IvermecPrev-Brazil: Protocol for a double-blind, randomised controlled trial using ivermectin for COVID-19 prophylaxis in asymptomatic adults without prior immunity to SARS-CoV-2 during the 2020-2022 pandemic in Brazil

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Abstract

Introduction: Coronavirus disease 2019 (COVID-19) emerged in China through an unknown aetiological agent in December 2019. Identified in 2021 as a beta-coronavirus, SARS-CoV-2 has high transmissibility and can cause an inflammatory thrombogenic syndrome that progresses to respiratory, renal and cardiac failure, severe acute organ dysfunction and death. There is no specific treatment for COVID-19. In Brazil, the national vaccination COVID-19 program has not achieved adequate coverage to block the transmission of SARS-CoV-2 in the population. In addition, studies have shown that, after vaccination, the specific immune response to SARS-CoV-2 does not always produce neutralising antibodies capable of preventing disease by new variants. Identifying a drug capable of reducing the transmissibility of this virus represents an essential contribution to pandemic control. Ivermectin seems to reduce the incidence and mortality of COVID-19 and has emerged as a possible pharmacological intervention for mass treatment strategy against SARS-CoV-2. IvermecPrev-Brazil trial proposes investigating the use of ivermectin to COVID-19 prophylaxis in asymptomatic adults without immunity to SARS-CoV-2 and exposed to this virus during the 2020/2022 pandemic. **Methods and analysis**: This is a phase III, double-blind, placebo-controlled, two-armed randomised controlled trial that aims to test the hypothesis that the use of ivermectin, combined with the usual prophylaxis recommendations, prevents the occurrence of COVID-19 or minimises the disease severity. A total of 600 adults ≥18 years of age, clinically asymptomatic, who did not develop immunity to COVID-19, will be included. To determine participant eligibility will be interviewed for COVID-19 symptoms and capillary blood sample test for assessing anti-SARS-CoV-2 immunity. Those included will be randomly allocated into two groups. The intervention group will receive ivermectin at a dose of 400 µg/kg of body weight and the control group a dummy drug (placebo) administered in single doses in both groups. All participants will receive the usual prophylaxis recommendations. After treatment, will be evaluated by applying questionnaires on days 7, 14, 30 and 90 to determine whether there are signs or symptoms of COVID-19, the primary outcome, confirmed by a positive immunological test (anti-SARS-CoV-2 IgM reactive). The secondary outcomes will be related to the clinical status of the disease presented by the participant, such as severity (need for hospitalisation, need for oxygen therapy, need for non-invasive and invasive ventilatory assistance, and need for haemodialysis), and death; treatment abandonment and drug safety (adverse reactions, evaluated up to 48 hours after the treatment). **Ethics and disclosure**: This preventive trial is part of the Clinical Trial approved by the National Commission for Research Ethics (CONEP), number 31523220.0.1001.0008 on 06/06/2020, before enrolling the first participant in the study. An independent safety monitoring committee is responsible for the direction of safety oversight of the trial conduction. The results of this research will be disseminated in oral presentations, in national and international meetings of medical specialities, and on the Scinet Institute website and published in the form of scientific articles in indexed journals. The authors have no financial conflict of interest.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) emerged in December 2019 in Wuhan, China, as a cluster of severe pneumonia cases with an unknown aetiological agent and later identified as a highly transmissible coronavirus (SARS-CoV-2) (1)(2)(3)(4). Infected individuals who develop COVID-19 may present different clinical manifestations, such as fever, continuous cough, sore throat, headache, muscle ache, diarrhoea and asthenia (2)(4). In addition, COVID-19 can trigger complications involving inflammatory and thrombotic processes, with systemic repercussions, and renal, cardiac and neurological lesions, among other more severe consequences, including death (5)(6)(4)(7)(8). Regarding COVID-19 transmission, the main route of infection is via the inhalation of saliva droplets or aerosols (9), which may be present in the air after a symptomatic or asymptomatic infected person coughs, sneezes or breaths without a mask, or via respiratory secretions containing SARS-CoV-2 inhaled by a person immunologically susceptible to infection by this virus (10–13). One aspect that hinders the control of transmissibility is that a significant portion of individuals infected by SARS-CoV-2 may not have clinical symptoms (14), considered asymptomatic carriers, who carry the virus in the airways eliminate it in the form of droplets and aerosols (15).

The standard intervention for the control of communicable infectious diseases is vaccination (16)(17)(18), which reduces transmissibility, illness, and death (19), i.e., brings substantial epidemiological impacts. For example, in Brazil, the National Immunizations Program (NIP), created in 1973, includes fifteen vaccines for children, nine for adolescents, and five for adults and elderly persons (20). Furthermore, the adoption of childhood vaccination programmes has been evident and highly cost-effective in reducing child mortality worldwide (21)(22).

Vaccination against COVID-19 is a control strategy recommended by the World Health Organisation (WHO) (23), Centers for Disease Control and Prevention (CDC) (24), a national public health agency of the United States and the Brazilian Ministry of Health (25). However, at the pandemic's beginning, no vaccination program was possible due to the lack of a vaccine against COVID-19 (26)(27). Moreover, after developing them, the supply was limited. In this context, Brazil followed the WHO recommendations and prioritised groups at higher risk of complications when defining the Covid-19 vaccination schedule (28) (25). In Brazil, the first registered vaccines against COVID-19 through emergency approvals on 17 January 2021 (25)(29)(30), and data on their efficacy and safety were limited (31).

Essential control measures involving environmental and behavioural changes to minimise exposure to SARS-CoV-2 are recommended (32)(33) and continue to be indicated to contain the spread of and infection by this virus (34)(35) through collective and individual measures, such as social distancing, mask use, frequent hand washing, hand and surface disinfection, and large-scale vaccination campaign initiatives (25). However, despite efforts to reduce SARS-CoV-2 transmission, the COVID-19 pandemic is not yet under control (36)(37).

Another vital strategy for the control of endemic or epidemic infectious diseases is chemoprevention using a drug with high clinical safety and efficacy in controlling the spread and transmissibility of the pathological agent to reduce the incidence of the disease and the burden of morbidity (38) alone or in combination with environmental control measures or vaccination (39). Examples include programmes through mass treatment to control onchocerciasis and lymphatic filariasis (38). Clinical trials show the efficacy of these strategies, and recently, the superiority of the combination of chemoprophylaxis and vaccination for the control of malaria was demonstrated (40).

Ivermectin was approved for clinical use in 1987 (41) and is widely used in many countries to treat a series of endo- and ectoparasitic diseases (41)(42). It is a safe drug that has few and mild side effects (43)(44)(39) and has been used in a mass treatment strategy in Africa since 1987 to control onchocerciasis,

a leading cause of blindness on that continent (41)(45). The WHO was the African Programme for Onchocerciasis Control (46) executive agency, which substantially reduced blindness on that continent, resulting in the two scientists who discovered ivermectin winning the 2015 Nobel Prize in Medicine and Physiology (47).

In Brazil, vaccination against COVID-19 started on 18 January 2021 (25). By 12 October 2021, 150 million Brazilians had received the first dose of the COVID-19 vaccine (48), with 62% of the campaign's target population completing the vaccine cycle in October 2021 (49). Nevertheless, the COVID-19 incidence and death rates remain high, presenting 601,574 deaths on 13 October 2021, with mortality rates of 286.3/100,000 inhabitants and lethality of 2.8% (37). The limitation of vaccination to block SARS-CoV-2 transmissibility results from both the scarce supply of vaccines for the population, resulting in slow vaccine administration and, consequently, low vaccination coverage, as well as the emergence of new SARS-CoV-2 variants (50)(51), considered by the WHO as variants of concern (VOCs) (52), which escape the action of neutralising antibodies induced by either, vaccines, natural previous SARS-CoV-2 infection, or both (53, 54). The emergence of the Alpha, Beta, Gamma and Delta VOCs (53) has hindered the control of SARS-CoV-2 transmission (52)(55)(56).

The Gamma VOC (initially named P1) of SARS-CoV-2 emerged in Brazil in the city of Manaus in December 2020, presenting mutations conferring evolutionary advantages to the virus, such as the ability to more easily infect host cells and trigger COVID-19. As a result, it shows a high viral replication load, approximately 3-4 times higher than for the original SARS-CoV-2 strain in Wuhan, China, in 2019; an increase in mortality from 1.1 to 1.8 times (53); and a reduction in the protective capacity of neutralising antibodies resulting from vaccination (54). In Manaus, the Gamma VOC caused an outbreak of COVID-19, resulting in a high lethality rate and the health system's collapse in that city (57). The increased incidence of COVID-19 was associated with severe forms and a substantial increase in the number of deaths in May 2020 (58). Excess mortality in Manaus occurred predominantly in the 60 years or older age group and young people, both in the hospital and in the home environment (58)(59). In addition, the Gamma VOC emerged when the population of Manaus had a high serological prevalence of the previous infection with SARS-CoV-2, with anti-immunoglobulin G antibodies detectable in 76% of this population (95% confidence interval (CI) 67–98) based on studies that included blood donors (58)(60). Therefore, the Gamma VOC outbreak in Manaus contradicted the population's expectation of protection against COVID-19 outbreaks based on herd immunity (58)(60). In Massachusetts, individuals vaccinated against COVID-19 were protected from severe forms, but the vaccine did not entirely prevent the transmission of the SARS-CoV-2 Delta variant; i.e., 75% of those infected were fully vaccinated (56).

Identifying a drug alternative with high clinical safety and low costs and is easily acquired by the population and the health system would bolster efforts to reduce the transmissibility of SARS-CoV-2, with a consequent reduction in the impact of the COVID-19 pandemic. In 2020, Caly et al. showed evidence of the antiviral effect of ivermectin on SARS-CoV-2 in vitro (61), a finding that led to the initiation of clinical studies with this drug. Evaluations of the prophylactic and therapeutic effects of ivermectin on COVID-19 in ecological studies (62), case-control studies (63), randomised clinical trials and meta-analyses have indicated that ivermectin may reduce the SARS-CoV-2 infection rate (64), the transmissibility and mortality associated with COVID-19 (65–68); however, the efficacy of ivermectin is still controversial (69)(67). A preclinical study with ivermectin using golden Syrian hamsters with COVID-19 and a single dose of 400 μg per kg improved the disease manifestations with immunomodulatory effects (70). In this context, ivermectin is a possible prophylactic pharmacological intervention that reduces the transmissibility of SARS-CoV-2. Given the promising findings regarding the clinical efficacy of ivermectin in reducing the incidence of COVID-19, clinical trials are recommended to evaluate the existence and magnitude of this effect, aiming to use a mass treatment strategy as an adjuvant measure in combating the COVID-19 pandemic. Thus, to test the hypothesis that ivermectin reduces the transmissibility of SARS-CoV-2, this protocol proposes a double-blind, randomised clinical trial that evaluates the efficacy of this drug in preventing COVID-19 in asymptomatic and immunologically susceptible adults. The research hypothesis is that a single dose of ivermectin, combined with the usual recommended protective safety measures,

significantly reduce the number of new cases of COVID-19 compared with the prophylaxis recommendations alone.

METHODS AND ANALYSIS

Administrative structure

This study is sponsored by a non-governmental resource, the Scinet Clinical Research Institute and a governmental resource, the local Brazilian National Health System (SUS, acronym in Portuguese). The Scinet Clinical Research Institute is responsible for conducting the study, training the personnel and managing the data. In addition, the Keizo Asami Immunopathology Laboratory (LIKA, for its acronym in Portuguese) of the Federal University of Pernambuco (Recife, Pernambuco, Brazil) monitors safety.

The compounding pharmacy Fórmula Farmácia de Manipulação (Recife, Pernambuco) and its pharmaceutical team are responsible for preparing the ivermectin and placebo capsules and for the randomisation and blinding of the trial. A senior statistician blinded to the type of intervention each patient will receive will enter the data collected from the groups into IBM SPSS version 25. This database will be analysed using the same software. The IvermecPrev-Brazil Management Committee comprises the scientific director of Scinet Institute, the principal investigator, LIKA's scientific advisers, and the local researchers from the study setting in the family health units of the Brazilian National Health System (SUS, acronym in Portuguese). This committee will collaboratively supervise all study design and protocol implementation aspects. In addition, an independent safety monitoring committee will be responsible for advising whether the trial should continue, be modified or be discontinued based on the results of severe adverse effects on participants.

Study design

This trial involves a drug intervention to prevent COVID-19, and the study design is a phase III, two-arm, double-blind, randomised and placebo-controlled trial with two arms. All participants must be adult, asymptomatic for COVID-19, without prior immunity and naturally exposed to SARS-CoV-2 during the COVID-19 pandemic in 2020, 2021 and 2022. We conduct this study in a primary care clinic with a 90-day follow-up. **Figure 1** shows an overview of the study design.

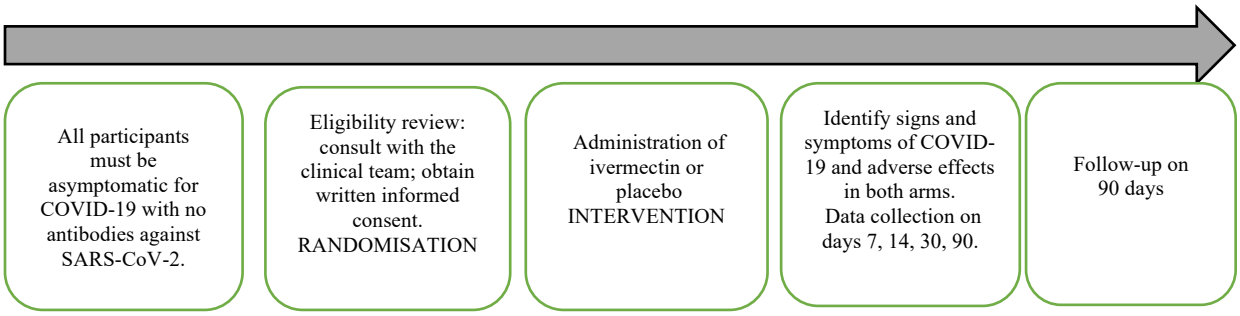

Figure 1. Overview of the study design (IvermecPrev-Brazil).

Development of the IvermecPrev-Brazil trial protocol

This protocol is part of the trial proposed and approved by the National Commission for Research Ethics (CONEP) under n. 31523220.0.1001.0008 and aims to investigate whether ivermectin, at different doses, can reduce the viral transmission of SARS-CoV-2 and be used to treat COVID-19.

In the protocol for the present trial, IvermecPrev-Brazil, we study the preventive condition; adult population in two arms trial to, i.e., an intervention arm and a control arm; use one single-dose, 400 µg/kg

body weight, in the intervention arm and placebo in the control arm; follow-up time of 90 days; a sample size of 600 participants.

This protocol is related to an ongoing trial available on the ISRCTN registry webpage: https://www.isrctn.com/ISRCTN90437126. The start date of participant recruitment was 15/09/2020, with a scheduled end date of 25/02/2022. The end date for collecting data will be 27/05/2022.

Study population

Adult patients aged 18 years or older, clinically asymptomatic for COVID-19 and do not present any immune response against SARS-CoV-2.

Participant eligibility

To be eligible for the trial, we must confirm that the participants are clinically asymptomatic for COVID-19, without previous SARS-CoV-2 infections and not vaccinated against this virus. Therefore, they must meet the inclusion criteria of adults not reporting past COVID-19, not showing signs or symptoms of COVID-19 and being negative for anti-SARS-CoV-2 IgM and IgG. To exclusion, we defined those who report at least one of the following: having allergies to ivermectin, using coumarin anticoagulants, or having previous neurological disease or trauma that compromised the blood-brain barrier. All the eligible participants have to sign the informed consent form to be enrolled. We will use three Case Report Form (CRF), CRF-01 and CRF -02 to all participants and CRF 03 for hospitalised (Supplements 1) to assess baseline data and primary and secondary outcomes.

Randomisation and blinding

After enrolment, all participants will be randomly allocated to the intervention or control groups using a 1:1 block randomisation scheme. Randomisation will be performed by generating a random sequence, in blocks, by an independent pharmacist. Participants, researchers and community health agents will not know about the treatment. The researchers, including the field data collection team, the community health agents and the statistician, will remain blinded to the study results until completion. After that, however, the patient safety monitor and the Data Safety and Monitoring Board (DSMB) can access the non-blinded study data. The randomisation codes will only be revealed after each group's complete data collection and analysis unless any severe adverse outcome occurs.

The pharmacist in charge performs blinding. Based on randomisation into blocks of ten treatments, the study site will distribute opaque and sealed packets with standardised treatments containing ivermectin in the form of a 12 mg capsule or placebo capsules alphanumeric codes linked to the randomisation sequence. The independent pharmaceutical researcher responsible for the treatment and the randomisation lists will not be part of the data collection or analysis teams. The placebo composition is 25% corn starch, 5% colloidal silicon dioxide, and microcrystalline cellulose 101 in sufficient quantity to reach 100% will be used; the contents will be packaged with the same external characteristics as those of the intervention drug, which is available in capsule form, and with identical visual and tactile aspects.

Allocation

After randomisation, each participant will be allocated to one of two groups: the intervention group, which will use ivermectin, or the control group, which will use a placebo. Study participants eligible for the trial will be randomly allocated to receive single oral doses of placebo or ivermectin. All participants will receive prophylaxis guidelines standardised by the health service.

Variable measures and forms

The following variables will be measured before the beginning of the study: age, sex, occupation, body weight, housing conditions (number of residents and number of rooms), protective measures adopted (mask use outside the home), contact with a COVID-19 patient in or outside the home in the last 14 days, signs and symptoms of COVID-19, and comorbidities (hypertension, diabetes, kidney injury, asthma, rheumatoid arthritis, systemic lupus erythematosus, and allergies).

For this protocol, we use three CRF: CRF-01 for assessing the participant eligibility, CRF-02 to collect baseline, intervention and outpatient follow-up data; and CRF-03 used to collect hospital follow-up data for severe or critical cases.

Intervention group

For participants randomly allocated to the intervention group, ivermectin in capsules will be administered orally. The treatment will be administered in only one day, in a single dose of 400 μg/kg body weight.

Control group

For participants randomly allocated to the control group, a simulated drug as placebo capsules will be administered in only one day, in a single dose.

Data collection

The following baseline data will be recorded:

1. SUS identification number and affiliated SUS health unit
2. Immunological status (previous SARS-CoV-2 infection, i.e., negative for anti-SARS-CoV-2 IgG and IgM)
3. Exposure to SARS-CoV-2 in the workplace or through intra-household contact with a recent COVID-19 patient and behavioural habits (mask use outside the home)
4. Demographic data (age, sex)
5. Comorbidities
6. Confirmation of the absence of clinical signs and symptoms for COVID-19

Outcomes

The primary and secondary outcomes will be verified and recorded during the *follow-up* performed for the two study arms for 90 days (7,14, 30 and 90) counted from the day of the intervention.

Primary outcome

The primary outcome will be the diagnosis of COVID-19 (conversion of the pre-treatment status from asymptomatic and non-immune to symptomatic COVID-19 and immune reactive post-treatment, presenting IgM anti- SARS-CoV-2 positive). The presence of clinical manifestations among the participants will be evaluated using a questionnaire for the clinical signs and symptoms of COVID-19 (CRF-02 Supplement 1). After confirming the presence of signs suggestive of COVID-19, anti-SARS-CoV-2 IgM and IgG serological tests will be performed to confirm the diagnosis.

Secondary outcomes

The secondary outcomes will be grouped into two blocks related to (1) efficacy assessing morbidity and mortality due to disease progression and (2) safety verifying adverse effects (Table 1). It shows the types of secondary outcomes by time of assessment and measure tools.

We will use the following study CRFs (Supplement 1) and international scales according to the secondary outcome of interest: (a) CRF 01 and 02 to collect outpatient data; (b) CRF 03 (Supplement 2) to collect data from a hospital stay, using patient records; (c) the WHO Clinical Progression Scale measured to assess clinical changes in the timeline; (c) using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 to graduate severity, and (d) the national mortality information system (MIS) to verify mortality outside the local health system (Table 1).

The secondary outcomes will be grouped into two blocks: related to morbidity and mortality and treatment safety (**Table 1**).

Table 1. Secondary outcomes of the COVID-19 related to morbidity and mortality and clinical safety of treatment using a single dose of ivermectin (400 μg/kg).

COVID-19 related morbidity and mortality outcomes	
Clinical status of flu-like symptoms (presence or absence).	The clinical status of COVID-19 will be assessed using the WHO Clinical Progression Scale measured on days 14 and 30 after a diagnosis of COVID-19 (if applicable).
Occurrence of severe cases of COVID-19	The incidence of severe cases of COVID-19 will be determined by the detection of active cases and defined by the WHO clinical scale on days 14 and 30 after treatment.
Need for hospitalisation; length of hospital stay; need for ICU admission; length of ICU stay; need for ventilatory assistance; and duration of ventilatory assistance	Hospitalisation rate; length of stay (in days); ICU admission rate; length of stay (in days) in the ICU; and use of ventilatory assistance. Days of use of ventilatory assistance will be recorded on days 7,14, 30 and 90.
Death by COVID-19	Death during the follow-up period (90 days) will be verified by the team of field researchers from medical records (if applicable) and by consulting the national mortality information system (MIS).
Safety outcomes related to the use of ivermectin	
Occurrence of adverse reactions The severity of the adverse reaction identified	Rate of adverse events, based on the detection of active cases with a questionnaire, and the determination of adverse events (mild, moderate and severe) using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 on days 2 and 7 after treatment.
Adherence to treatment	Administration of the treatment with pill count with confirmed ingestion of the pills in the presence of a research member team.

Outcome measure results

In the two trial groups, the participants will be monitored for 90 days, after treatment, through home visits made by the research team on days 7, 14, 30 and 90. During these visits, data will be collected via questionnaires regarding the conditions presented by the participant to determine the occurrence of clinical

manifestations of COVID-19; symptomatic patients will be referred for confirmatory testing (primary outcome) at the family health unit.

Confounding factors

a) Susceptibility to severe forms

During the COVID-19 pandemic, evidence has shown that certain groups of patients tend to have a higher chance of progressing to severe COVID-19 because they have chronic diseases, advanced age, obesity or other comorbidities (72). However, it was decided not to exclude such individuals from the present study because they constitute an essential population contingent. The use of randomisation will reduce the bias associated with these conditions. The presence of chronic comorbidities (pre-existing diseases) and weight, height, age and sex will be collected, and we will analyse the effect of such factors on the study results.

b) Environmental exposure to the SARS-CoV-2 virus

Data will be collected on work status, education level, number of people in the household, number of rooms in the home and presence of COVID-19 patients in the same household.

Statistical methods

Sample size estimation

The sample size was calculated for the primary dichotomous outcome presence or absence of COVID-19 disease, assuming a type I error (alpha error) of 0.05, a power of 95%, a primary outcome event rate of 95% in the control group (p2 in the control group) and of 85% in the treatment group (p1 in the treatment group) (71). The sample size was calculated in G*Power version 3.1.9.2 using the two-tailed Fisher's exact test to compare the two proportions, with equal sample sizes in both groups. The calculation resulted in 239 participants for each group. With an estimated loss to follow-up of 20%, the sample size calculated for the primary outcome was 287 participants in each group.

Storage and Data analysis

The statistical software IBM SPSS version 25 will be used for data storage and analysis. The data will be analysed descriptively using absolute frequencies and percentages for the categorical variables and measures of central tendency (mean, standard deviation, median and 25th and 75th percentiles) for numerical variables.

For categorical variables, for comparisons between the two groups or categories, the Pearson chi-square test or Fisher's exact test will be used when conditions for the chi-square test are not met. For numerical variables, the Student's or Mann–Whitney tests will be used to compare two groups or two categories, and the F (ANOVA) or Kruskal–Wallis tests will be used to compare more than two categories. In the comparisons between evaluations, the McNemar test will be used for categorical variables and the F test (ANOVA) or Friedman test for numerical variables. In the presence of significant differences by the F (ANOVA), Kruskal–Wallis or Friedman tests, appropriate multiple comparisons will be performed for each test between pairs of categories or evaluations.

Other measures calculated will be the absolute and relative risk (AR and RR), with their respective confidence intervals, reduction in the respective measures (RAR and RRR), number needed to treat (NNT), variation in means between evaluations (decrease or increase), and effect size to evaluate the magnitude of the differences, by Cohen's d method.

Survival analysis techniques will be used to evaluate the time until the primary outcome (COVID-19). In addition, the log-rank and Peto-Peto tests will be used to test the difference between groups or categories regarding survival, and Cox proportional hazards regression analysis will be performed.

The Shapiro–Wilk test will test data normality, and Levene's F test will test the equality of variance. The significance level used for the statistical tests will be 5%, and 95% CIs will be calculated. Data entry and statistical calculations will be performed in IBM SPSS, version 25.

Interim analysis and trial interruption

The independent safety monitoring committee may interrupt the trial for safety reasons at any time in case of severe adverse effects. We do not propose an interim analysis or an early stop rule to evaluate efficacy before collecting data from the calculated sample. The sample size to determine the CI for the parameters would be insufficient for fixed reliability.

Safety and ethics

Safety data will be verified and recorded via the detection of cases of adverse events using CTCAE V5.0, with the application of a specific questionnaire on days 2 and 7 after treatment administration. *Adverse events* will be defined as "unexpected" or "expected", classified by severity (mild, moderate, severe, life-threatening or death) and categorised as "severe" or "non-severe". As our population of participants is, by definition, non-hospitalised and asymptomatic for COVID-19, it is expected that the participants will not have severe adverse events. In addition, ivermectin is safe and widely used in mass treatment programmes with large populations (41)(45). Therefore, we will limit the scope of monitoring and recording of severe adverse events, which will be defined as follows: (a) death related to the treatment used in the study or an unexpected death unrelated to the drug, and (b) a life-threatening experience that is believed to be related to the drug.

Role of the independent safety monitoring committee

Safety oversight will be under the direction of an independent safety monitoring committee. All severe adverse effects will be reported to this committee and CONEP within 24 hours, online, after the research team is notified of the adverse event, followed by a detailed report. In addition, the centres will inform the sponsor of the clinical trial of any related events (non-severe) within 14 days after being identified. The sponsor will prepare summaries of all reports and provide them to the independent safety monitoring committee for each record of a severe adverse event.

Ethics approval

Approval of the clinical trial protocol and forms, including the informed consent form, were obtained from the National Research Ethics Committee (CONEP) of the Ministry of Health under CAAE n. 31523220.0.1001.0008 on 06/06/2020 before enrolling the first study participant.

DISCUSSION

The expected contribution of the study is to generate knowledge to answer if ivermectin reduces COVID-19 incidence when administered in a single dose to asymptomatic participants susceptible to SARS-CoV-2 infection, during a highly transmissible period, COVID-19 pandemic in 2020-22. This trial aims to determine whether participants treated with ivermectin have a significantly lower incidence of COVID-19 than those who did not receive the drug. In addition, the present trial purposes of evaluating, among participants who acquired COVID-19, whether the disease is less severe in those who receive a single dose of ivermectin than those who did not receive it. Another relevant aspect is that this drug is

available through the SUS, is low-cost and has a good safety profile. Last, the contribution of this study will depend on the results obtained. If the efficacy of that preventive treatment using ivermectin in reducing the incidence of COVID-19 will be confirmed, recommending its use in mass treatment as a protective prophylactic pharmacological measure might be considered and significantly impact the prevention of disease outbreaks in populations susceptible to SARS-CoV-2.

Collaborators: Denia Palmeira Fitipaldi Duarte and Taciana Padilha de Castro participated in the protocol's design, writing, revising the manuscript, and final approval of the submitted version. The sample size calculations and the statistical analysis plan were supervised by Prof. José Edmilson Mazza Batista, statistician and retired professor from the Department of Statistics, Federal University of Pernambuco, Brazil. The randomisation of participants and the blindness plan of the treatment was performed by an independent pharmaceutical researcher Tibério Silva Medeiros. Finally, the trial methodology of the manuscript was supervised by Prof. Sabrina Joany Felizardo Neves from the Institute of Pharmaceutical Sciences, Centre for Studies in Pharmacotherapy, Federal University of Alagoas (Universidade Federal de Alagoas – UFAL, Brazil)

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