randomizado por ocasião do atendimento.
4. As visitas subsequentes: D_3, D_7, D_{10}, D_{14}, D_{28}, D_{60} serão realizadas através de contato telefônico, entretanto com possibilidade de visitas presenciais em D_7 e D_{14}. Em qualquer momento visitas extras de segurança poderão ser realizadas. As visitas D_{14} e D_{28} são consideradas visitas de desfecho para a pesquisa. 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 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.
5. Contato diário por telefone (assinaladas acima) serão realizadas entre os Dias 1 a 7 de tratamento. 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.
6. Nos braços Doxazosina e de medicações administradas por via subcutânea o contato telefônico será realizado diariamente até o D_{14}.

Figure 4- Flow chart of the research

3.2 Justification of the study design

The Study Steering Committee for COVID19_MG_AMB_2 has reviewed current literature data on the potential efficacy treatments of the drugs proposed in this trial. The

proposed medications were listed based on the current literature on treatments in outpatient, symptomatic COVID-19, as well as preclinical studies with robust data on the potential of the study medications and justification for their adoption in a clinical trial.

3.3 Rationale for the use of fluvoxamine

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) and an SR receptor$_1$ agonist[78]. 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 $_1$SR - IRE.

$_1$SR 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[79]. 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[80] production. These anti-inflammatory effects may be the most likely explanation for the beneficial effects of fluvoxamine. In COVID-19, an excessive inflammatory process, known as a "cytokine storm", can contribute to 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[81]. 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."[82,83] 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[84,85] pathway. Additional Nsp6 has been shown to physically associate with$_1$ SR[86]. 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[87] 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[88,89].

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[90]. In the case of COVID-19, this may increase the effects of the treatment on the airway[91] epithelium. 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[92,93] nutrient-sensing pathway.

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[94,95,96]. SR agonists$_1$ (such as fluvoxamine) regulate ER-associated stress. SR ligand$_1$ effects during ER-mediated stress and other ER functions may reduce the organ dysfunction/damage [97,98].

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[99,100].

3.3.5 Elevation of melatonin levels in the body.

The SARS-CoV2 virus can activate the NLRP343 inflammasome, which may contribute to the cytokine[101,102] storm. Melatonin may act on this NLRP3 pathway to reduce inflammation[103,104]. Fluvoxamine inhibits melatonin metabolism, so it may increase the level of melatonin in the body, which may be beneficial in COVID-19[105].

3.4 Rationale for the use of Ivermectin

In vitro studies have shown that ivermectin inhibits the replication of many viruses, including influenza, zika, dengue and others. It has also been seen to inhibit the replication of SARS-CoV2 in infected cell cultures, leading to the absence of almost all viral material within 48h. In addition to these, in several animal models, when infected with SARS-CoV2 or similar coronaviruses, the use of ivermectin in several preclinical and clinical studies resulted in a significant drop in viral load and blocked several inflammatory pathways associated with proteolysis, cell lysis, and consequent reduction of organ[106,107,108,109,110,111,112,113,114] damage.

Similarly, several *in vivo* studies with animal models using ivermectin resulted in activation of several anti-inflammatory pathways, potentiating these mechanisms by inhibiting both several cytokines associated with inflammatory activation as well as transcription of nuclear factor-κB (NF-κB), a factor involved in uncontrolled[115,116,117] inflammatory response.

Some observational studies and open randomized trials with small numbers of patients using ivermectin in patients with COVID-19 suggest that (1) ivermectin prevents transmission and development of COVID-19 disease in healthy persons exposed to infected[118,119,120,121] patients; (2) accelerates clinical recovery, minimizing the progression to complications in patients with mild to moderate clinical picture if treated soon after symptoms[122,123,124]; (3) accelerates recovery and avoids ICU admission and death in hospitalized[125,126,127,128] patients, and in regions where its use has been widespread, it (4) indicates a possible reduction in mortality, however, these studies have not adjusted for covariates nor have they performed a sample size calculation to support the conclusions obtained.[129,130].

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

For an updated rationale on ivermectin, a summary document on the main pharmacokinetic, pharmacodynamic, safety and preclinical data concerning the use of this drug in several mRNA viruses and initial data on clinical trials in COVID-19 was added to the previous amendment (see document 17_IVERMECTIN_REVIEW_SUMMARY_FARMACOLOGY_FARMACOKINETICS_CLINICAL_REVIEWS_DOC).

3.5 Rationale for the use of Doxazosin

Recently it has been shown that the cytokine release syndrome is often seen in bacterial infections, CAR-T cells and other T-cell activation therapies are accompanied by a surge in catecholamine release[131]. Catecholamines enhance inflammatory injury by increasing the production of IL-6 and other cytokines through a self-amplifying feed-forward loop in immune cells (macrophages and T-cells) that requires alpha-1 adrenergic receptor signaling[131]. Other

studies have shown in animal models that catecholamine production from immune cells increases downstream cytokine production and increases inflammatory lung injury while blocking catecholamine signaling decreases lung inflammation [132,133]. Prophylactic inhibition of catecholamine synthesis by treatment with metyrosine, a tyrosine hydroxylase antagonist, reduces catecholamine levels and cytokine responses and results in a marked increase in survival after various inflammatory stimuli in mice63. Similar protection against a hyperinflammatory stimulus was observed following prazosin[131]demonstrating that alpha-1 adrenergic receptor antagonism can also prevent cytokine storm in mice.

Additional studies have explored the effects of alpha-adrenergic blockade in preventing or protecting inflammatory cascades and cytokine-induced injury. In models of pulmonary edema that are characterized by inflammation and neutrophil accumulation, adrenergic blockade with phentolamine or prazosin attenuated the increase in proinflammatory cytokines in the lung and peripheral blood and resulted in the restoration of normal fluid transport capacity of the alveolar epithelium after hemorrhagic[134,135] shock. In a brain stem encephalitis model, early blockade of the alpha-1 adrenergic receptor allowed the preservation of cardiac output, reversal of neutrophil infiltration into the lungs, and prevention of hemorrhagic[136,137] pulmonary edema. Prazosin was also found to suppress the clinical and histological expression of experimental autoimmune encephalomyelitis in preclinical[138,139,140] models.

In a mouse model of ischemia-reperfusion injury, prazosin administration led to decreased expression levels of IL-6, TNF-α, IL-10 and IL-1, and prevented mortality[141]. In humans, prazosin is a first-line treatment for scorpion poisoning, a process that involves dysregulated inflammatory responses that can progress to ARDS[142]. Alpha-1 adrenergic receptor expression is increased during sepsis[143], and catecholamine levels are elevated in septic[144] shock. Finally, alpha-1 adrenergic receptor antagonism has been shown to block cytokine production in human peripheral blood mononuclear cells from patients with juvenile polyarticular arthritis, and doxazosin treatment abrogated any catecholamine-induced[145] IL-6 secretion.

Together, these findings provide a rationale for studying alpha-1 adrenergic receptor antagonists such as doxazosin or prazosin in the prophylaxis of patients with COVID-19. Prospective, randomized clinical trials of alpha-1 adrenergic receptor antagonists administered

before the onset of severe symptoms, as proposed here, are needed to evaluate their utility in preventing cytokine release syndrome and reducing morbidity and mortality in patients with COVID-19[20]. Prazosin has a significantly shorter half-life than doxazosin mesylate (2-3 hours versus 22 hours, respectively)[146,147]. As such, doxazosin mesylate may facilitate dosing in the outpatient setting, increase compliance, and thus reduce subtherapeutic[148] episodes. While we have used prazosin in preclinical cytokine storm models, doxazosin - like prazosin - inhibits all three alpha-1 adrenergic[149] receptor subtypes. Because doxazosin does not inhibit alpha-2 adrenergic receptors (which do not mediate the desired immunomodulatory effects) and binds all three alpha-1 adrenergic receptors as a pure antagonist (and not as a reverse agonist)[131] . The use of doxazosin may have an even more favorable safety profile.[150] This is supported by crossover design clinical trials comparing doxazosin with a prostate alpha-1 adrenergic receptor antagonist, which showed no significant differences in blood pressure-related adverse events.

3.5.1 Known potential risks

Doxazosin is a quinazoline derivative drug commonly used in the long-term treatment of patients with benign prostatic hyperplasia and hypertension.[146]. Similar to other alpha-1 adrenergic receptor antagonists, doxazosin is inexpensive and safe for outpatient use. Although the safety profile of doxazosin for modulating hyperinflammation is unknown, its common use for hypertension and benign prostatic hyperplasia has been well documented, particularly in the older age cohort that COVID-19 impacted most seriously.

Given the role of alpha-adrenergic signaling in the regulation of vascular tone and blood pressure, adverse reactions related to decreased systemic vascular resistance are expected to be the most common. The risk associated with changes in blood pressure is associated with increasing the dose[146].

Although alpha-1 adrenergic receptor blockade lowers blood pressure in hypertensive patients with increased peripheral vascular resistance, doxazosin did not result in a clinically significant blood pressure-lowering effect in normotensive men treated for benign prostatic hyperplasia. The percentage of normotensive patients with a sitting arterial systolic blood pressure less than 90 mmHg and/or diastolic blood pressure less than 60 mmHg at any time during treatment with doxazosin (dose range 1-8 mg daily) did not differ significantly between

doxazosin vs. placebo (6.7% vs. 5%, respectively)[146]. In pooled data from 7 placebo-controlled trials for benign prostatic hyperplasia in hypertensive and normotensive patients, the reported incidence of hypotension was 1.7% for patients receiving doxazosin (n=665) and 0% for patients receiving placebo (n=300) (Table 1)[146]. In patients with hypertension, doxazosin (at doses of 1-16 mg daily) decreased blood pressure by about 10/8 mmHg compared with placebo in the standing position and about 9/5 mmHg in the supine position over 24 hours. In controlled clinical trials for hypertension, the reported incidence of hypotension with immediate-release doxazosin was 1% in the treatment group (n=339) compared with 0% in the placebo group (n=336) (Table 2)[146].

In clinical trials of > 1500 patients with hypertension, syncope was reported in 0.7% of patients. None of these events occurred at the initial mg1 daily dose, and 1.2% (8/664) occurred at 16 mg daily. In placebo-controlled clinical trials of patients with benign prostatic hyperplasia, only 0.5% (3/665) taking doxazosin reported syncope[146]. In the long-term extension follow-up of ~450 patients with benign prostatic hyperplasia, syncope was reported in 0.7%[146]. The risk of orthostatic hypotension is minimized by starting therapy at 1 mg daily and titrating every two weeks to 2, 4, or 8 mg daily[146]. In controlled clinical trials for hypertension, the reported incidence of postural hypotension with immediate-release doxazosin was 0.3% in the treatment group (n=339), compared with 0% in the placebo group (n=336) (Table 2)[146]. In placebo-controlled trials in benign prostatic hyperplasia, the incidence of orthostatic hypotension with doxazosin was 0.3% and did not increase with increasing dosage to mg8 daily. The incidence of drug discontinuation due to hypotensive or orthostatic symptoms was 3.3% with doxazosin and 1% with placebo[146]. To decrease the likelihood of hypotension and syncope, treatment in this study will be started at 1 mg daily with subsequent dose increases informed of symptoms.

The incidence of other adverse events was determined from clinical trials in 965 patients with benign prostatic hyperplasia (combined adverse event data from seven placebo-controlled trials of doxazosin at doses of 1-16 mg in hypertensive patients and 0.5-8 mg in normotensive patients are summarized in Table 1). No significant difference was observed in the incidence of adverse events compared with placebo, except for dizziness, fatigue, hypotension, edema, and dyspnea[146]. In patients with cirrhosis (Child-Pugh Class A), administration of doxazosin mg 2showed a 40% increase in doxazosin exposure. The use of doxazosin in patients with severe hepatic impairment (Child-Pugh Class C) is not recommended (patients with known cirrhosis are

excluded from this study)[151]. Intraoperative loose iris syndrome has been observed during cataract surgery in some patients on or previously treated with alpha-1 adrenergic receptor blockers. Mild reversible leukopenia and neutropenia have been reported. No patient became symptomatic as a result of low WBC or neutrophil counts. Very rarely, priapism may occur, which requires rapid recognition and management. Concomitant administration of doxazosin with a phosphodiesterase 5 inhibitor may result in additive effects of decreased blood pressure and symptomatic hypotension.

Potent CYP3A inhibitors may increase doxazosin exposure[151]. There are no adequate and well-controlled studies on pregnant women. A single case study reports that doxazosin is present in human milk, which resulted in an infant dose of less than 1% of the maternal weight-adjusted dosage and a milk-to-plasma ratio of Adverse reactions0,183. with an incidence of less than 1% but of clinical interest are (doxazosin vs. placebo): angina pectoris (0.6% vs. 0.7%), postural hypotension (0.3% vs. 0.3%), syncope (0.5% vs. 0.0%), tachycardia (0.9% vs. 0.0%); dysuria (0.5% vs. 1.3%); decreased libido (0.8% vs. 0.3%). Overall, doxazosin has a side effect profile comparable to other alpha-1 adrenergic receptor blockers.

Table 7. Adverse events reported for doxazosin compared with placebo in clinical trials for benign prostatic hyperplasia

ADVERSE REACTIONS DURING PLACEBO-CONTROLLED STUDIES

BENIGN PROSTATIC HYPERPLASIA

Body System	CARDURA (N=665)	PLACEBO (N=300)
BODY AS A WHOLE		
Back Pain	1.8%	2.0%
Chest Pain	1.2%	0.7%
Fatigue	8.0%*	1.7%
Headache	9.9%	9.0%
Influenza-like Symptoms	1.1%	1.0%
Pain	2.0%	1.0%
CARDIOVASCULAR SYSTEM		
Hypotension	1.7%*	0.0%
Palpitation	1.2%	0.3%
DIGESTIVE SYSTEM		
Abdominal Pain	2.4%	2.0%
Diarrhea	2.3%	2.0%
Dyspepsia	1.7%	1.7%
Nausea	1.5%	0.7%
METABOLIC AND NUTRITIONAL DISORDERS		
Edema	2.7%*	0.7%
NERVOUS SYSTEM		
Dizziness†	15.6%*	9.0%
Mouth Dry	1.4%	0.3%
Somnolence	3.0%	1.0%
RESPIRATORY SYSTEM		
Dyspnea	2.6%*	0.3%
Respiratory Disorder	1.1%	0.7%
SPECIAL SENSES		
Vision Abnormal	1.4%	0.7%
UROGENITAL SYSTEM		
Impotence	1.1%	1.0%
Urinary Tract Infection	1.4%	2.3%
SKIN & APPENDAGES		
Sweating Increased	1.1%	1.0%
PSYCHIATRIC DISORDERS		
Anxiety	1.1%	0.3%
Insomnia	1.2%	0.3%

*p ≤0.05 for treatment differences

†Includes vertigo

Table 8. Adverse events reported for doxazosin compared with placebo in hypertension clinical trials

ADVERSE REACTIONS DURING PLACEBO-CONTROLLED STUDIES

	HYPERTENSION	
	DOXAZOSIN (N=339)	PLACEBO (N=336)
CARDIOVASCULAR SYSTEM		
Dizziness	19%	9%
Vertigo	2%	1%
Postural Hypotension	0.3%	0%
Edema	4%	3%
Palpitation	2%	3%
Arrhythmia	1%	0%
Hypotension	1%	0%
Tachycardia	0.3%	1%
Peripheral Ischemia	0.3%	0%
SKIN & APPENDAGES		
Rash	1%	1%
Pruritus	1%	1%
MUSCULOSKELETAL SYSTEM		
Arthralgia/Arthritis	1%	0%
Muscle Weakness	1%	0%
Myalgia	1%	0%
CENTRAL & PERIPHERAL N.S.		
Headache	14%	16%
Paresthesia	1%	1%
Kinetic Disorders	1%	0%
Ataxia	1%	0%
Hypertonia	1%	0%
Muscle Cramps	1%	0%
AUTONOMIC		
Mouth Dry	2%	2%
Flushing	1%	0%
SPECIAL SENSES		
Vision Abnormal	2%	1%
Conjunctivitis/Eye Pain	1%	1%
Tinnitus	1%	0.3%
PSYCHIATRIC		
Somnolence	5%	1%
Nervousness	2%	2%
Depression	1%	1%
Insomnia	1%	1%
Sexual Dysfunction	2%	1%
GASTROINTESTINAL		
Nausea	3%	4%
Diarrhea	2%	3%
Constipation	1%	1%
Dyspepsia	1%	1%
Flatulence	1%	1%
Abdominal Pain	0%	2%
Vomiting	0%	1%

3.5.2 Known potential benefits

3.5.2.1 Potential benefits of treatment

To date, no prospective, controlled clinical trial has examined the role of alpha-1 adrenergic receptor antagonists in preventing hyperinflammation and mortality in pneumonia, ARDS, or COVID-19. Researchers at Johns Hopkins University, led by Prof. Chetan Bettegowda, conducted a series of cohort studies, covering different populations, age groups, demographics, and countries.

Active use of alpha-1 adrenergic receptor antagonists in patients diagnosed with acute respiratory distress or pneumonia was evaluated from the MarketScan Research Database. The Agency for Healthcare Research and Quality (AHRQ) pneumonia category was adopted to identify patients with pneumonia and ICD-9 code 518.82 to identify acute respiratory distress. Men older than 45 years of age were considered in this evaluation because less than 10% of treated patients were women, and an even smaller fraction of patients were younger than 45 years of age, making sample sizes in these subpopulations insufficient to reliably estimate causal associations. The odds ratio (OR), confidence intervals (CI), and p-values for the unadjusted models were estimated using Fisher's exact test. Models were then adjusted for age, fiscal year, previous hospital admission, total previous days as an inpatient, and comorbidities identified in health care encounters in the previous year (including hypertension, ischemic heart disease, acute myocardial infarction, heart failure, chronic obstructive pulmonary disease, and diabetes mellitus). For adjusted models, we used logistic regression to estimate ORs, maximum likelihood profile to estimate ICs, and classical asymptotic theory to obtain p-values. We also adopted 5:1 matching via Mahalanobis distance and used a Cochran-Mantel-Haenszel test to calculate ORs, CIs, and p-values. To achieve a better covariate balance between the treatment and control groups for all the above analyses, the sample was restricted to the range with propensity score overlap. To assess the invariance of our results to methodological choices, other doubly robust methods and nonparametric causal relationships were adopted. The primary analysis method in all cases is the combined approach reported in the Cochran-Mantel-Haenszel results.

3.5.2.2 Benefit on mortality in acute respiratory distress

The effect of alpha-1 adrenergic receptor antagonists on ventilation and mortality in patients presenting with acute respiratory distress was investigated using the MarketScan database (years 2007-2015). In this cohort (n=13,125), the use of alpha-1 adrenergic receptor antagonists, compared to patients who did not use these medications, was associated with a 22% lower incidence (relative risk reduction) of mechanical ventilation (p≤0.009) and a 38% lower incidence of ventilation and death (p≤0.023). For tamsulosin, the most commonly used alpha-1 adrenergic receptor antagonist, patients presenting with acute respiratory distress had a 35% lower incidence of mechanical ventilation and a 55% lower incidence of ventilation and death (p≤0.002 and p≤0.015, respectively) (Figure 5).

3.5.2.3 Benefit on mortality in pneumonia

Then the analysis was expanded to patients presenting with pneumonia (n=108,956), of which 5% were also included in the acute respiratory distress cohort. In this model, the use of alpha-1 adrenergic receptor antagonists was associated with a 13% lower incidence of mechanical ventilation (p≤0.001 and a 16% lower incidence of ventilation and death (p≤0.040). Patients with pneumonia using tamsulosin had a 16% lower incidence of mechanical ventilation and a 20% lower incidence of ventilation and death associated with artificial ventilation compared to patients who did not use these medications (p≤0.001 and p≤0.042, respectively) (Figure 6).

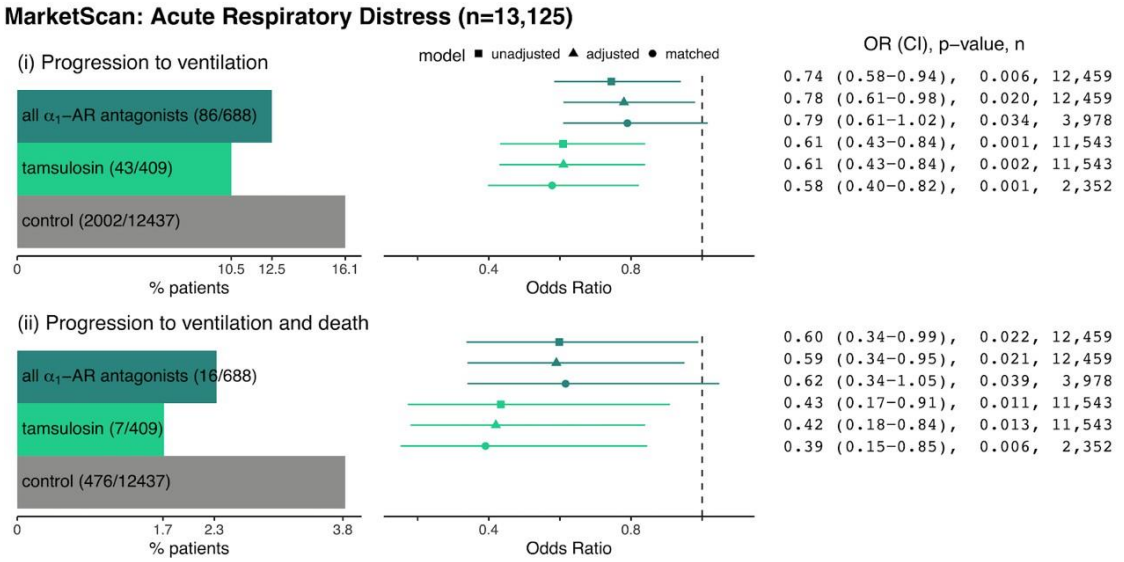


Figure 5. Risk of mechanical ventilation and death in hospitalized patients presenting with acute respiratory distress (MarketScan Research Database). (i) Number and proportion of patients who required mechanical ventilation based on the use of alpha-

1 adrenergic receptor antagonists (any), tamsulosin, or neither (controls) at baseline (left); odds ratios and confidence intervals (unadjusted, adjusted, and combined) and p-values for the same groups (right). (ii) Same as (i), but for patients who required ventilation and died. Alpha-1 adrenergic receptor antagonists were associated with a reduced risk of ventilation and death.

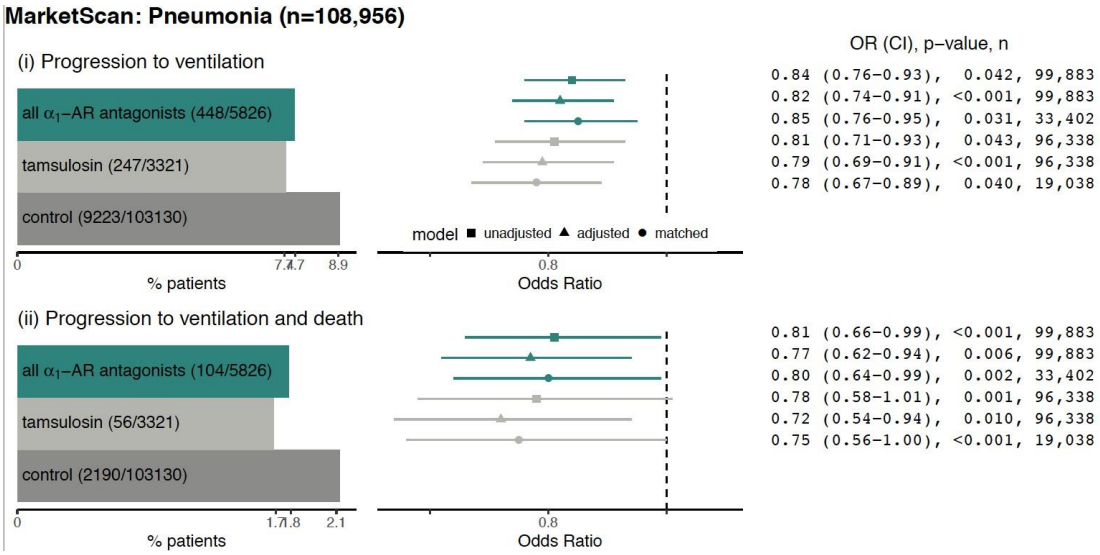


Figure 6. **Risk of mechanical ventilation and death in hospitalized patients presenting with pneumonia (MarketScan Research Database).** (i) Number and proportion of patients who required mechanical ventilation based on the use of alpha-1 adrenergic receptor antagonists (any), tamsulosin, or neither (controls) at baseline (left); odds ratios and confidence intervals and p-values for the same groups (right). (ii) Same as (i), but for patients who required ventilation and died.

3.5.2.4 Benefit on mortality in a Swedish cohort

The analyses of the US data (above) focused exclusively on men due to prescription trends in the United States. Therefore, we expanded our analyses to Swedish national health data (n=196,635). In Sweden, alpha-1 adrenergic receptor antagonists are more commonly prescribed for hypertension, making the gender balance more equal (almost 20% of individuals taking alpha-1 adrenergic receptor antagonists in Sweden are women compared to less than 10% in the United States).

Because mechanical ventilation is not coded in the Swedish database, only mortality was considered as an outcome, which probably underestimates the effect size due to deaths from other causes. However, the use of alpha-1 adrenergic receptor antagonists was associated with a reduced risk of death in a matched patient9.882 model (OR CI0,78, 0.64- 0.93; p=0.004) (unpublished data).

3.5.3.5 Benefit on mortality in a Danish cohort

A cohort study evaluating the relationship between alpha-adrenergic blockade and mortality in influenza-associated and pulmonary sepsis was recently published[152]. This cohort evaluated 528.467 Danish residents (aged 40 years or older, mean age 75.0 years) who were hospitalized for pneumonia or influenza specifically; 21,772 (4.1%) of the patients were actively using alpha-1 adrenergic receptor antagonists with 9,119 (1.7%) in chronic use. A total of hospitalizations41.276 included ICU admission, and a total of 77,197 patients died within 30 days of hospitalization. Among patients with pneumonia or influenza, mortality within days30 was 15.9% in users of alpha-1 adrenergic receptor antagonists and 18.5% in non-users, with a corresponding relative risk of 0.86 (95% CI 0.83-0.88). The outcomes of current users of alpha-1 adrenergic receptor antagonists and users of 5-alpha reductase inhibitors who served as controls were then compared.

Patients who were using alpha-1 adrenergic receptor antagonists had a lower 30-day mortality rate than those who were not using these medications (15.9% vs. 18.5%, respectively). The corresponding relative risk was 0.8 5(95% CI 0.8-03,88)[152]. Importantly, previous, prior chronic use of alpha-1 adrenergic receptor antagonists was not associated with improved survival, suggesting an acute role in modulating the cytokine release syndrome (Figure 7).

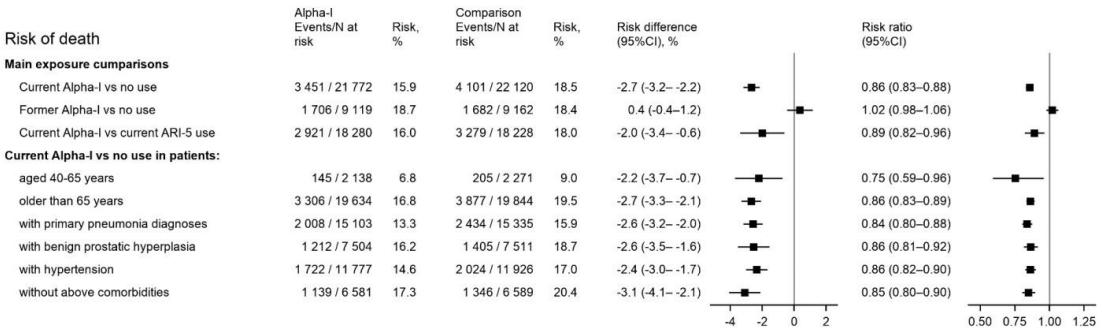


Figure 7. Risk of death in a Danish cohort of patients hospitalized with pneumonia or influenza. The risk reduction in patients currently using alpha-1 adrenergic receptor antagonists compared with nonusers is consistent with other cohorts. This risk reduction was also observed when comparing patients who were using alpha-1 adrenergic receptor antagonists at the time of hospitalization with patients who were using 5- alpha-reductase antagonists. The specificity of the observed effect is supported by the finding that patients with previous, chronic use of alpha-1 adrenergic receptor antagonists were not protected[152].

3.5.2.6 Benefit on mortality in patients with COVID-19

These analyses were replicated in a cohort of Veterans Administration (VA) patients with COVID-19. In patients with COVID-19, the use of any α1-AR antagonist compared with non-users was associated with an 18% lower incidence of death compared with non-users (OR=0.73, p≤0.001, n=22,847). Surprisingly, the use of doxazosin, a non-selective α1-AR antagonist like prazosin used in preclinical cytokine storm studies, resulted in a 74% lower incidence of death (OR=0.23, p=0.028) (Figure 8). Furthermore, the results of the VA cohort are consistent with preliminary data from high-risk kidney transplant patients in the UK who developed COVID-19. In these patients, doxazosin use was associated with a reduced risk of requiring hospitalization (use in patients requiring hospitalization 18% vs 55% in patients not requiring hospitalization, p=0.019) (data not shown).

In unpublished data from New York City, baseline use of any α1-AR antagonist was associated with significantly reduced mortality, showing an OR for death of 0.26 (p=0.002) for patients aged 45-65 years with confirmed α1-AR antagonist use as an inpatient and OR of 0.451 (p=0.003) in patients aged 55-75 years. A similar trend was observed in older patients.

Mirroring the results of preclinical models, these data provide a robust clinical rationale for studying alpha-1 adrenergic receptor antagonists for the prevention of local and systemic immune dysregulatory states. In patients with COVID-19, we expect that preventive treatment with doxazosin will decrease the risk of developing severe disease complications (e.g., ARDS, cytokine storm, and death) and reduce morbidity if they develop.

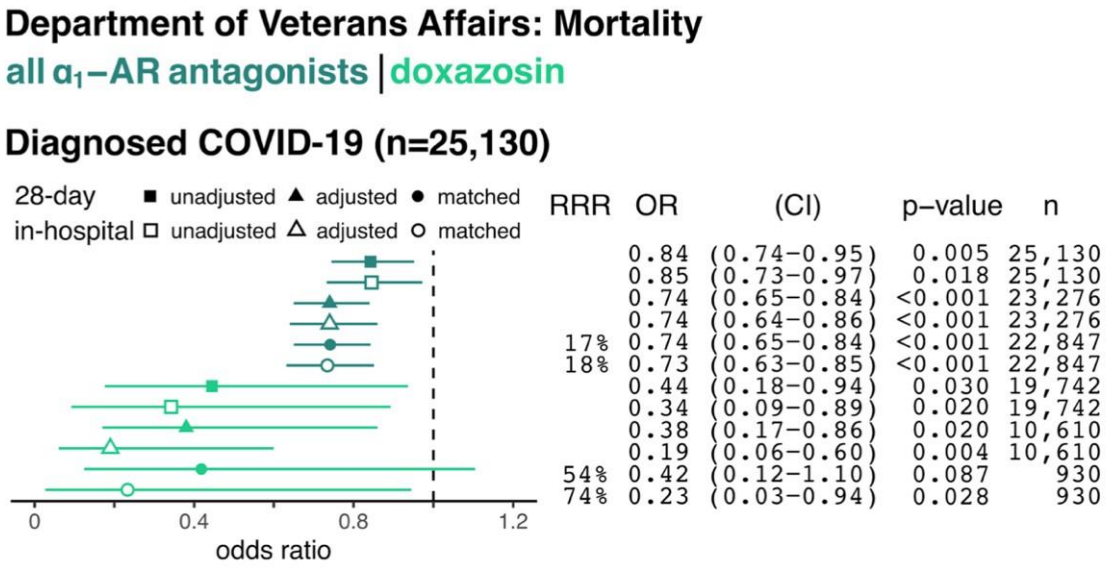


Figure 8. Risk of death in patients hospitalized with COVID-19 (United States Veterans Affairs Hospital System). Proportion of patients who died based on baseline use of alpha-1 adrenergic receptor antagonists (>70% tamsulosin) or doxazosin specifically compared with controls not receiving alpha-1 adrenergic receptor antagonists. The odds ratios, confidence intervals (unadjusted, adjusted, and pooled), and p-values in patients are shown for both in-hospital and 28-day mortality (https://www.medrxiv.org/content/10.1101/2020.12.18.20248346v2.full.pdf).

3.6 - Interferon (IFN) beta-1A

Interferons (IFNs) are part of a family of α-helicoid cytokines, induced in response to extra-cellular biomolecules through stimulation of Toll-like receptors (TLRs) and are part of a major circulating component of the natural defense system of animals[153]. Following viral infection, cells release IFNs, which provide protection to neighboring cells against viral infection. It is well established that this family of cytokines is the basis of the innate antiviral immune response that follows viral infection.[153]. The production of Type I (alpha, beta) and Type III (lambda) IFNs, initiated after viral infection, drives a potent antiviral response by inducing a broad set of genes, collectively known as IFN-stimulated genes[154,155]. Type II (gamma) IFN is considered the immune IFN and is activated by several pro-inflammatory cytokines, including interleukin 12 (IL-12).

Although both Type I and Type III IFNs signal through the JAK-STAT pathway to trigger IFN-stimulated[156,157,158,159,160] gene induction. While their antiviral activity is similar, their systemic effects differ significantly as a result of actions at distinct receptors, with

different tissue distribution depending on the IFN. In general, type I and II interferons have both activating and regulating roles in the immune response. Induction in type I and III IFN expression occurs in virtually all cell types through recognition of viral components, especially nucleic acids, by cytoplasmic and endosomal receptors, whereas type II IFN is induced primarily by the presence of cytokines, such as IL-12, and its expression is restricted to immune cells such as T cells and "natural killer" (NKT) cells.

Interferon beta-1A is a member of the Type 1 IFN family of pro-inflammatory cytokines that have been used to treat a wide range of human diseases, including some m-RNA viruses, some forms of cancer, and multiple sclerosis [161,162]. Although widely used for the treatment of multiple sclerosis, IFN beta-1A is not considered to be a curative agent for this disease, but to slow the progression of the disease, especially when its use is initiated in the early stages [163,164,165]. Preliminary clinical data have supported the efficacy of Type 1 IFN against potential m-RNA-like viral pandemic pathogens such as Ebola and SARS[162].

3.6.1 - Mechanism of action of IFN beta-1A

IFN's are considered circulating cytokines that induce non-specific resistance to viral infection by several mechanisms, including inhibition of protein synthesis, inactivation of viral RNA, and enhancement of phagocytic and cytotoxic mechanisms. IFN beta-1A is a member of the Type 1 IFN family and class of drugs called immune-modulators. These medications are commonly used in the treatment of multiple sclerosis, and their mechanism of action is fundamentally to reduce the inflammatory process and thus prevent and/or minimize nerve damage. Type I interferons, including IFN beta-1A, can improve respiratory distress, relieve pulmonary abnormalities, and produce better arterial oxygen and thus reduce the need for supplemental[166] oxygen support. Type I interferons appear to be well-tolerated and do not cause life-threatening adverse effects.

3.6.2 - Pharmacokinetics and Pharmacodynamics

ReciGen® or Avonex® (Biogen) are recombinant IFN beta-1a and are indicated for the treatment of relapsing and severe forms of multiple sclerosis, in order to reduce the frequency of clinical exacerbations, delay disease progression, the development of physical disability as well as to reduce the number and volume of active brain lesions.

The end result is a significant reduction in the speed of disease progression and the inability to perform minimally necessary activities.

IFN beta-1a is a 166 amino acid glycoprotein with a molecular weight of approximately 22,500 daltons. It is produced by recombinant DNA technology using ovarian cells from a genetically modified Chinese Hamster breed, into which the human interferon beta gene has been introduced. The amino acid sequence of recombinant IFN beta-1a is identical to that of natural human IFN beta-1A. Using the World Health Organization (WHO) international standard for Interferon, recombinant IFN beta-1A has a specific activity of approximately 200 million international units of antiviral activity per mg of interferon beta-1A determined specifically by an in vitro cytopathic effect bioassay using lung carcinoma cells (A549) and encephalomyelocarditis virus (ECM).

Peginterferon beta-1A

Peginterferon beta-1A (Plegridy®, Biogen) is a pegylated interferon developed for the treatment of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease, and secondary, progressive active-phase disease in adults (chromext://oemmndcbldboiebfnladdacbdfmadm/https://www.plegridy.com/content/dam /commer cial/plegridy/pat/en_us/pdf/plegridy-prescribing-information.pdf). Interferon Beta 1A is conjugated to a single, linear 20,000Da molecule of methoxy poly(ethylene glycol)-O-2-methylpropionaldehyde (mPEG-O-2-methylpropionaldehyde of 20 kDa) at a substitution level of 1 mol polymer/mol of protein. The average molecular mass is approximately 44 kDa, of which the protein fraction constitutes approximately 23 kDa.

The mechanism of action is not fully elucidated, but peginterferon beta 1A binds to the type I interferon receptor on the surface of cells and initiates the intracellular cascade of events leading to up-regulation of interferon-responsive gene expression. Biological effects that may be mediated by this medication include increased expression of anti-inflammatory cytokines (e.g. IL-4, IL-10, IL-27), reduced pro-inflammatory cytokines (e.g. IL-2, IL-12, IFN- γ, TNF-α) and inhibition of the migration of activated T cells across the blood-brain barrier; however, additional mechanisms may be involved.

Peginterferon beta 1A is only administered subcutaneously or intramuscularly and is considered superior to recombinant IFN beta-1a because it has a much longer half-life and the recommended dose for patients with multiple sclerosis is 125 µg every 14 days. The drug is supplied in a 1 ml long (0.18 mg/syringe) Type I glass syringe with a standard 29-gauge, ½ inch, thin-walled, 29-gauge (gauge) needle. The syringes are

pre-mounted with a 0.5 ml solution of peginterferon beta-1a, mannitol, L-histidine, polysorbate 80, hydrochloric acid and water for injection and are intended for single-use, in adjustable doses.

Pharmacodynamics

Pharmacodynamic responses were assessed by measuring the induction of interferon responsive genes, including those encoding 2′,5′-oligoadenylatosynthetase (2′,5′-OAS), myxovirus-resistant protein A (MxA), and many chemokines and cytokines, as well as neopterin (D-erythro-1, 2, 3,-trihydroxypropylpterin), a product of the interferon-inducible enzyme, GTP cyclohydrolase I. Gene induction in healthy human subjects was higher in terms of the peak level and exposure (area under the effect curve) for betapeginterferon 1A compared to non-pegylated beta interferon 1A (IM), when both were administered at the same dose per activity (6 MUI). The duration of this response was sustained and prolonged for peginterferon beta 1A, with elevations detected up to 15 days compared to 4 days for non-peginterferon 1A. Increased neopterin concentrations were observed in healthy patients and in multiple sclerosis patients treated with peginterferon beta 1A, with a sustained and prolonged elevation over 10 days compared with 5 days observed for non-peginterferon beta 1A. Neopterin concentrations returned to the baseline level after a 2-week administration interval.

Pharmacokinetic properties

The plasma half-life of beta peginterferon 1A is prolonged when compared to non-pegylated beta interferon 1A. The plasma concentration was dose-proportional in the range of 63 to 188 micrograms as observed in a single-dose and multiple-dose study in healthy subjects. Pharmacokinetic parameters, including Cmax and AUC, did not differ significantly between healthy subjects and patients with multiple sclerosis or between single-dose and repeated-dose administrations. However, the coefficient of variation among patients for AUC, Cmax, and half-life was high (41% to 68%, 74% to 89%, and 45% to 93%, respectively).

- **Absorption:**

After subcutaneous administration of beta peginterferon 1A in patients with multiple sclerosis, the peak concentration was reached between 1 and 1.5 days after dosing. The observed Cmax (mean ± standard error) was 280 ± 79 pg/mL after repeated

dosing of 125 micrograms at two-week intervals. Subcutaneous administration of beta peginterferon 1A resulted in approximately 4-, 9- and 13-fold higher exposure in values (AUC168h) and approximately 2-, 3.5- and 5-fold higher Cmax after single doses of 63 (6 MUI), 125 (12 MUI) and 188 (18 MUI) micrograms respectively, when compared to intramuscular administration of 30 (6 MUI) micrograms of non-pegylated beta interferon 1A.

- **Distribution:**

After repeated doses of 125 micrograms at two-week intervals by subcutaneous administration, the volume of distribution uncorrected for bioavailability (mean ± standard error) was 481 ± 105 L.

- **Biotransformation and elimination:**

Urinary (renal) clearance is thought to be the primary route of excretion of betapeginterferon 1A). The process of covalently conjugating the PEG fraction to a protein can alter the in vivo properties of the unmodified protein, including decreased renal clearance and decreased proteolysis, thus extending the circulating half-life. As such, the half-life (t½) of betapeginterferon 1A| is approximately 2 times longer than unpegylated betainterferon 1A in healthy volunteers. In patients with multiple sclerosis, the t½ (mean ± standard error) of betapeginterferon 1A was 78 ± 15 hours, at a steady-state. The mean steady-state clearance of betapeginterferon 1a was 4.1 ± 0.4 L/h.

3.6.3 - IFN beta-1A and COVID-19

With the emergence of the global pandemic COVID-19, there has been a growing interest in this class of drugs, especially because of the encouraging results obtained in other diseases caused by m-RNA viruses and also during the SARS pandemic, where a reduction in severity and duration of illness was observed.[162,167,168]. Although SARS-CoV-2 has been shown to inhibit the production of IFN beta-1A, thereby blocking the innate[169] immune response, it is also known that SARS-CoV-2 is very sensitive to the antiviral activity of IFN beta-1A[167] when administered externally. Consubstantiating these findings, a recent study demonstrated that multiple sclerosis patients on regular recombinant human interferon beta-1A treatment were significantly

less likely to develop COVID-19 compared to individuals where this drug was not being administered[170].

The first clinical trial on the use of IFN beta 1A in patients with COVID-19 was performed by Payandemehr et al. and published in May 2020. In this open-label study without a control group, the efficacy and safety of using a 44 µg dose of IFN beta-1A subcutaneously for 5 consecutive days in 20 RT-PCR-confirmed COVID-19 patients hospitalized with a moderate to severe form of the disease were evaluated [171]. Although the study has serious limitations, the authors observed good tolerability and no significant side effects. The authors noted that when compared to the epidemiology of the inpatient cases, patients who received IFN beta 1A had a better outcome; however, due to important biases, these data cannot be considered.

Davoudi-Monfared et al. also evaluated the efficacy and safety of IFN beta-1A (ReciGen) in the treatment of patients with severe forms of COVID-19[172]. In this study, 92 patients were evaluated, and 42 patients were eligible to receive IFN beta-1A treatment in combination with the national standard drug protocol adopted in Iran at the time (hydroxychloroquine plus lopinavir-ritonavir or atazanavir-ritonavir). IFN beta-1A was injected subcutaneously three times a week (44-µg/ml) for two consecutive weeks. In this study, there was a control group consisting of 39 patients who received only the drugs adopted by the country's national protocol (Iran). The primary endpoint of the study was the time to reach a clinical response. The secondary endpoints consisted of the assessment of the length of hospital stay, intensive care unit stay, 28-day mortality, and the effect of early or late IFN administration on mortality, adverse effects, and complications during hospitalization. No significant improvement in the primary outcome was observed in the group receiving IFN beta-1A treatment and the control group (9.7 +/- 5.8 versus 8.3 +/- 4.9 days of hospital stay, respectively, p=0.95). On day 14, 66.7% versus 43.6% of patients in the IFN beta-1a group and control group, respectively, were discharged from the hospital (odds ratio [OR], 2.5; 95% confidence interval [CI], 1.05 to 6.37). Overall 28-day mortality was significantly lower in the IFN beta-1a than in the control group, although the study was not designed to assess mortality as a primary endpoint (19% versus 43.6%, respectively, p=0.015). Although IFN beta-1A treatment did not alter the time to achieve clinical response, its addition to the institution's standard COVID treatment protocol resulted in shorter hospital stays on day 14 and decreased mortality on day 28 after starting medication.

Another prospective, non-placebo-controlled study evaluated 20 patients using IFN beta-1A (ReciGen) at a dose of 44 µg administered subcutaneously every other day up to 10 days from randomization.[168]. These authors identified a significant reduction in viral load at the end of treatment. Imaging studies including lung computed tomography and chest X-ray showed less lung impairment after 14 days in all patients receiving IFN. No significant adverse reactions were observed in the follow-up period, and a reduction in COVID-19-associated symptoms was identified in treated patients.

In March 2021, Baghaei et al. [173]reported the efficacy of IFN beta-1A (ReciGen®) in 456 hospitalized patients with a COVID-19 condition, with patients 152randomized to the IFN beta-1A group and 304 patients allocated to the placebo group, in a prospective, double-blind study. Patients allocated to IFN beta-1A received the dose of 44 µg (12 million IU) three times over a 7-day interval. All patients also received Lopinavir/ritonavir at the standard doses (400 mg/ 100 mg every 12 hrs) for 14 days. It was observed that patients in the IFN group had a longer hospital stay compared to the placebo group (13 vs. 6 days, p = 0.001) and required more non-invasive ventilation than the control group (34% vs. 24%, p = 0.04). However, the authors observed a lower mortality rate in the treatment group, although not significant (11% vs. 13% respectively in the IFN and Placebo groups). In multivariate analysis, receiving IFN was associated with lower mortality after adjustment for variables.

Alavi et al.[167] conducted an open-label randomized clinical trial in critically ill patients with COVID-19, comparing both IFN beta-1A and IFN beta-1B, with an open-label control group as standard treatment, which was published in April 2021. Patients were randomly allocated in a 1:1:1 ratio to IFN beta-1A (subcutaneous injections of 12,000 IU on days 1, 3, 6), IFN beta-1A (subcutaneous injections of 8,000,000 IU on days 1, 3, 6), or the control group. All patients received treatment with Lopinavir/ Ritonavir at standard doses (400 mg/100 mg twice daily) for 10 days and a dose of hydroxychloroquine as per standard protocol adopted in Iran). Sixty patients admitted to an intensive care unit with RT-PCR-confirmed COVID-19 were evaluated in this open clinical trial. In the intention-to-treat analysis, IFN beta-1A was associated with a significant difference compared to the control group regarding the length of hospital stay (HR: 2.36; 95% CI: 1.10-5.17; p= 0.031) while IFN beta-1A showed no significant difference compared to the control group (HR: 1.42; 95% CI: 0.63-3.16; p= 0.395). Mortality was observed to be numerically lower in both groups receiving IFN (20% mortality in the IFN beta-1A group and 30% in the IFN beta-1B group vs. 45% in the

control group). No significant differences were observed between the three arms with regard to adverse events. In patients with laboratory-confirmed SARS-CoV-2 infection, the benefit of a significant reduction in length of stay was observed in the IFN beta-1A arm.

In a study initially released online in November 2020 and published in February 2021, Monk et al. evaluated the efficacy and safety of IFN beta 1A in the nebulized/inhaled form of IFN beta-1A (SNG001) for the treatment of hospitalized patients with COVID-19[174,175]. This randomized, double-blind, placebo-controlled, phase 2 pilot study was conducted in nine healthcare facilities located in the UK. Adults aged 18 years or older hospitalized with symptoms of COVID-19, determined by a positive RT-PCR, rapid antigen test, or both, were randomly assigned (1:1) to receive SNG001 (6 MIU) or placebo by daily inhalation for 14 days. The primary outcome was defined as the change in clinical condition on the WHO Clinical Improvement Ordinal Scale, where 0 corresponds to no infection, and 8 corresponds to death, assessed during the treatment period. In this intent-to-treat protocol, during the dosing period in the intent-to-treat population (all randomized patients who received at least one dose of the study drug). Safety was assessed by monitoring adverse events for 28 days. In this study, 101 patients were randomly assigned to SNG001 (n=50) or placebo (n=51). Of these, 66 (67%) patients required oxygen supplementation at randomization (29 in the placebo group and 37 in the SNG001 group). Patients who received SNG001 had a better outcome on the WHO clinical improvement scale (OR: 2-32; [95% CI: 1-07-5-04]; p=0-033) on day 15 or 16 and were more likely to have clinical improvement compared to those who received placebo (OR: 2-19; [95% CI 1-03-4-69]; p=0-043). The inhaled formulation of IFN (SNG001) was well tolerated for the duration of the study, with the most frequently reported emergent adverse event during treatment being headache (seven [15%] patients in the SNG001 group and five [10%] in the placebo group). Three deaths were reported in the placebo group and none in the SNG001 group.

Given the promising results with the inhaled form, a phase III, randomized, prospective, placebo-controlled clinical trial of SNG001 in hospitalized COVID- 19 patients (named SG018) is currently underway.

Reduced length of hospital stay and improved prognosis, as well as a lower mortality rate, was a consistent finding in these clinical trials where recombinant IFN

beta-1A was administered for the treatment of COVID-19 in hospitalized patients. This was consistent with the results of other clinical trials using IFN beta-1A in nebulization/ inhalation form. The use of IFN beta 1A was shown to be safe and without major side effects in a large population of patients with COVID-19 and hospitalized due to disease complications. Considering the antiviral efficacy of IFN beta 1A and its effects on the inflammatory cascade and modulation in interleukins, it is possible that these effects are promising for its use in patients with mild forms of COVID-19 prior to activation of the inflammatory cascade.

In this sense, the "*Containing Coronavirus 19"* (COVID-19; "ConCorD-19") clinical trial is a prospective, cluster-randomized trial of peginterferon beta-1a versus standard of care aimed at contact management of cases diagnosed with COVID-19 early, before the development of acute influenza symptoms. In this clinical protocol proposed by researchers at the Catholic University of Chile, 1240 people with COVID-19 will be evaluated, and their asymptomatic contacts will be invited to receive a dose of 125 µg of pegylated IFN beta-1a subcutaneously or placebo on days 1, 6 and 11 of randomization, with the primary endpoint being the reduction of COVID-19 cases in family members participating in the research after 11 days of randomization[176].

A proposed initiative to evaluate patients with mild to moderate, non-hospitalized COVID-19 has been proposed at a single Italian center, and the study design has recently been published. In this study, the proposal is to use treatment with non-pegylated interferon at a dose of 44 µg administered 3 times a week for two consecutive weeks with a sample size of approximately 126 patients to be allocated in a 2:1 ratio, with a clinical picture of COVID-19 and mild to moderate symptoms being treated on an outpatient[177,178] basis.

3. 7- 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)[179]. 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 (figure 9)[179]. 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 central nervous system cells [180].

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[181] outbreak; 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[182] virus, hepatitis B[183] virus and, more recently, hepatitis delta[184] virus infections, showing antiviral activity comparable to IFN-, but with much better safety and tolerability profile.

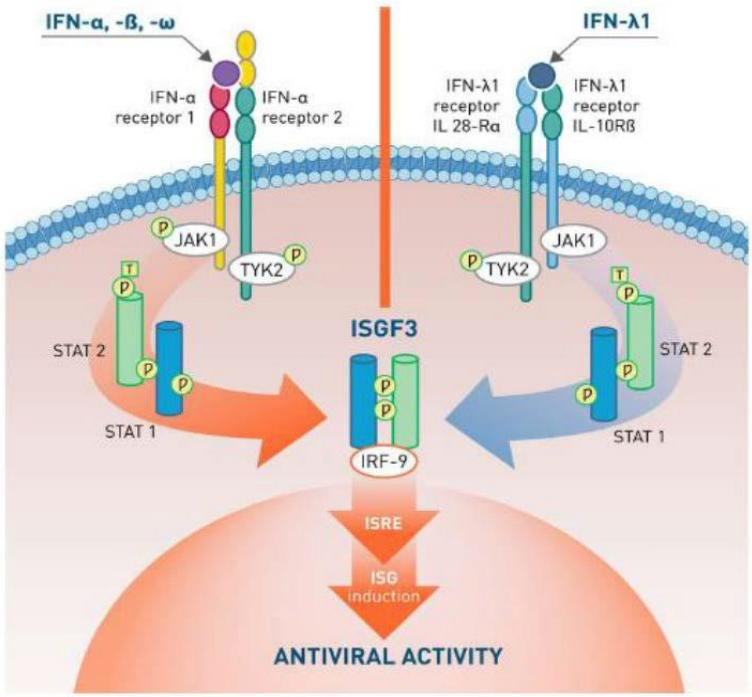


Figure 9: Mechanism of action: IFN Lambda and IFN signaling via the JAK-STAT transduction signaling pathway

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

Table 1 - PK parameters after a single dose of pegylated interferon lambda

	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)

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 lambda interferon 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 ng/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 180µg 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 epithelium (figure 10). 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[185] 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[186]. However, when IFNs were given after infection, IFN-ß worsened outcome, whereas IFN- treatment improved survival[186]. 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[187], which would address the intestinal and hepatic involvement documented in patients with COVID-19[188]. In addition, the lack of the lambda receptor in hematopoietic cells limits concerns about the potential for worsening cytokine[189] storm syndrome.

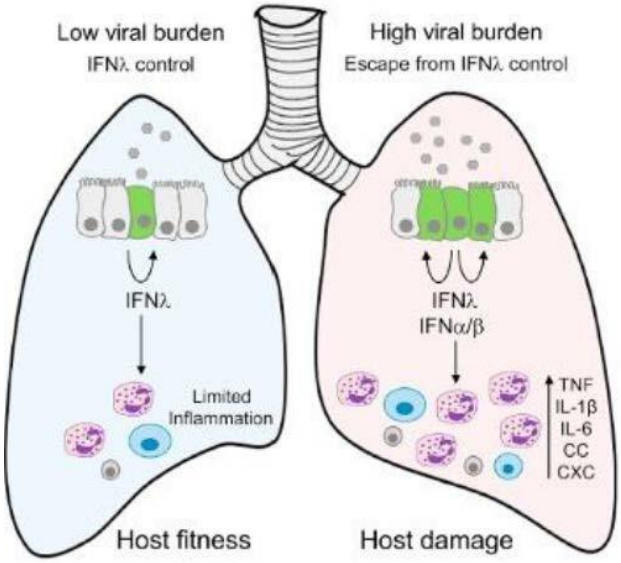


Figure 10. IFN-lambda reduces viral load and inflammation in lung tissue

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[190]. 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 than 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[191] 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 subjects (including 248 healthy subjects; 3.275 subjects with HCV; and 197 subjects with HBV; and subjects59 with HDV) have received peginterferon lambda or comparator in 19 phase 1, 2, or 3 studies. One hundred 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. 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[192]. 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_1 receptors, apparently, the dose of 200 mg/ day is sufficient for the expected SR_1 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 Ivermectin

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

Initially, we proposed in this clinical trial to use a treatment regimen with ivermectin at the dose commonly proposed for treatment of ectoparasites, intestinal parasitoses and parasitic infestations. Thus, we chose to use the fixed-dose regimen by weight range. Thus, patients weighing less than 60 kg will receive 12 mg of ivermectin,

between 60 and 80 kg will receive a dose of 18 mg, and patients weighing more than 80 kg will receive a dose of 24 mg of ivermectin. This dose has been shown to be safe in these studies and in studies in patients with COVID-19.

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

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

Considering the available evidence, including in patients with COVID-19, we are proposing the administration of ivermectin at an average dose of 400 mcg/kg/day, not to exceed mcg/kg/day470 in a single dose for 3 consecutive days.

3.8.2.1 Justification for changing the dosing regimen of ivermectin in the clinical trial

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

- from 40 to kg50 . . . . 03 tablets - 18 mg
- from to 51kg65 . . . . 04 tablets - 24 mg
- from 66 to 80 kg . . . . 05 tablets - 30 mg
- > 80 kg . . . . 06 tablets - 36 mg

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

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

Since then, a number of clinical studies have been published in peer-reviewed scientific journals and posted on pre-publication sites evidencing that the average dose of 400 mcg/kg/day in a single daily dose taken consecutively over three to five days is safe in the COVID-19 population, confirming the previous pharmacokinetic studies with high doses of ivermectin in three takes over 7 days where doses up to 60 mg/kg per take were used (cumulative weekly dose: 180mg as reviewed above) and with no evidence of adverse events compared to the placebo group. Furthermore, the accumulated experience with single doses of 800 mcg/kg taken every 12 weeks in studies conducted in the African continent for the treatment of onchocerciasis and the clinical trials conducted in DENV where the dose of 400 to 600 mcg/kg/day was administered orally for 03 consecutive days allow us to conclude that both doses are safe and the adverse events resulting from this dosage are comparable to the adverse events occurring in the placebo[193] group.

Data obtained from clinical trials using ivermectin in patients with COVID-19 were compiled according to a meta-analysis, where studies published in peer-reviewed scientific journals, submitted for publication and made available on online platforms, and ongoing studies where authors shared ongoing data were compiled and summarized by Hill et al[194]. Considering only the randomized studies (data as of February 05, 2020), the author identified more than 600 patients allocated to the active treatment arm, where the observed adverse reactions were similar to those observed in the placebo group.

There were approximately 240 patients treated with 400 mcg/kg/day ivermectin for 2-3 days and 230 patients treated with the same dose for 5 consecutive days. In this meta-analysis, there is the suggestion that the use of ivermectin 400 mcg/kg/day for 2-3 takes translates into a lower incidence of relevant clinical outcomes. While this may be open to criticism, such a dosage is in line with experimental studies in LPS-mediated sepsis models, where an intermediate dose of this drug (350-400 mcg/ kg) apparently resulted in lower mortality than a higher[195] dose. Similarly, previous studies have shown a reduction in inflammatory cytokines and other important mediators

in the inflammatory cascade using the average dose of 400 mcg/kg/day for 03 consecutive[196] days.

Thus, in order to obtain the best clinical results with the use of the drug within the safety observed in several clinical trials conducted using ivermectin for Malaria, Dengue, and COVID-19, we are proposing to extend the treatment in this clinical trial to use for 03 days instead of a single dose, according to table 9 below:

Table 9. Ivermectin/ ivermectin placebo dosage

Weight (kg)	Number of pills 06 mg	Total dose mg	Dose (mcg kg)
40 - 45	3	18	400 - 450
46 - 50	3	18	360 - 391
51 - 55	4	24	436 - 470
56 - 60	4	24	400 - 428
61 - 65	4	24	369 - 393
66 - 70	5	30	428 - 450
71 - 80	5	30	422 - 375
80 - 90	6	36	400 - 450
> 91	6	36	Up to 400

3.8.3 Doxazosin

Doxazosin is approved by ANVISA for the treatment of benign prostatic hyperplasia and hypertension, alone or in combination with other drugs. The starting dose of doxazosin is 1 mg per day to establish tolerability, with more commonly employed therapeutic target doses ranging from 1 mg to 16 mg orally daily. Clinical trial data suggest a significant increase in adverse events (orthostasis) at doses >8 mg PO daily[146].

The minimum effective dose of doxazosin to prevent hyperinflammation has not been established. In preclinical models of preventing hyperinflammation in rats, a total daily dose equivalent to ~10 mg prazosin in humans (equivalent to ~10 mg doxazosin) was used[131].

Real-world retrospective data from patients using doxazosin for blood pressure control and/or benign prostatic hyperplasia provide the best evidence of the doses needed to observe significant clinical benefit in preventing mechanical ventilation or death with lower respiratory tract infection. In preliminary data from high-risk renal transplant patients who developed COVID-19, baseline use of doxazosin was associated with a reduced risk of requiring hospitalization (use in patients requiring hospitalization 18% vs 55% in patients not requiring hospitalization, p=0.019, unpublished data). The doses of doxazosin used for blood pressure control in this high-risk cohort of COVID-19 patients ranged from 2 mg to 8 mg orally daily. These data suggest that doxazosin doses of 8 mg or less daily may be sufficient to show substantial clinical benefit in humans.

Given that doxazosin is exceptionally prescribed in the US, a dose-benefit association was only obtained in a large cohort of hospitalized patients with pneumonia (n=308,764) but not in COVID-19 (unpublished results). In patients with pneumonia, the use of doxazosin in clinically prescribed dose ranges was associated with a relative risk reduction of death (RRR) of 0,79. In this cohort, the risk of death was not significantly different among patients using doxazosin at daily doses of 1-8 mg orally compared to those using 8 mg or more daily. However, there was a trend toward some additional benefit in the 8 mg and higher dose group.

When repeating these analyses comparing patients taking doxazosin at daily doses of <4 mg compared to ≥4 mg PO daily, we also detected no statistically significant differences in the risk of ventilation and death in patients using higher doses (RRR 7%, OR 0.96 [0.74-1.25], p=0.388). However, there was a significant reduction in the risk of ventilation in patients using daily oral doses of 4 mg and higher (RRR 19%, OR 0.83 [0.70-0.99], p=0.019) (Vogelstein et al., unpublished data). These data suggest that doxazosin given at doses less than 8 mg orally daily, i.e. below the target dose of doxazosin, is sufficient to see clinical reductions in mortality, while higher doses may provide additional mortality benefits.

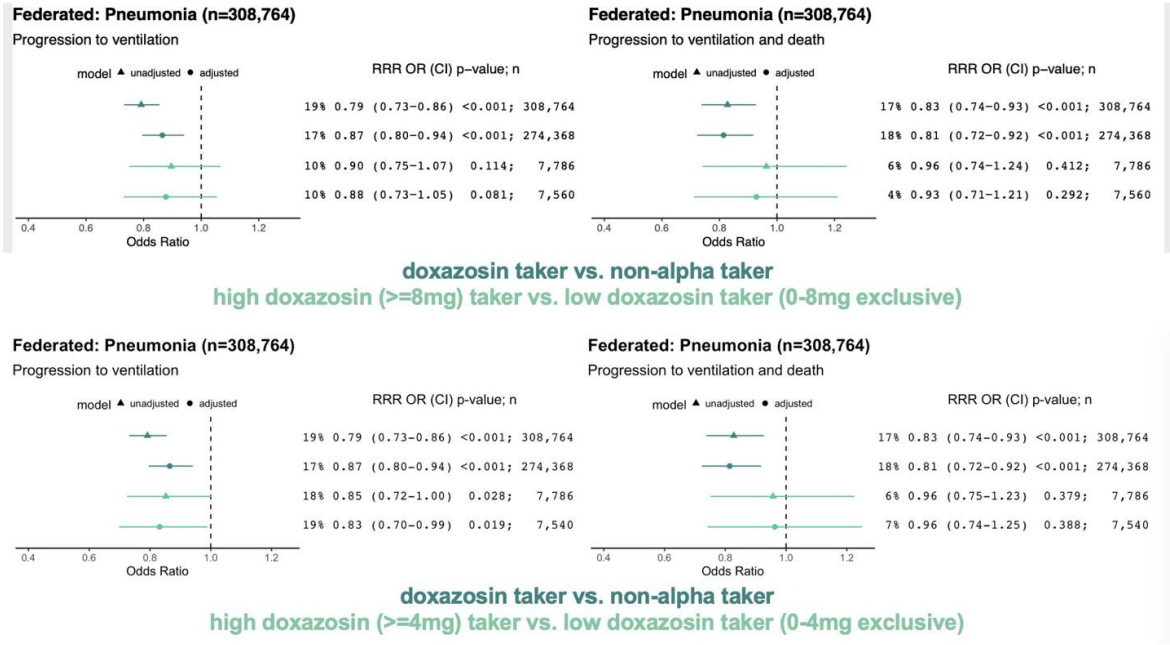


Figure 11 - Risk of death in hospitalized patients with pneumonia: Doxazosin use versus patients who did not use doxazosin

Because some of the blood pressure-related side effects of doxazosin are considered dose-dependent, with a significant increase in frequency at doses >8 mg daily[146]we designed this study to allow the careful increase of doxazosin dose over an 8-day period to reach a treatment target dose of 8 mg daily. Considering that lower doses are also likely to provide benefit, the protocol allows for individualized dosing based on the highest tolerated daily dose of doxazosin identified following the dose-escalation protocol described below.

3.8.3.1 Specific dosage and dose escalation considerations for doxazosin

1. **<u>First dose (day 1) for patients with SBP <120 mmHg at the time of randomization:</u>**

   The patient will begin taking doxazosin0 1 mg orally daily on the first day of therapy to see if the medication is tolerated or if signs or symptoms of hypotension develop (e.g., lightheadedness, dizziness, presyncope).

   - At randomization, the patient will receive an automated blood pressure cuff and instructions on how to monitor and record blood pressure at home at least once a day. The patient will be instructed on how to complete the Study Patient and Blood Pressure Diary.

- Before the first dose, a baseline blood pressure measurement should be recorded at rest (sitting for at least minutes5 before the measurement).
- The patient should be advised about possible adverse effects of doxazosin and advised about the measures to be taken if symptoms of hypotension, i.e. dizziness and lightheadedness, appear. The patient should be advised that mild dizziness with a rapid change of position is not uncommon. Thus, they should be instructed to change positions slowly and take seconds30 to move from supine to sitting position, from sitting to standing position, and from standing to ambulation (until they complete the dose increase protocol and know that their current dose is tolerated). Patients should be advised to use caution when getting up and walking to the bathroom at night, as they are at increased risk for syncope, falling, and injury. Patients should be advised to sit to urinate until they have completed the dose-escalation protocol and have tolerated stable doses for several days.

2. Blood pressure (BP) should be measured and recorded before the first dose on day 2 (24 hours after the first dose): if the patient remains asymptomatic (e.g., no intolerable dizziness or lightheadedness after standing, no [near] fainting, no confusion), the patient will continue oral mg1 daily.

3. Blood pressure measurement on day 3 (before the first dose): if the patient remains asymptomatic, the dose will be increased to 2 mg orally daily.

4. Blood pressure measurement on day 5 (before the first dose): if the patient remains asymptomatic, the dose will be increased to 4 mg orally daily.

5. Blood pressure measurement on day 8 (before the first dose): if the patient remains asymptomatic, the dose will be increased to 6 mg orally daily.

6. Blood pressure measurement on day 11 (before the first dose): if the patient remains asymptomatic, the dose will be increased to 8 mg orally daily.

7. Patients will continue on this dose (or the highest tolerated dose) for the remainder of the study unless they develop signs or symptoms of hypotension that warrant dose reduction.

8. The maximum dose of doxazosin in this study is 8 mg orally daily.
    - If SBP is < 90 mmHg on repeated spot measurement and the patient is symptomatic of hypotension (e.g., intolerable dizziness or lightheadedness when standing, [near] fainting, confusion, new blurred vision), the next dose of doxazosin should be delayed *until symptoms resolve,* and the patient instructed to continue with the highest previously tolerated dose (not the escalating dose). For patients with low baseline BP of ≤90/50 mmHg who are not symptomatic (prior to starting the first dose of drug or placebo), a drop of 10 mmHg or more in systolic BP should trigger dose adjustment to the highest previously tolerated dose (i.e., dose at which systolic BP was not 10 mmHg below baseline measurement and at which the patient had no symptoms of hypotension).
    - An attempt to introduce the higher dose can be made if the patient remains asymptomatic on the highest dose previously tolerated for 24 hours and without a fall in systolic BP.
    - Repeated occurrences of postural vertigo should trigger a reduction in the doxazosin drug dose.
    - Treatment is discontinued after 14 days of treatment.

2. First dose (day 1) for patients with SBP ≥120 mmHg at the time of randomization:

The patient will begin taking doxazosin 2 mg orally daily on the first day of therapy to see if the medication is tolerated or if signs or symptoms of hypotension develop (e.g., lightheadedness, dizziness).

1. At the time of randomization, the patient will receive an automated blood pressure cuff and instructions on how to monitor and record blood pressure at home at least once a day. The patient will be instructed on how to complete the Pressure and Study Patient Diary.
2. Before the first dose, a baseline blood pressure measurement should be recorded at rest (sitting for at least minutes5 before the measurement).
3. The patient should be advised about possible adverse effects of doxazosin and

advised about the measures to be taken if symptoms of hypotension, i.e. dizziness and lightheadedness, appear. The patient should be advised that mild dizziness with a rapid change of position is not uncommon. Thus, they should be instructed to change positions slowly and take seconds30 to move from supine to sitting position, from sitting to standing position, and from standing to ambulation (until they complete the dose increase protocol and know that their current dose is tolerated). Patients should be advised to use caution when getting up and walking to the bathroom at night, as they are at increased risk for syncope, falling, and injury. Patients should be advised to sit to urinate until they have completed the dose-escalation protocol and have tolerated stable doses for several days.

4. Blood pressure (BP) should be measured and recorded before the first dose on day 2 (24 hours after the first dose): if the patient remains asymptomatic (e.g., no intolerable dizziness or lightheadedness after standing, no [near] fainting, no confusion), the patient will continue oral mg2 daily.
5. Blood pressure measurement on day 3 (before the first dose): if the patient remains asymptomatic, the dose will be increased to 4 mg orally daily.

6. Blood pressure measurement on day 5 (before the first dose): if the patient remains asymptomatic, the dose will be increased to 6 mg orally daily.
7. Blood pressure measurement on day 8 (before the first dose): if the patient remains asymptomatic, the dose will be increased to 8 mg orally daily.
8. Patients will continue on this dose (or the highest tolerated dose) for the remainder of the study unless they develop signs or symptoms of hypotension that warrant dose reduction.
9. The maximum dose of doxazosin in this study is 8 mg by mouth daily.

10. If SBP is < 90 mmHg on repeated spot measurement and the patient is symptomatic of hypotension (e.g., intolerable dizziness or lightheadedness when standing, [near] fainting, confusion, new blurred vision), the next dose of doxazosin should be delayed *until symptoms resolve,* and the patient instructed to continue with the highest previously tolerated dose (not the escalating dose). For patients with low baseline BP of ≤90/50 mmHg who are not symptomatic (prior to starting the first dose of drug or placebo), a drop of 10 mmHg or more in systolic BP should trigger dose adjustment to the highest previously tolerated dose (i.e., dose at which systolic BP was not 10 mmHg

below baseline measurement and at which the patient had no symptoms of hypotension).

a. An attempt to introduce the higher dose can be made if the patient remains asymptomatic on the highest dose previously tolerated for 24 hours.
b. Repeated occurrences of postural vertigo should trigger a reduction in the doxazosin drug dose.
c. Treatment is discontinued after 14 days of treatment.

Table 10. Overview of the active drug and placebo dosing schedule in the study arms for <u>patients with initial systolic blood pressure <120 mmHg:</u>

Arm 1: Doxazosin*	**Drug**	**Dose**	**Total daily dose**
Day 1-2	**Doxazosin 2 mg**	0,5 tablet	1 mg
Day 3-4	**Doxazosin 2 mg**	1 tablet	2 mg
Day 5-7	**Doxazosin 2 mg**	2 tablets	4 mg
Day 8-10	**Doxazosin 2 mg**	3 pills	6 mg
Day 11-14	**Doxazosin 2 mg**	4 pills	8 mg
Arm 2: Placebo*			
Day 1-2	Placebo	0,5 tablet	AT
Day 3-4	Placebo	1 tablet	AT
Day 5-7	Placebo	2 tablets	AT
Day 8-10	Placebo	3 pills	AT
Day 11-14	Placebo	4 pills	AT

Table 11. Overview of the active drug and placebo dosing schedule in the study arms for <u>patients with initial systolic blood pressure ≥120 mmHg:</u>

Arm 1: Doxazosin*	**Drug**	**Dose**	**Total daily dose**
Day 1-2	**Doxazosin 2 mg**	1 tablet	2 mg
Day 3-4	**Doxazosin 2 mg**	2 tablets	4 mg
Day 5-7	**Doxazosin 2 mg**	3 pills	6 mg
Day 8-14	**Doxazosin 2 mg**	4 pills	8 mg
Arm 2: Placebo*			
Day 1-2	Placebo	1 tablet	AT
Day 3-4	Placebo	2 tablets	AT

Day 5-7	Placebo	3 pills	AT
Day 8-14	Placebo	4 pills	AT

3.8.4 - Peginterferon beta 1A

In the study, considering the pharmacodynamic and pharmacokinetic properties of pegylated interferon beta 1A as per the approved package insert of the medication as well as the accumulated data regarding the administration of this drug in phase II clinical trials in COVID-19, associated with the safety profile of the drug, we are proposing the dose of 125 µg as a single subcutaneous dose at the time of patient randomization.

Additional information can be found in the package insert extracted from ANVISA's website and attached to this regulatory filing

3.8.5 - Pefinterferon 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.

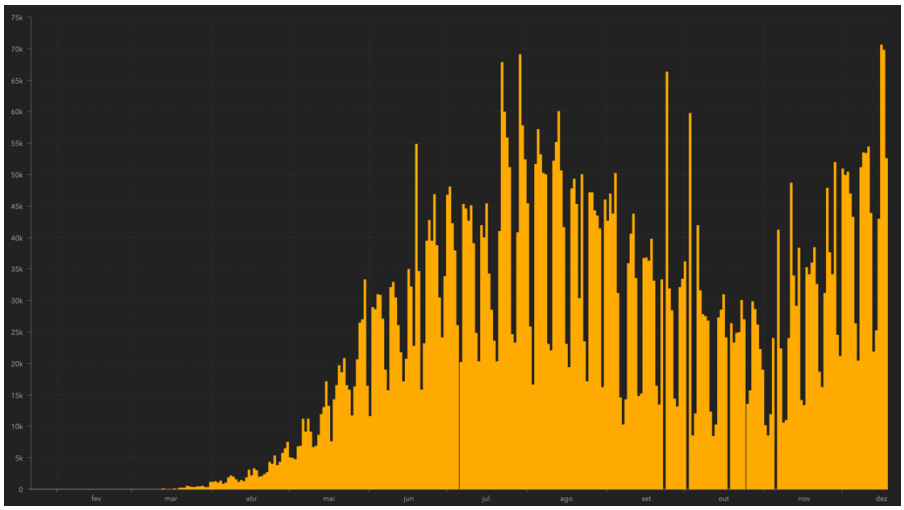
3.9 Justification for the study

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 [197].

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

However, both morbidity and mortality have been reduced little, and continuity of this academic effort is essential to cope with the ongoing pandemic. Today, December

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



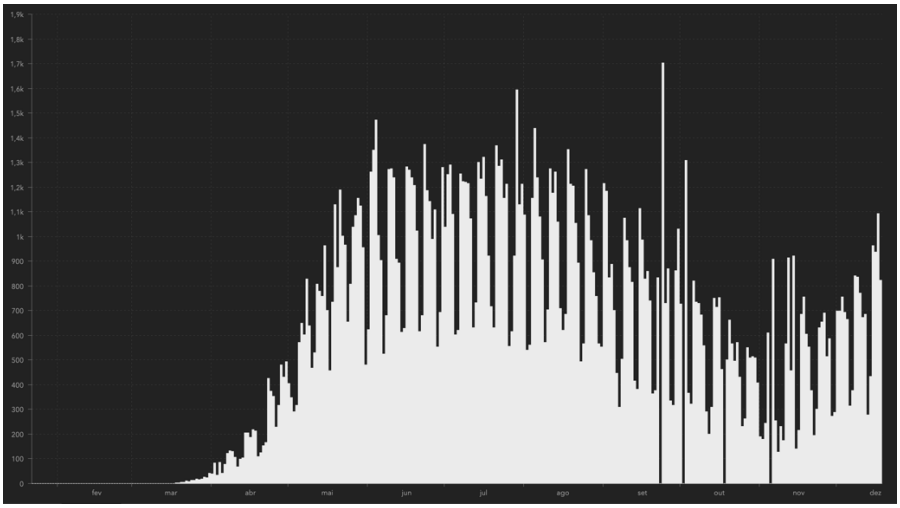


Figure 12 and 13 - Number of cases (yellow) and deaths (white) diaries associated with COVID-19
Source: Johns Hopkins university data Center (12/17/2020)

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

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

The world health organization has been following this disease since the first cases began, compiling data from virtually every country on the progress of COVID-19. The world academic community has made an unprecedented effort in recent scientific history in an attempt to find an alternative to alleviate this high mortality rate. On the www.clinicaltrials.gov platform alone, there are currently 4,195 clinical trials targeting COVID-19, many of which have been conducted under less than ideal conditions or with inadequate[199] designs.

From the beginning of the pandemic until now, the Brazilian scientific community has made an unprecedented effort, through hundreds of research programs directed to the confrontation of COVID-19, existing until now 777 clinical studies approved in Brazil[200]. The need to offer a rapid response to an epidemic that has been ravaging our country since March 2020, coupled with the exuberance of contemporary data from patients with CODIV-19 and the need to find an effective treatment for this pandemic would in itself justify foregoing a study containing a placebo arm.

Nevertheless, considering the absence of efficient treatments in patients with initial and acute presentation of COVID-19, the presence of the placebo group becomes an important tool to ensure that we have a control group being exposed to the same 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 verify 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 fluvoxamine and fluvoxamine placebo arm (10-day treatment), the Ivermectin and ivermectin placebo arm (03-day treatment) and the pegylated Interferon beta 1A, interferon gamma and respective placebo arms (single dose administered subcutaneously at the randomization visit:

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

The following visit design will be performed for the doxazosin and doxazosin placebo arm (14 days of treatment):

- V1 (D_0) - Screening visit
- V2 (D_0) - Baseline Visit + Randomization (Start of treatment phase)
- V3 - V15 ($_1$ From D_{13}) - Phone Contact from Day 1 to Day 13 (+ 1 day)
- V61 (D_{14}) - Day 14 Telephone Contact (±2 days)
- V71 (D_{28}) - Day 28 Telephone Contact (±3 days)
- V81 (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.

Participants who already have a positive RT-PCR test for SARS-CoV2 at screening and meet all the research inclusion criteria will not require further confirmatory testing for COVID-19 and can be considered eligible for the randomization/treatment phase.

Treatment phase (Randomization):

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

This randomization process will be performed centrally using the IWRS system, and treatment KITs will be allocated and identified by random numbering. The KITs will be made available in a way that no individual will be able to identify the medication being studied.

Participants will start their assigned treatments (Fluvoxamine; Ivermectin; Doxazosin or placebo).

4.2 Duration of participation in the study

Participation for each eligible research subject includes a screening visit (D_0), followed by the treatment phase, which can be for one day (in the case of subcutaneously administered medications, for 03 days in the case of medications administered for 03 days, for 10 days in the case of medications administered for 10 days, and for days14 if the participant is allocated to the 14-day doxazosin or doxazosin placebo arm). In all situations, the first day of medication 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 contact anticipated on days 28 and after60 the randomization date.

For verification of the primary endpoint, follow-up up to 14 and 28 days, respectively, will be used. For assessment of late complication outcomes of COVID-19, post-study follow-up by telephone contact on the day after 60randomization will be used.

Patients who discontinue the investigational product prematurely will remain in the study for the collection of data on the events of the composite endpoint and will receive usual care.

5 SELECTION AND WITHDRAWAL OF PARTICIPANTS

5.1 Number of participants

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

5.2 Inclusion Criteria

a) Patients over the age of 18 with the capacity to provide informed consent;
b) Patients seen at a Primary Care Unit of the Brazilian National Health System (SUS) or patients seen at SUS or supplementary care units with an acute clinical picture compatible with COVID 19 and symptoms beginning within 7 days of the screening date;
c) Patients over 18 years of age and with at least ONE of the following criteria
    1. Age 50≥ years (no other risk criteria needed)
    2. *Diabetes mellitus* requiring oral medication or insulin
    3. Hypertension requiring at least 01 oral medication for treatment
    4. Known cardiovascular diseases (heart failure, congenital heart disease, valve disease, coronary artery disease, myocardiopathy under treatment, clinically manifest heart diseases with clinical repercussions)
    5. Lung disease symptomatic and/or under treatment (emphysema, fibrosing diseases)
    6. Patients with symptomatic asthma requiring chronic use of agents for symptom control
    7. Obesity defined as BMI > 30 kg/m^2 on weight and height information provided by the patient
    8. Transplant Patients
    9. Patient with stage IV chronic kidney disease or on dialysis.
    10. Patient with fever measured at screening > 38º C
    11. 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)

12. Immunosuppressed patients/in use of corticotherapy (equivalent to a maximum of 10 mg prednisone per day) and/or immunosuppressive therapy)
13. Patients with a history of cancer in the past 05 years or currently undergoing oncological treatment

d. Patient with a positive rapid test for SARS-CoV2 antigen performed at the time of screening or patient with a positive diagnostic test for SARS-CoV2 within 7 days of symptom onset.
e. 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. Patients who received the first dose of the SARS-CoV-2 vaccine more than 14 days from the screening date.
5. Dyspnea secondary to other acute and chronic respiratory causes or infections (e.g., decompensated COPD, acute bronchitis, pneumonia, primary pulmonary arterial hypertension);
6. Patients needing hospitalization due to COVID-19
7. Patients taking serotonin reuptake inhibitors (Donepezil, Sertraline);
8. Exclusion criteria valid only for the oral medication administration arms:
    a. Continued use of monoamine oxidase inhibitors (MAOI): Phenelzine, Tranylcypromine, Selegiline, Isocarboxazid, moclobemide;
    b. Use of Antiretroviral Agents (Treatment of Acquired Immune Deficiency Syndrome - AIDS)

   c. use of alpha-1 adrenergic receptor antagonists, combined alpha-1/beta adrenergic receptor antagonists, sotalol, clonidine, phosphodiesterase type 5 inhibitors, nitrates, asenapine, alpha-methyldopa
   d. history of hypersensitivity or serious adverse reactions to the use of quinazolines (Prazosin, Doxazosin or Terazosin);
9. Patients with severe psychiatric disorders schizophrenia, uncontrolled bipolar disorder, major depression with suicidal ideation.
10. Pregnant or nursing patients;
11. History of severe ventricular cardiac arrhythmia (ventricular tachycardia, recovered ventricular fibrillation patients) or Long QT Syndrome;
12. Known history of orthostatic hypotension, unexplained history of syncope, postural orthostatic tachycardia syndrome (POTS), neurally mediated hypotension (within the past year), heart failure (NYHA III or IV), myocardial infarction (within 3 months of screening), stable or unstable angina, coronary bypass surgery (within 3 months of screening), stroke (within 3 months of screening), symptomatic carotid disease, or moderate to severe mitral or aortic stenosis;
13. Surgical or contrast use planned to occur during treatment or within 5 days of the last dose of study medication;
14. Current daily and/or uncontrolled alcoholism, which in the view of the investigator could compromise participation in the study;
15. History of seizures in the last month or an uncontrolled seizure condition;
16. Clinical history of moderate to severe liver impairment or cirrhosis of the liver with a Child-Pugh C classification;
17. Patients with known severe degenerative neurological diseases and/or severe mental illness;
18. Inability of the patient or representative to give consent or adhere to the procedures proposed in the protocol;
19. Any medical conditions, including psychiatric conditions, which in the investigator's view would preclude the use of the investigational medicinal products
20. Hypersensitivity and/or known intolerance to Fluvoxamine, Ivermectin, Pegylated Interferon beta 1A or Pegylated Interferon Lambda;
21. Inability to take oral medications;

5.4 Randomization criteria

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

5.5 Discontinuation of the product under investigation or withdrawal of participants

5.5.1 Discontinuation of the product under investigation

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

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

5.5.2 Withdrawal from the study

5.5.2.1 Withdrawal of consent

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

Every effort will be made to contact a participant who fails to attend and/or attend a study visit by phone to ensure that the participant is in satisfactory health.

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

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

5.5.2.2 Participant 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 Ivermectin

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

6.2.3 Doxazosin

It will be provided to the participant in the form of 02 mg tablets for oral use.

6.2.4 Pegylated Interferon Beta 1A

It will be provided to the participant in the form of a pre-filled injection, ready for immediate administration, at a dose of 125 µg for single-dose administration at the time of randomization.

6.2.5 Lambda Pegylated Interferon

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.

6.3 Dosage and administration

6.3.1 Treatment groups

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

- **Ivermectin:**
  - Doses to be administered once a day always ± 03 hours from the time of medication intake on the day of randomization, for three consecutive days, according to the table below:

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

Tabela 2 – Posologia considerando comprimidos de ivermectina 06 mg

- **Doxazosin**
  - 02 mg tablets to be administered once a day always ± 03 hours from the time of medication intake on the day of randomization. The doxazosin escalation schedule should always be preceded by blood pressure measurement and will be as follows:

Doxazosin*	Drug	Dose	Total daily dose
Day 1-2	**Doxazosin 2 mg**	0,5 tablet	1 mg
Day 3-4	**Doxazosin 2 mg**	1 tablet	2 mg
Day 5-7	**Doxazosin 2 mg**	2 tablets	4 mg
Day 8-10	**Doxazosin 2 mg**	3 pills	6 mg
Day 11-14	**Doxazosin 2 mg**	4 pills	8 mg

Table 03 - Doxazosin dosage if BP < 120 mmHg at baseline visit

Doxazosin*	Drug	Dose	Total daily dose
Day 1-2	**Doxazosin 2 mg**	1 tablet	1 mg
Day 3-4	**Doxazosin 2 mg**	2 pill	2 mg
Day 5-7	**Doxazosin 2 mg**	3 pills	4 mg
Day 8-14	**Doxazosin 2 mg**	4 pills	6 mg

Table 04 - Doxazosin dosage if BP > 120 mmHg at baseline visit

- **Pegylated Interferon Beta 1A**
  - Pre-filled syringe containing 125 µg of the drug for single-dose administration at the time of randomization.

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

6.3.2 Dosage and administration guidelines

6.3.2.1 Fluvoxamine

The dose on the day of randomization will be 100 mg to be taken at the end of the visit, followed by 100 mg every 12 hours until completing 10 days of treatment (If the randomization is with an interval of less than 06 hours from the subsequent dose, the same will not be administered. Example: Patient randomized at 2 pm will not take the 7 pm dose foreseen. If the patient is randomized at 11:00 am, he will take the 7:00 pm dose)

6.3.2.2 Ivermectin

The dose on the day of randomization will be according to the table below, in a single dose and repeated in the next 02 days, always with an interval of ± 03 hours from the time of ingestion on the day of randomization. The first intake should occur at the end of the randomization visit.

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

Tabela 2 – Posologia considerando comprimidos de ivermectina 06 mg

6.3.2.3 Doxazosin

The dose on the day of randomization will be 0.5 or 01 mg to be taken at the end of the randomization visit, depending on the patient's baseline blood pressure. Subsequent doses will follow a progressive titration scheme, based on symptoms and blood pressure measured prior to taking the medications as shown below:

Active drug and placebo dosing schedule in the study arms for patients with initial systolic blood pressure <120 mmHg:

Arm 1: Doxazosin*	**Drug**	**Dose**	**Total daily dose**
Day 1-2	**Doxazosin 2 mg**	0,5 tablet	1 mg
Day 3-4	**Doxazosin 2 mg**	1 tablet	2 mg
Day 5-7	**Doxazosin 2 mg**	2 tablets	4 mg
Day 8-10	**Doxazosin 2 mg**	3 pills	6 mg
Day 11-14	**Doxazosin 2 mg**	4 pills	8 mg
Arm 2: Placebo*			
Day 1-2	Placebo	0,5 tablet	AT
Day 3-4	Placebo	1 tablet	AT
Day 5-7	Placebo	2 tablets	AT
Day 8-10	Placebo	3 pills	AT
Day 11-14	Placebo	4 pills	AT

Active drug and placebo dosing schedule in the study arms for patients with initial systolic blood pressure > 120 mmHg:

Arm 1: Doxazosin*	**Drug**	**Dose**	**Total daily dose**
Day 1-2	**Doxazosin 2 mg**	1 tablet	2 mg
Day 3-4	**Doxazosin 2 mg**	2 tablets	4 mg
Day 5-7	**Doxazosin 2 mg**	3 pills	6 mg
Day 8-14	**Doxazosin 2 mg**	4 pills	8 mg
Arm 2: Placebo*			
Day 1-2	Placebo	1 tablet	AT
Day 3-4	Placebo	2 tablets	AT
Day 5-7	Placebo	3 pills	AT
Day 8-14	Placebo	4 pills	AT

6.3.2.4 - Pegylated Interferon Beta 1A

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 (125 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).

6.3.2.5 - Lambda Pegylated Interferon

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).

6.4 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 medication 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 groups6 via an internet-accessible remote randomization system (IWRS), namely:

- Fluvoxamine
- Ivermectin
- Doxazosin
- Pegylated interferon beta 1A
- Pegylated Interferon lambda
- Placebo (pills without medicine)

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

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

Participants will also be instructed to keep the empty/unused medication blister packs which will be collected by research staff in D_{10} for compliance assessment in the treatment phase. Participants will be instructed to return the empty/unused medication blister packs in 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_{14}. All used investigational product blister packs and containers will be retained at the site by the study pharmacist/qualified representative for verification by the study monitor. Accounting and investigational product adherence verification for all investigational products will be performed by the study pharmacist or qualified representative at each scheduled study visit.

6.7 Changing the dose of the drug

6.7.1 Adverse reactions during the use of medications

The research participant should contact you when he/she presents any adverse reactions that he/she feels may be associated with the product under investigation. Likewise, the patient will be monitored daily by safety telephone contacts to ascertain the presence of any undesirable symptoms, adverse reactions, and other signs/symptoms

that may be present. The participant may be scheduled for an extra safety consultation whenever the investigator deems it necessary, with reference to the information obtained during the telephone contact.

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

6.7.2 Usual care

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

6.8 Prohibited therapy, special considerations and concomitant treatment

6.8.1 Prohibited medications

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

- Monoamine-Oxiety Inhibitors (MAOI): Phenelzine, Tranylcypromine, Selegiline, Isocarboxazid, moclobemide;
- Use of Antiretroviral Agents (Treatment of Acquired Immune Deficiency Syndrome - AIDS);
- Sertraline, Donepezil
- Use of alpha-1 adrenergic receptor antagonists, combined alpha-1/beta adrenergic receptor antagonists, sotalol, clonidine, phosphodiesterase type 5 inhibitors, nitrates, asenapine, alpha-methyldopa

6.8.2 Concomitant medications

Information on concomitant medications (prescription drugs, over-the-counter medications, herbal and naturopathic medications, etc.) will be collected starting at screening and throughout the study (including at the Early Termination/EoS visit, follow-up phone call).

In general, participants should continue the same medications and regimens that were ongoing at the time of study entry. The doses of these concomitant medications should be kept as stable as possible during the study. Medications that the investigator considers indicated for the treatment of any intercurrent disease or a preexisting condition that are not on the list of prohibited medications or do not form an exclusion criterion for participation in this study will generally be allowed.

7 RISKS AND PRECAUTIONS

7.1 Precautions

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

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

7.2 Adverse Reactions

7.2.1 Fluvoxamine

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

7.2.2 Ivermectin

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

7.2.3 Doxazosin

Most adverse reactions reported in clinical studies are self-limiting and resolved with nonpharmacological measures. Dizziness (up to 19%), headache (14%), drowsiness (5%), MMII edema (4%), nausea (3%), vertigo (2%), and secular dysfunction (2%) are the most common symptoms. Hypotension (1%), peripheral nervous system changes (1%), depression (1%), weakness (1%), postural hypotension (0.3%), tachycardia (0.3%), may appear with continued treatment. Other adverse reactions: urticaria, allergy, MMII ischemia are very rare (incidence less than 1: 10,000).

All doxazosin shots must be preceded by blood pressure measurement. The Patient will take notes and, at the end of the treatment, will take a picture of the blood pressure diary and send it by cell phone or through social media applications.

7.2.4 Pegylated interferon beta 1A

Most adverse reactions reported in clinical studies are self-limiting and resolved with non-pharmacological or anti-inflammatory measures. Mild flu-like symptoms (chills, myalgias, fever) may occur in up to 47% of patients. Injection site reactions (pain, local erythema, edema, and pruritus) may occur in up to 66% of patients. Other common symptoms are headache and nausea, usually within 24 hours of drug administration. Elevations in the liver and hematologic enzymes occur in 2% and 7% of patients with repeated use of peginterferon beta 1A, respectively. 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 to 8% of patients and appear after repeated and prolonged administration of the drug.

7.2.5 Pegylated Interferon lambda

Most adverse reactions reported in clinical studies are self-limiting and 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.

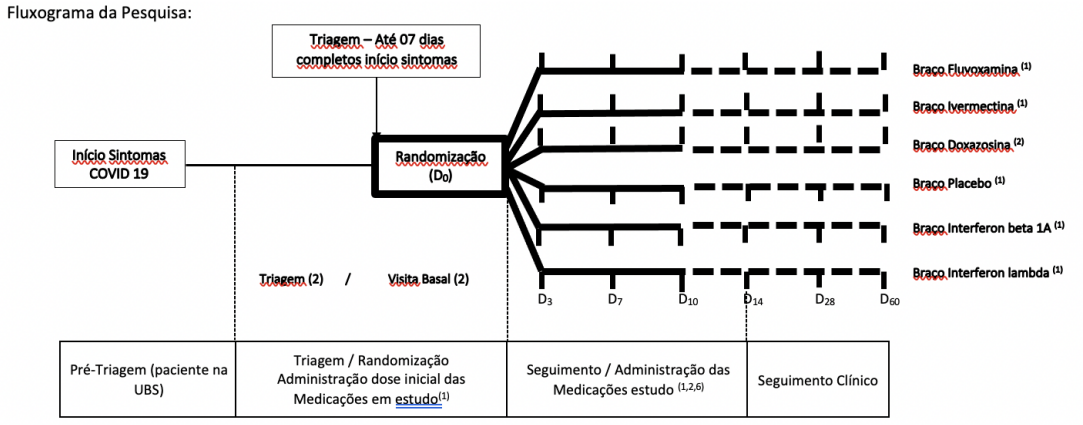
8 STUDY PROCEDURES

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 procedure specific to the study is performed, the participant will receive an explanation of all study procedures and will be required to 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 the SUS or from supplementary medicine and will be carried out according to the flowchart below:



1. Tratamento: Fluvoxamina, Doxazosina, Interferon Pegilado Beta 1A e Interferon Pegilado Lambda em grupos paralelos pelo período planejado. Posologia das medicações varia conforme a alocação do paciente em um braço do estudo (Fluvoxamina: 10 dias; Ivermectina: 03 dias; Interferon pegilado beta 1A: dose única; interferon pegilado lambda: dose única. Para cada braço há o correspondente placebo, inclusive ajustado pelo pelo (braço ivermectina). Medicações serão interrompidas a qualquer momento se houver evidência de reação adversa ou a critério do sujeito da pesquisa.
2. Doxazosina com titulação crescente, a partir de 01 ou 2 mg até 08 mg/ dia. Dose pode ser reduzida em caso de sintomas clínicos e/ou níveis de pressão arterial conforme programa de medição da mesma durante a administração do medicamento.
3. Triagem e Randomização devem ser realizadas na mesma visita. Assegurar que o paciente seja randomizado por ocasião do atendimento.
4. As visitas subsequentes: D_3, D_7, D_{10}, D_{14}, D_{28}, D_{60} serão realizadas através de contato telefônico, entretanto com possibilidade de visitas presenciais em D_7 e D_{14}. Em qualquer momento visitas extras de segurança poderão ser realizadas. As visitas D_{14} e D_{28} são consideradas visitas de desfecho para a pesquisa. 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 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.
5. Contato diário por telefone (assinaladas acima) serão realizadas entre os Dias 1 a 7 de tratamento. 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.
6. Nos braços Doxazosina e de medicações administradas por via subcutânea o contato telefônico será realizado diariamente até o D_{14}.

Table 5 - Procedures Flowchart

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

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

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

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

8.1.1.1 Retrying participants

In this study, restriping 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
- 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
- Orientation regarding the D_3 and V_7 visits and the procedures associated with them (600 initial patients)
- COVID-19 guidelines and quarantine recommendations

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

Participants who meet all inclusion criteria and do not have exclusion criteria will be randomized within 7 full days of symptom onset, preferably following the screening visit (both performed at the same time). The procedures to be performed from the randomization visit will be considered as procedures from the V2 visit. In patients allocated to treatment with oral medications, the same will be delivered according to the randomization and offered the global orientations referring to the treatment group (if for medications for 03 days, for 10 days or for 14 days). If the patient is allocated to treatment with injectable medications, they will be administered in a single dose at the end of the randomization procedures. The first 400 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 procedures associated with 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. If face-to-face care is needed, the research team will arrange a home visit, preferably

8.2.1 Daily telephone contacts

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

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

Patients allocated to take medication under investigation for 03, 10 or 14 days will be contacted by phone and/or social media app as described in section 4.1 of this protocol.

In the first 400 patients allocated to a single dose of subcutaneous medication, the viral load test will be performed. 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 medical product for 3, 10, and 14 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, and in the case of doxazosin, its mechanism of action does not involve changes in the viral load of patients.

8.2.2 Visit 3 to V15: D_1 to D_{13} (+ 1 day)

The flowchart of these visits is variable, depending on the patient's allocation. If for single dose, 03 or 10 day treatment, the patient will make daily telephone contacts until D_7 and then D_{10}, D_{14}, D_{28} and D_{60}. The first 400 patients who received subcutaneous dose will do nasopharyngeal and/or sputum SWAB self-collection.

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

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

Patients allocated for 14 days of treatment will be contacted daily BEFORE the day's scheduled medication is taken, as provided in section 4.1 of this protocol. In these daily telephone contacts, the following procedures will be checked:

- Adverse Events
- Concomitant Medications
- WHO Flu Symptoms Questionnaire
- Respiratory Symptoms
- Clinical outcomes
- Remote Product Accounting under Investigation
- WHO ordinal scale of clinical improvement
- Measurement of blood pressure by the patient and recording in a BP diary.

Taking the medical product under investigation will depend on the assessment of blood pressure and symptoms presented by the patient. This decision will be made daily by the research staff.

8.2.3 Visits (D_{14}, D_{28}) and D_{60} - Ending 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 kits 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
- WHO ordinal Clinical Improvement Scale

At the $_{28}$ Do patient visit, you will also answer the TICSM 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 (Visit 8).

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 visit$_{28}$

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.
- Blood pressure (only for the arm allocated to 14-day treatment with the investigational medical product)*
- Weight and height (informed by the patient)

*Blood pressure measurement by automated blood pressure device provided for patients allocated to 14-day treatment arm (doxazosin and doxazosin placebo).

9.2.1 Heart rate and blood pressure

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.

For patients allocated to the 14-day arm of investigational medicinal product treatment, considering the possibility of being allocated to the doxazosin arm and its known hypotensive effect, an automated blood pressure monitor will be provided to monitor blood pressure always BEFORE daily intake of the investigational medicinal product or at another time when the patient deems it necessary. The measured data will be recorded in a blood pressure diary to be given to the patient, and these measurements will be passed on daily during the telephone contact. At the D_{14} visit, the patient will make a copy (Photo) of the diary and send it via social media applications to our defendant in the research record.

9.3 Physical Examination

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

9.4 ECG Evaluation

Evaluation of an ECG tracing should be performed to check for any changes due to COVID-19 and will be performed at the Screening visit. We will not monitor the QT interval in this research since the medications being used do not alter the QT interval.

The participant should rest at rest for a minimum of 5 minutes before the exam and the procedure to be performed as per the Kardiamobile® manufacturer's guidelines.

9.5 Patient-reported outcomes

Patient-reported outcome questionnaires (EQ-D-5L5, and WHO Flu Syndrome Questionnaire) will be completed by participants before the study team conducts any further assessments during the telephone contact or face-to-face visit in order to avoid

influencing participant responses. The study coordinators will review the participant's responses immediately after the participant completes the questionnaires to ensure that all questions are answered.

Clinical Worsening Questionnaire - WHO

We will assess the clinical condition of the participants using the WHO scale: 0-1: ambulatory (no clinical deterioration during the RCT phase), 2: activity limitation but no hospitalization; 3: hospitalization but no O2 required; 4: hospitalization, O2 required; 5: non-invasive ventilation or high-flow oxygen; 6: ventilator required; 7: ventilation plus organ support required; 8: death. The scale can be found on page 6 at the following link: https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf. 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)[201]. 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.

TICSM 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.

9.6 Contraception in women of childbearing potential

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

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

Considering the above data, pregnant and breastfeeding women may not 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[202]. 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 the 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 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 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 the visit ($7D_{28}$).

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 ($8D_{90}$), 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 AE 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.

The 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 the death; and a necropsy report should be provided when possible. If the cause of death becomes known later (e.g., after the autopsy), this work 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 his/her 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 days 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 trial 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 a single case basis to determine that there is a reasonable possibility that the study drug caused the event. As a result, they would not meet the definition of suspected adverse reaction.

The DSMC will monitor events identified during the conduct of the trial and alert if there is evidence of a causal relationship between the product under investigation and the event after its analysis.

10.7.3 SUSARs

The definition of a suspected unexpected serious adverse reaction (SUSAR) is any ADR (Adverse Drug Reaction) that is serious and unexpected.

For the purposes of this protocol, the occurrence of SUSARs is not expected since the medications have been approved for several years by ANVISA and used in hundreds of thousands of patients, where possible adverse reactions from and/or idiosyncrasies are already widely known to the regulatory authorities.

10.8 Special Situations

10.8.1 Definition of special situations

The following situations are defined as special:

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

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

10.8.2 Registration and special situation reporting

All special situations must be documented in the participant's source documents. If any special situation leads to an 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, ivermectin and metformin allows us to conclude that these medications should not be prescribed to pregnant patients without a careful evaluation of the risks and benefits of their use during this phase. Therefore, pregnancy is not expected to occur during the treatment phase (10 days), and women should use contraceptive methods to avoid pregnancy (if necessary, we will provide an effective method of contraception for use during the medication period).

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

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

The investigator is responsible for monitoring the participant and the pregnancy outcome and for reporting this information to the sponsor. Every effort should be made

to collect information about the pregnancy outcome by 90 days after delivery (or, if not, as appropriate).

10.8.3.2 Exposure during pregnancy and recording and reporting of birth events

Pregnancies should be reported throughout the conduct of the study, including up to 4 weeks after the last dose of the study drug received. Pregnancy reporting includes exposure of the female partner of a male participant. Although pregnancy is not considered an 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).

11 STUDY COMMITTEES

11.1 Data Security Monitoring Committee (DSMC)

An independent DSMC will be established, consisting of scientists of unimpeachable reputation and expertise who have no involvement with this research protocol. The DSMC will act as a research advisor to monitor the safety of participants who participate in this trial.

The DSMC is governed by a charter that explains the working procedures and responsibilities of the DSMC.

The research steering committee will define the working procedures and responsibilities of the DSMC. The charter will be agreed upon in advance by the DSMC and will follow good research practice.

11.2 Event Adjudication Committee

The independent Event Adjudication Committee (EAC) will evaluate all events related to the trial endpoints based on pre-established criteria and in a prospective, blinded manner.

CAT members should not be direct research members, and among them should be at least two qualified members. The CAT will operate on a blinded basis for trial treatment allocations to assess events. Outcome adjudication will occur continuously throughout the treatment phase of the blinded trial.

12 STATISTICAL CONSIDERATIONS

12.1 Study Design

The study will be conducted in two phases:

12.1.1 Internal pilot phase

Due to the rapidly evolving pandemic of COVID-19 and the challenge that public health systems will face in responding to this devastating infection, there are several aspects related to the feasibility of the study that 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.

12.2 Randomization

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

a. Fluvoxamine
b. Ivermectin
c. Doxazosin
d. Pegylated interferon beta 1A
e. Pegylated Interferon Lambda
f. Placebo

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

For each active drug arm, there will be a placebo arm, including for the different doses of ivermectin, based on the patient's weight. E.g., If a patient is allocated to 3-day treatment and is 80 kg, they may receive 05 ivermectin tablets or 05 ivermectin placebo tablets if allocated to 3-day treatment. If allocated for 10 days of treatment, he may receive either a bottle of fluvoxamine or a placebo bottle of fluvoxamine.

In the injectable medication arms, there will be a placebo counterpart.

12.3 Sample Calculation

The sample size calculation is based on the test for the hypothesis that each of i) Fluvoxamine, ii) Ivermectin, iii) Doxazosin, iv) Interferon Pegylated Beta 1A and Interferon Pegylated Lambda will be better than placebo in reducing the risk of hospitalization and/or emergency room care with a length of stay greater 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 1:1:1:1:1:1), the study will have a power of 80% to produce a statistically significant result using logistic regression (assuming an

intention-to-treat principle of analysis) of the reduction in the odds of hospitalization at alpha = 0.05.

These estimates used in the design of this study are based on global and Brazilian data of patients infected with COVID as of December 10, 2020. It is important to note that this is an evolving situation. Therefore, we calculated the sample size table showing the sensitivity of sample size estimates based on different baseline risks for hospitalization and expected treatment effects (see Table below 15).

As there are interim analyses, such data are rechecked against the actual global numbers of events occurring 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.

Table 12. Sample calculation using paired samples in relation to the control group. For these calculations, we focused on a paired comparison between Treatment 1 and Treatment 2 (Fluvoxamine, Ivermectin, Metformin). The treatment group proportions were estimated by the baseline risk change and assumed relative risk reduction. We used these simulations considering the following breakdown:

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

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

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

12.4 Statistical Analysis

The analysis and reporting of the results follow the CONSORT guidelines (www.consort-statement.org). The statistician/data analyst will be blinded to the study

group. The process of patient selection and flow throughout the study will be summarized using a flow chart. The results of the analysis of patient demographics and baseline (primary and secondary) outcome variables will be summarized using descriptive summary measures: expressed as mean (standard deviation) or median (minimum-maximum) for continuous variables, as appropriate, and number (percentage) for categorical variables. We will adopt an intention-to-treat principle to analyze all results.

We will also use multiple imputations to deal with missing data. All statistical tests will be performed using two-tailed tests at the 0.05 significance level. For all models, results will be expressed as effect reported as hazard ratio [HR] or *odds ratio* [OR] for binary outcomes and mean difference for continuous outcomes, corresponding 95% confidence intervals on both sides and associated p-values.

P-values will be reported to three decimal places with values less than 0.001 reported as <0.001. All analyses will be performed using SAS 9.4 (Cary, NC). A detailed analysis plan will be developed prior to locking the database.

12.5 Analysis of the feasibility results

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

12.6 Analysis of primary and secondary results

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

12.7 Sensitivity Analysis

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

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

12.8 Subgroup Analysis

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

e. Age - assumption that younger patients will benefit more than older patients
f. Gender - we think that women will benefit more than men.
g. 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 day 03 and 07 (150 patients per stratum)	Negative viral load treatment with medications	Negative/viral load reduction	Descriptive Analysis
Time to clinical improvement (28 days)	Treatment will shorten time to clinical improvement	Interval of days between randomization and clinical improvement	Cox Regression/Logistic Regression
Time to clinical failure (28 days)	Treatment will prevent clinical failure	Interval of days between randomization and hospitalization	Cox Regression/Logistic Regression
Number of days with respiratory symptoms since randomization	Treatment will shorten the number of days with respiratory symptoms	Interval of days between randomization and normalized WURSS scale	Cox Regression/Logistic Regression
Change in EQ-5D-5L quality of life scale	Treatment will improve quality of life	EQ-5D-5L scale improvement in 28 days	Cox Regression/Logistic Regression
Hospitalization for any cause	Treatment will prevent hospitalizations for any cause	Measurement of hospitalization in the groups	Cox Regression/Logistic Regression
Safety of Fluvoxamine, Ivermectin and Doxazosin in patients with COVID-19	Drugs are safe in patients with COVID-19	Measurement of adverse events in the treatment groups	Descriptive Analysis
Cardiovascular mortality	Treatment will prevent cardiovascular mortality	Measurement of cardiovascular deaths in the groups	Cox Regression/Logistic Regression
Mortality from any cause	Treatment will prevent global mortality	Measurement of deaths in the groups	Cox Regression/Logistic Regression
3) **Subgroup Analysis:** i) age (young vs. old) ii) Sex (male vs.	Elderly have a higher risk of complications	Risk Measurement	Regression methods with appropriate interaction terms.

woman) iv) Diabetes v) Hypertension vi) Chronic kidney disease KDIGO IV or hemodialysis vii) Chronic lung disease viii) Solid-organ transplantation ix) Heart Failure	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		
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[203] Medical Association's Declaration of Helsinki, and the International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, as amended.[202]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 CEP

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 ensure 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 must retain all records at the health care facility. The investigator will notify 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/CEP should review and approve the amendments prior to their implementation. Regulatory authority/CEP approval does not need to be obtained prior to the removal of an immediate hazard to participants.

16.3 Study Closure

The Steering Committee reserves the right to terminate the study in its entirety or at a site at any time. Reasons for termination may include (among others) unsatisfactory participant enrollment with respect to quality and/or quantity, the site cannot meet protocol or GCP requirements, or data recording 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 the prior consent of the steering committee. The confidentiality agreement to be established with the participating research centers will establish the publication policy.

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

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