Title: Efficacy, Safety and Tolerability of Ivermectin in Subjects Infected With SARS-CoV-2 With or Without Symptoms "SILVER BULLET"

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Protocol

Content

1. Background

1.1 COVID-19

At the end of 2019, an unidentified viral type pneumonia was detected in Wuhan, China. Later, it was declared that it was pneumonia due to a new coronavirus. The WHO officially called it COVID-19 disease (1),and the international virus taxonomic committee called the virus acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2).

SARS-CoV-2 belongs to the β-coronaviruses, a large class of viruses prevalent in nature. Like other viruses, SARS-CoV-2 has several natural hosts, its genetic similarity with the SARS bat coronavirus indicates that it is probably originated in bats, which presents many challenges in the prevention and treatment of infection of this virus. Compared to SARS and Middle East respiratory syndrome (MERS), this virus has a high rate of transmission and infection (1).

The World Health Organization, in its report of April 8, 2020, showed a total of 1,353,361 infected cases and 79,235 deaths worldwide (3).

1.1.1 Clinical picture of the disease

The clinical presence of COVID-19 closely resembles viral pneumonias such as SARS and MERS. Most of the cases are mild (81%), and their symptoms and recovery occurs in two weeks (1).

The reported symptoms (listed from highest to lowest frequency) are: fever, cough, myalgia or fatigue, dyspnea, headache, diarrhea, palpitations, hemoptysis, and expectoration (4).

Regarding laboratory findings, a significant decrease in the number of lymphocytes is observed; those who did not survive developed greater lymphopenia over time. They show a high concentration of pro-inflammatory cytokines: interleukins 2,7 and 10 (IL-2, IL-7, IL-

10), granulocyte colony stimulating factor (GSCF), the chemokine IP-10; monocyte chemotactic protein 1 (MCP1), macrophage inflammatory protein 1A (MIp1A) and tumor necrosis factor alpha (TNFα); which are even higher in patients who are in intensive care compared with those who are not. Similarly, patients in intensive care have higher levels of D-dimer, neutrophils, leukocytes, creatine kinase, and creatine (1).

Viral load in throat swab and sputum samples has been observed to peak 4-8 days after onset of symptoms (5).

Serious cases of the disease have been defined by the appearance of some of the following four criteria (6):

1. Shortness of breath (≥30 breaths per minute);
2. Oxygen saturation at rest ≤93%;
3. Relationship between arterial oxygen partial pressure and fractional concentration of inspired air in oxygen ≤300 mmHg;
4. Severe complications such as respiratory failure, need for mechanical ventilation, septic shock, non-respiratory organ failure.

1.1.2 Risk factors for morbidity and mortality

As for other viral respiratory diseases such as influeza A H1N1, SARS-CoV-1 and MERS, a high prevalence of diabetic patients with COVID-19 has been observed, and the presence of this is a determinant of the severity and mortality of the subjects. Glycemic control is important for all subjects with these pathologies, since subjects with glycated hemoglobin levels greater than 9% have a 60% risk of being hospitalized for pneumonia. In addition to diabetes, the presence of other chronic-degenerative diseases has been associated in patients with COVID-19, such is the case of systemic arterial hypertension, with up to 11% of cases, and cardiovascular diseases, up to 8% of the cases. Other less related co-morbidities are: chronic obstructive pulmonary disease (COPD), chronic kidney disease and chronic liver disease (7).

1.1.3 Vaccination schedule and possible immunity

Interestingly, Miller et al. Conducted an epidemiological analysis where they managed to negatively correlate the death rate from COVID-19 and the vaccination policies for Bacillus Calmette-Guérin (BCG) tuberculosis. They observed that, in countries where the national BCG vaccination scheme began in the 1950s, the mortality rate is lower; This is perhaps due to the immunity it provides to the elderly population. In countries where there is no BCG vaccination policy, such as Italy and the United States, the mortality rate is higher (8). In Mexico, the national vaccination scheme includes the BCG vaccine since 1951, so understanding its effect on Mexican patients with COVID-19 is of special interest (9).

1.1.4 Treatments

There is currently no standard treatment for COVID-19

1.1.5 Paracetamol

Although a standard therapy has not been established, it has been suggested, for the management of symptoms such as fever and pain, that the first line of treatment is paracetamol, over other non-steroidal anti-inflammatory drugs (NSAIDs) (10–12).

1.2 Ivermectin

Ivermectin is a broad spectrum antiparasitic agent, developed to combat parasitic worms in veterinary use and in human medicine. This compound has been used in humans, orally, to treat filariasis, but it is also effective against other infections associated with worms, as well as parasitic skin diseases and infections by insects. It is approved for human use in several countries, to treat onchocerciasis, lymphatic filariasis, strongyloidiasis and scabies, and recently in hair pediculosis. When avermectins were discovered, they represented a new class of compounds that kill various ranges of disease-causing organisms, as well as vectors of pathogens, inside and outside the body. Ivermectin is a semi-synthetic mixture of two chemically modified avermectins, comprising 80% 22,23-dihydroavermectin B1 and 20% 22,23-dihydroavermectin-B1b.

Other diseases that have been treated with ivermectin are: trichinosis, vector insects, malaria, trypanosomiasis, allergic asthma, rosacea, bed bugs, schistosomiasis, Chagas disease, epilepsy, neurological diseases. In addition, it has been observed to have antibiotic and anticancer effects (13).

In turn, Ivermectin has been described as a broad spectrum antiviral, inhibiting nuclear import due to its ability to inactivate host nuclear transport proteins, such as integrase and NS5, limiting the ability to infect western viruses. of the Nile in low concentrations (14), as well as inhibiting the replication of the yellow fever virus and other flavoviruses, such as dengue, and encephalitis, probably attacking the activity of non-structural helicase 3 (13).

1.2.1 Pharmacokinetics

Oral consumption is the only one approved for human use so far.

1.2.1.1 Absorption

In healthy subjects who received 12 mg of ivermectin in oral solution, tablets or capsules, the solution was shown to have twice the systemic availability compared to the solid presentations, while the capsules and tablets showed similar availability. The absorption rate was similar in all three cases (15).

1.2.1.2 Distribution

Because ivermectin is fat soluble, this compound is widely distributed in the body. In healthy subjects, the volume of distribution in the central compartment, Vc, was 3.1 and 3.5 l · kg − 1, after ingesting 6 and 12 mg of ivermectin respectively (15).
Distribution to the brain is hampered by the blood-brain barrier, this is mediated especially by the size of the molecule and is not driven by passive diffusion (17). Ivermectin is strongly bound to plasma proteins (93.2%) with specific affinity to albumin (15).

1.2.1.3 Disposal

Ivermectin is metabolized in liver microsomes by cytochrome P450, the predominant isoform of the biotransformation of this compound in the liver is P-4503A4, converting this drug to at least ten metabolites, most of them hydroxylated and demethylated derivatives . Its excretion occurs mainly through feces and only 1% is excreted in urine (15).

1.2.2 Pharmacodynamics

1.2.2.1 Mechanism of action

In invertebrates, ivermectin blocks sympathetic transmission by binding to glutamate input chlorine channels in nerves and muscles, resulting in hyperpolarization, paralysis, and death of invertebrates (mosquitoes, worms). These channels are part of a family of linked cis-loop ion channels, and ivermectin has shown effects on other members, such as GABA, histamine, and pH-sensitive chlorine channels (16,17).

1.2.2.2 Interactions

The pharmacological interactions of ivermectin in humans have been evaluated, mainly, according to its capacity as an antiparasitic. The combination of ivermectin with doxycycline is highly effective in the treatment against onchocerciasis and filariasis, even more so than if ivermectin is used as the only therapy (15).

No effects on the kinetics of albendazole, amorcazine or levamisole have been observed in parasitic diseases when given in combination with ivermectin compared to monotherapy, nor was there a change in the efficacy of these drugs, however, levamisole combination therapy increases the bioavailability of ivermectin in plasma (15).

In other animal models, drug interactions have been observed that compete for the binding site of transporter proteins, such as P-glycoprotein (P-gp), which is located in various tissues (intestine, blood, liver, kidney). For example, verapamil, an anti-hypertensive drug, produces higher plasma ivermectin levels in rats and sheep. Effects similar to those of

verapamil have been observed with the antifungals ketoconazole (in dogs and ruminants) and itraconazole (in sheep and rats). In mice, an increased neurotoxicity of ivermectin has been observed when combined with the immunosuppressant cyclosporine A, or the antipsychotic trifluoperazine. On the other hand, in horses, a decrease in the availability of fexofenadine was observed when a previous treatment with ivermectin was given orally, but not when it was administered by vein. In vitro, ivermectin increased the amount of moxidectin in rat hepatocytes (18).

1.2.3 Safety and tolerability

Ivermectin, at a dose of 150-200 mcg / kg, is the first line of treatment for river blight disease (onchocerca volvulus), lymphatic filariasis, and strongyloidiasis.

The French authorities approved ivermectin for humans in 1987. Shortly thereafter, Merck & Co Inc donated ivermectin for the control of onchocerciasis. Since then, more than two billion treatments have been distributed in Africa and Latin America for onchocerciasis and lymphatic filariasis (19,20).

In this context, ivermectin adverse events have been mild, transient, and associated with the intensity of the infection. No significant association has been found between plasma ivermectin levels and adverse events.

Neurological adverse events include: encephalopathy and coma after administration in patients infected with Loa loa. These reactions were associated with microfilarial discharge due to parasite lysis and not with drug toxicity (20).

According to the FDA SmPC, the adverse events observed with ivermectin include: asthenia / fatigue (0.9%), abdominal pain (0.9%), anorexia (0.9%), constipation (0.9%), diarrhea (1.8%) , (1.8%), vomiting (0.9%), dizziness (2.8%), drowsiness (0.9%), vertigo (0.9%), tremors (0.9%), itching (2.8%), skin irritation (0.9%) and urticaria (0.9%) (16).

7.2.4 Use in children, pregnancy and lactation

The use of ivermectin is allowed in children weighing more than 15 kg.

In a prospective study in Liberia, where 200 pregnant women were treated (inadvertently), no differences were observed in rare birth defects, growth status, or disease patterns compared to untreated mothers in the same population. These findings have been confirmed in hundreds of women in northern Cameroon, Mali, Ghana, and Uganda, where pregnant women are not excluded from ivermectin treatment.

Ivermectin levels in breast milk are low. After a dose of 150 mcg / kg in healthy women, levels of 14.12 ± 0.43 ng / ml were found after 6.5 hours. Therefore, a newborn would obtain a dose of 2.75 mcg / kg, so it is not recommended to exclude lactating women in endemic places from the onchocerciasis scheme (20).

7.2.5 Dosage

A range of doses has been indicated for different indications.

The Food and Drug Administration (FDA) approved dose for strongyloidiasis is 150 mcg / kg (annually) (16). The French authorities recommend up to 400 mcg / kg for the control of lymphatic filariasis (21). In the United States (22)and Australia (23) up to seven doses of 200 mcg / kg in one month are recommended for severe scarring scabies, in combination with topical treatment. The Australian label includes the possibility of using more than 3 doses for the treatment of moderate or severe scabies (24).

In the Guzzo et al study, they administered a dose ten times higher than the recommended dose to 16 healthy volunteers in the United States, and they did not report a much higher rate of adverse events than controls (25).

The Center for Disease Control and Prevention has recommended doses of up to 1,400 mcg / kg in one month for the treatment of severe scabies(22).

7.2.5.1 Dosage as antiviral

Although ivermectin has not been approved for use as an antiviral, a search was carried out for clinical protocols registered in the National Library of Medicine (ClinicalTrials.gov), in which ivermectin with antiviral function is being used; the search returned two clinical studies for COVID-19 registered as of April 16, 2020, which included:

1. For patients with COVID-19, in which the dose to be administered is not documented (26).

2. For patients with COVID-19, where you will use a dose of 0.2 mg / kg weekly; administered as 2 tablets of 6 mg each (27).

In addition to these two protocols, a third was found aimed at pediatric patients with dengue, where a dose of 400 mcg / kg / day, two or 3 consecutive days, will be used as the only scheme (28).

The results of such clinical studies are still unknown, however, they may provide guidance on possible dosages for the use of ivermectin as antiviral therapy.

Very recently, Wagstaff et al. Published preliminary in vitro studies in Vero/hSLAM cells cultures, where they observed a 5000-fold reduction in the viral RNA content of cells infected with the SARS-CoV-2 virus, treated with a single dose of ivermectin, compared to control at 48 hours (29).

Ivermectin has been used for more than three decades to treat parasitic infections in mammals and has a very good safety profile: even doses well above those approved by the FDA showed good tolerability, with numerous studies reporting low levels of adverse events in treatment. orally for parasitic infections.

2. Justification

This is a multicenter, randomized, double-blind, placebo-controlled study in adult subjects diagnosed with COVID-19 by RT-PCR; asymptomatic or with mild symptoms, with placebo of ivermectin for 3 days in combination with paracetamol for 14 days 500 mg QID or ivermectin (12 mg / day) for 3 days in combination with paracetamol for 14 days 500 mg QID, in addition to base therapy.

A randomized double-blind design is used to control for bias in the reporting of safety, efficacy, and biological activity data and in the selection of subjects.

Ivermectin therapy has not been tested in subjects with COVID-19 and is therefore intended to be used as adjunctive therapy; therefore, all study subjects will receive ivermentin or placebo in addition to the therapy that their treating physician deems appropriate. Since ivermectin is in an early phase of clinical development, the use of base therapy will ensure that all subjects, including subjects randomized to placebo, have the benefit of receiving treatment with the base therapy that is available.

The use of placebo will allow discrimination of the efficacy and tolerability profile of ivermectin treatment in conjunction with the recommended therapy and in comparison with the use of recommended therapy.

The use of the dose (12 mg / day, for 3 days) is justified in relation to the levels reported as safe (200-400 mcg / kg / day) in parasitic diseases, in addition to the fact that they are doses similar to those used in trials clinicians with antivirals, one of them also for COVID-19.

3. Objectives

3.1 Main objective

The main objective of this study is to evaluate the efficacy, safety and tolerability of ivermectin in patients with mild SARS-CoV-2 infection, at the rate of progression to severe COVID-19.

3.2 Secondary objectives

• Quantify the replication rate of the SARS-CoV-2 virus 5 and 14 days after diagnosis quantitatively by real-time RT-PCR.

• Evaluate the presence and frequency of symptoms associated with the COVID-19 disease (fever, cough, myalgia, fatigue, shortness of breath, headache, diarrhea and expectorations) daily for 14 days.

• Investigate the presence of adverse events associated or not with the study drug for 14 days.

• Look for associations between the morbidities of the evaluated subjects and the intensity of the disease.

• Look for a relationship between medical history of BCG vaccines and the intensity of the disease.

• Evaluate the frequency of death in subjects associated with COVID-19.

4. Hypothesis

The primary efficacy endpoint is defined as: the proportion of participants with a disease control status defined as no severe disease progression.

Null Hypothesis (H0): There is no difference between group A (ivermectin + paracetamol) and group B (ivermectin + paracetamol) in terms of the primary endpoint at day 14.

Alternative hypothesis (H1): There is a difference between group A (ivermectin + paracetamol) and group B (placebo + paracetamol) in terms of the primary endpoint at day 14.

5. Methodology

5.1 Study design

This is a phase 2, multicenter, randomized, double-blind, parallel-group, placebo-controlled study in adult subjects with mild COVID-19.

In the selection period, the subjects will give their informed consent and, after this activity, all the procedures will be carried out.

Approximately 66 adult subjects with COVID-19 will be randomized in a 1: 1 ratio to receive ivermectin 12 mg / day for 3 days, in combination with standard paracetamol therapy (500

mg QID) for 14 days, and placebo in combination with standard paracetamol therapy (500 mg QID) for 14 days.

The study will be carried out at the private research site, Biomedical Research for Drug Development, located in Zapopan, Jalisco, Mexico.

5.1.1 Primary evaluation criteria

The primary endpoint for this study is:

The proportion of participants with a disease control status defined as no disease progression to severe.

The subject is considered to have progressed to severe disease when one or more of the following criteria are present:

a) Shortness of breath (≥30 breaths per minute);

b) Oxygen saturation at rest ≤93%;

c) Severe complications such as: respiratory failure, need for mechanical ventilation, septic shock, non-respiratory organ failure.

5.1.2 Secondary evaluation criteria

The secondary evaluation criteria in this study are:

• SARS-CoV-2 viral load, 5 and 14 days after diagnosis, quantitatively by real-time RT-PCR in nasopharyngeal exudates.

• Presence and frequency of symptoms associated with the COVID-19 disease (fever, cough, myalgia, fatigue, shortness of breath, headache, diarrhea and expectorations) daily for 14 days.

• Presence of adverse events.

• Presence of co-morbidities: diabetes, hypertension, cardiovascular diseases, COPD, chronic liver disease and chronic kidney disease.

• Medical history of BCG vaccines.

5.2 Treatment

5.2.1 Investigational Product

The sponsor will provide the following investigational products:

Treatment 1 (Group A): Placebo of ivermectin for 3 days in combination with paracetamol for 14 days 500 mg QID.

Treatment 2 (Group B): Ivermectin (12 mg / day) for 3 days in combination with paracetamol for 14 days 500 mg QID.

All ivermectin and ivermectin placebo tablets needed for the study will be donated by the pharmacy in identical bottles, labeled with the patient number, the treatment code, and the information required by local laws. Active and inactive tablets will be identical in appearance. This will ensure the double blind.

Paracetamol will be purchased by the research site.

Patients will be instructed to take two 6 mg / placebo tablets on an empty stomach, with water, for 3 days, in combination with 500 mg of paracetamol four times a day for 14 days.

5.2.2 Storage of Investigational Product

The researcher must ensure that the product under investigation is stored in the conditions of ambient temperature (less than 30o C), lighting and humidity recommended by the supplier.

The researcher, or the person previously designated in the delegation of responsibilities form, is obliged to keep a daily record of humidity and temperature of the warehouse of the product under investigation.

The product under investigation should be stored in a safe and locked place, in accordance with local regulations. It is the investigator's responsibility to ensure that the investigational product is released only to study patients.

5.2.3 Responsibilities for the Investigational Product

The researcher, the study coordinator or any personnel authorized to deliver the investigational drug will be responsible for ensuring that it is kept safe and under the conditions stipulated by the sponsor, as well as in accordance with local regulations.

All the product under investigation must be delivered according to the prescription of the investigator and it is the responsibility of the investigator to ensure that an adequate record of the receipt, delivery and return thereof is carried out. Any matter detected related to the quality of the product under investigation (changes in appearance, defects in the labeling, expiration date, etc.), must be notified immediately to the sponsor.

Under no circumstances will the product under investigation be supplied to a third party, will it be allowed to use it in a way other than that indicated in this protocol, or will it be disposed of in some other way.

5.2.4 Medication counting

The subject will be asked to complete a medication administration diary that will be provided on the day of randomization, during the period that the treatment will last (14 days), indicating the date and time of ingestion of the two study medications; ivermectin for three days, and paracetamol for 14 days.

The patients recruited into the study will be requested to deliver the bottles of the investigational product (with the leftover tablets, if applicable) on the day of the final visit. The investigator will note the date of return of the same and proceed, where appropriate, to count the remaining tablets and write them down in the Case Report Format (CRF, for its acronym in English), calculating the percentage of adherence to treatment and recording the result in the CRF. Adherence to 100% ivermectin and 80% paracetamol is recommended.

5.2.5 Disposal of surplus investigational product

At the end of the study, all the excess research product will be taken to destruction with an external supplier who will issue a destruction control sheet once it has been accounted for.

5.2.6 Blanking opening

The investigator can open the target of the investigational product when a patient presents a serious adverse event that could compromise the life or health of the patient.

The opening of the blind will be recorded in the corresponding format, which can be found in the center's file.

5.3 Study population

5.3.1 Eligibility

Patients of both genders with a diagnosis of mild SARS-CoV-2 infection, through the quantitative test by real-time polymerase chain reaction test (RT-PCR) and compatible symptoms will be invited to participate in the study.

5.3.2 Inclusion Criteria

1. Adult subjects who are capable of giving their informed consent in writing.

2. Men and women.

3.> 18 years old.

4. Diagnosis of severe acute respiratory syndrome due to coronavirus infection (SARS-CoV) -2, confirmed by polymerase chain reaction (PCR) test prior to randomization, of no more than 14 days of presence of the first symptom.

5. Subjects who are asymptomatic or with a mild degree of COVID-19 disease.

5.3.3 Exclusion Criteria

1. Patients with severe COVID-19 disease, defined by the presence of one or more of the following criteria:

to. Shortness of breath (≥30 breaths per minute);

b. Rest oxygen saturation ≤93%;

c. Severe complications such as respiratory failure, need for mechanical ventilation, septic shock, non-respiratory organ failure.

2. Positive proof of infection by some other virus, such as H1N1, SARS, etc.

3. Recurrent urinary tract infections (defined as more than three UTIs per year during the previous year or one urinary tract infection in the three months prior to the start of the study).

4. Alanine Aminotransferase (ALT) or Aspartate Aminotransfers (AST)> 5 times above its normal limits.

5. Pregnant or lactating patients.

6. Patients who are participating in another clinical study.

7. Patients undergoing antibiotic treatment for any reason.

8. Patients undergoing treatment for parasitic diseases.

9. Patients receiving the antihypertensive drug verapamil, the immunosuppressant cyclosporine A and / or the antipsychotic trifluoperazine.

10. Patients with a known allergy or hypersensitivity to antiparasitics.

11. Patients who are using an antioxidant supplement.

12. Patients with a history of filariasis, strongyloidiasis, scabies, river blindness, or any parasitic disease in the last twelve months.

13. Patients with disorders or a history of the blood-brain barrier.

14. Patients who have more than three comorbidities at the time of selection.

15. Subjects who cannot tolerate the oral route.

16. Subjects with intestinal or malabsorptive problems that prevent proper absorption of the drug.

17. Subjects for whom the (SARS-CoV)-2 test, by PCR obtained during selection, was negative or indeterminate.

5.3.4 Elimination Criteria

1. Serious adverse event.

2. Withdrawal of informed consent.

3. Loss of patient follow-up.

4. Worsening of the disease, defined as severe COVID-19 infection, following the same criteria as in exclusion criterion 1.

5.3.5 Withdrawal from the study

Each patient can voluntarily decide to withdraw from the study at any time and without any specific reason. If a patient wishes to terminate her participation in the study, her information will no longer be collected immediately.

A serious adverse event (eg pregnancy) and loss of patient follow-up will also be reasons for withdrawing the patient from the study.

Subjects who progress to severe disease, will be withdrawn from study treatment; however, a follow-up will be carried out until resolution of the subject's illness or death.

In all these cases, the patient will be analyzed within the group in which he was originally assigned, as treatment failure.

In all the above cases, the cause for withdrawal of the study must be documented in the clinical record and in the CRF.

5.3.6 Subject replacement.

Patients who drop out of the study will not be replaced, losses are within the sample size.

5.4 Visits

The researcher will document the selection, initiation and follow-up visits, as well as the final study visit for each patient in the patient's clinical file, from which part of the information required by the study will be extracted.

All study visits will be carried out at the patient's home, since, due to the infectious-contagious nature of the disease; This measure is intended to reduce the risks of contagion.

The follow-up period for each patient will be 14 days.

The general information to be collected at each patient visit to the site is summarized in

For all visits, the site staff will act with the security measures stipulated in NOM-007-SSA3-2011 and under the recommendations of the World Health Organization, expressed in its laboratory biosafety guide for COVID-19 (30), in order to protect the safety of the personnel, as well as that of the subjects.

All site personnel must wear the following biosafety equipment; medical protective mask (N95), disposable medical protective uniform, disposable latex gloves, disposable boot covers and face shields (31).

5.4.1 Selection visit (-3 days)

Once the center's research team identifies a patient eligible for the study, the researcher will inform the patient about the study and invite them to participate. The procedure for obtaining informed consent and signing it will then be carried out if the patient decides to participate in the study. The informed consent will be signed by the patient, the researcher and two witnesses, in duplicate. One original will be kept on site and the other will be delivered to the patient. Each patient who is invited to participate in the study will be registered within the center's selection list, only with their initials, a document in which, in addition, it will be established whether or not the patient entered the study and the reasons (eg, lack of fulfillment of selection criteria, did not accept, etc.).

These procedures will be followed during this visit:

• Explanation of the nature and objectives of the study to the patient and invitation to participate.

- Informed consent

• Review of all inclusion and exclusion criteria.

- Medical history.

The researcher will carry out an interrogation aimed at obtaining data on the presence or personal-pathological history of: type 2 diabetes mellitus, systemic arterial hypertension,

cardiovascular diseases, COPD, chronic liver or kidney disease, as well as questioning the vaccination history, aimed at obtaining information on BCG vaccine (if the subject has a vaccination record, a copy will be requested to be attached to the file).

• Vital signs and physical examination (oxygen saturation, weight, height, heart rate, respiratory rate, blood pressure, and body temperature).

• Blood samples will be taken to obtain: blood count (BH), 29-element blood chemistry, and glycated hemoglobin.

• Urine sample to perform general urine examination and pregnancy test for women of reproductive age.

• Nasopharyngeal swab sample for evaluation of SARS-COV-2 by RT-PCR.

• Review of concomitant medications.

• Review of adverse events.

The patient will be summoned for the initial visit with the indication to go on an 8-hour fast.

5.4.2 Initial Visit / Randomization (Day 1)

Candidates must have fasted for at least 8 hours.

These procedures will be followed during this visit:

• Review of inclusion / exclusion criteria.

• Patient randomization: Assignment to treatment will be done by a simple randomization procedure, balanced by treatment and by gender (1: 1). The research site will have a list with the consecutive patient number, the corresponding ID according to the randomization, this will be carried out by a non-blind pharmacist, who will be in charge of assigning the drug, as well as the identification of the treatment and its batch. The person in charge of assigning treatment should enter in this list the initials of the patient and the date on which this assignment is being made. You should then take the treatment bottle with the corresponding patient ID, write the date and initials on the label, and give it to the patient.

• Instruction for taking the drug: The researcher will instruct the patient to take two ivermectin / placebo tablets, before food, for three consecutive days on an empty stomach, with water, without chewing or breaking it, taking the first one in front of the researcher

with water, and the time will be recorded. And, for 14 days, take paracetamol 500 mg every six hours.

• Delivery of the patient diary: a diary will be given to the patient, which must be filled in for 14 days with information on symptoms and medication intake. The patient will be instructed to fill out the symptom diary every night after taking body temperature, and to fill in the diary.

• Ask about concomitant medications.

• Ask yourself about the presence of adverse events.

The patient will receive a study participation card and will be told that, if there is any doubt or increase in symptoms, or an adverse event, she should contact the Principal Investigator as soon as possible.

5.4.3 Follow-up Visit (Day 5 ± 1)

Patients should have 8 hours of fasting.

These procedures will be followed during the visit:

• Vital signs.

• You will be asked about symptoms related to the condition and adverse events.

• Interrogation of change in concomitant medications.

• Review of the patient's diary.

• Nasopharyngeal swab sample for evaluation of SARS-COV-2 by RT-PCR

5.4.4 Follow-up Visit (Day 10 ± 1)

This will be a telephone visit in which the researcher will question the subject about adverse events and symptoms associated with the disease.

5.4.5 Final Visit (Day 14 ± 1)

The final visit will be the day after the day the 14 days of paracetamol treatment have been completed.

Subjects will be asked to fast for 8 hours.

These procedures will be followed during the visit:

- Physical exploration.
- Vital signs.
- Taking blood samples to obtain: hematic biometry (BH) and blood chemistry of 29 elements.
- Urine sample to perform a general urine test.
- Nasopharyngeal swab sample for evaluation of SARS-COV-2 by RT-PCR.
- You will be asked about symptoms related to the condition and adverse events.
- The remaining tablets will be counted, if any, and the percentage of adherence to the treatment will be calculated.
- The patient's diary will be collected and reviewed.

5.4.6 Safety follow-up visits (every seven days, until the total resolution of the disease)

For those subjects who, on the 14th day visit, have not been considered in total remission of the disease according to the criteria of the principal investigator, they will be followed up weekly by telephone where they will be questioned about adverse events and symptoms of the disease.

5.5 Variables

The investigator will collect the patient's medical history, information about his current condition, physical examination, etc., in the patient's medical record. The researcher will empty the relevant information for the study of each patient to the CRF. The CRF will be available upon request.

5.5.1 Primary objective measurement variables

The variables for measuring the main objective of this study are:

• Progression of disease to severe, defined as the frequency of subjects progressing from mild to severe disease; What happens when they meet one or more of the following criteria:

1. Shortness of breath (≥30 breaths per minute);

2. Oxygen saturation at rest ≤93%;

3. Severe complications such as: respiratory failure, need for mechanical ventilation, septic shock, non-respiratory organ failure.

5.5.2 Measurement variables of secondary objectives

The variables for measuring the secondary objectives are:

• Replication rate of the SARS-CoV-2 virus at 5 and 14 days after starting the study treatment valued in Ct (in relation to a reference gene, used in the local laboratory).

• Symptoms associated with the COVID-19 disease (fever, cough, myalgia, fatigue, shortness of breath, headache, diarrhea and expectorations).

• Serious adverse events.

• Comorbidities (diabetes, hypertension, cardiovascular diseases, COPD, chronic liver disease and chronic kidney disease)

• Medical history of BCG vaccine.

5.5.3 Detailed description of the variables

5.5.3.1 Visits

The information for each of the visits includes:

- Date of the visit

5.5.3.2 Demographics

For the demographic / sociodemographic evaluation, the following variables will be collected:

• Year of birth (dd / mm / yyyy)

• Age (years)

• Sex (woman / man)

• Educational level (primary / secondary / baccalaureate / bachelor / master / doctorate / none)

5.5.3.3 Vital Signs

The vital sign information that should be documented will include:

• Size (cm)

• Weight (kg)

• Body Mass Index (kg / m2)

• Blood Pressure (mm / Hg)

• Temperature (° C)

5.5.3.4 History of disease

The history of the disease describes any medical findings relevant to the disease. Findings and diagnoses that meet the following criteria should be documented:

• Date of onset of symptoms.

• Signs and symptoms (urinary urgency, dysuria, urgency, suprapubic pain, frequency, hematuria, nausea, vomiting, fever).

5.5.3.5 Comorbidities (medical history, comorbidities)

Comorbidities are any medical finding, regardless of whether or not they belong to the study indication, that were present before the start of ivermectin treatment, regardless of whether or not they continue to be present throughout the study. They must be documented in the patient's clinical record, as well as in the Clinical History / Concomitant Diseases section of the CRF.

Findings that meet the criteria listed below are considered relevant to the study and should be documented:

- Diabetes mellitus type 2
- Systemic arterial hypertension
- Chronic obstructive pulmonary disease

- Liver disease
- Chronic kidney disease
- Infectious diseases
- Cancer
- Overweight or obese
- Asthma
- Smoking
- Hyperuricemia
- History of BCG vaccination by direct questioning, or if possible, obtain a copy of the subject's vaccination record.

For any comorbidity, the diagnosis, start date and end / continuation date must be documented. Other comorbidities should also be documented.

5.5.3.6 Concomitant medications / treatments

All medications taken / treatments received in addition to ivermectin for any indication (started before or during the start of the study) are called concomitant medications / treatments and must be documented.

Information to be collected for medications includes:

- Generic name
- Start date, end date / continues.
- Dose
- Units
- Frequency
- Route of administration
- Indication

5.5.3.7 Laboratory parameters

The laboratory parameters that must be documented in the CRF are:

- Glucose

• Ureic Nitrogen (BUN)

• Creatinine

• Uric acid

• Lipid profile

o Cholesterol

o Triglycerides

o High-density cholesterol (HDL-C)

o Low-density cholesterol (LDL-C)

o Very low-density cholesterol (VLDL-C)

• Hepatic profile

o Bilirubins

o Total proteins

o Alanine Aminotransferase (ALT)

o Aspartate Aminotransferses (AST)

o Pyruvic transaminase (TGP)

o Gamma Glutamyl Transferase (GGT)

o Total cholesterol

o Alkaline phosphatase

• Electrolytes in blood:

- Sodium
- Potassium
- Chlorine
- Calcium in serum
- Magnesium
- Phosphorus

• Amylase

• Glycated hemoglobin

• Hematic biometry

o Erythrocytes

o Leukocyte

o Hemoglobin

o Hematocrit

o Corpuscular volume

o Platelets

o Mean Globular Hemoglobin

o Mean Globular Hemoglobin Concentration

o Lymphocytes

• General urine test:

o Color

o Density

or pH

o Proteins

o Creatinine

o Erythrocytes

o Leukocytes

o Cylinders

o Crystals

o Glucose

o Bacteria

o Ketones

5.5.3.8 Exposure / treatment

Information on Ivermectin treatment that should be documented includes:

• Start and end date (or if it continues)

• Dose

• Units

• Frequency

• Route of administration

• Percentage of attachment

5.5.3.9 Treatment evaluation

The information to be documented includes: the appearance and frequency of symptoms associated with the disease. The subject will fill out a symptomatology diary (Annex 1) where they will record the presence of symptoms associated with the disease every night during the 14 days that the treatment lasts, if after 14 days the subject persists with symptoms, then this evaluation it will be by phone weekly. During the call, the researcher will ask the subject if in the last week the subject had symptoms, until total remission or death.

5.5.3.10 End of study

If available, the main reason for termination / interruption of the study should be specified:

• End of the treatment period described in the protocol
• Loss of patient follow-up
• Withdrawal of informed consent
• Investigator's decision
• Serious adverse event / adverse drug reaction
• Pregnancy
• Change of treatment (indicate to which treatment and reasons for change)
• Closure of the research site
• Completion of the study by the sponsor
• Disease worsening to severe (by the criteria described in section 10.5.1).

5.5.3.11 Adverse Events

Adverse Events (AE) and Serious Adverse Events (EAS) should be collected as described in section 16. The information to be collected includes:

• AD diagnosis, or symptom (if diagnosis is unknown)
• Start and end date / continues

- Seriousness
- Relationship to treatment
- Taken actions
- Conclusion of the event
- Other specific treatment (s) for AD

5.6 Data sources

The researcher will collect the information on this study from the patient's medical record and the documents it contains, such as: clinical history, progress notes, laboratory results, emergency notes, etc. These will be considered as the source documents. It is extremely important that the clinical record contains as much information as possible to collect in this study, and that it is complete and accurate.

Each patient will be identified by a unique patient identification code, used solely for the purposes of this study. During the duration of the study and after it, only the researcher and authorized persons at the research site will be able to identify the patient based on this patient identification code.

5.7 Sample size

A total of 66 subjects will be randomized, considering an infinite population size with a power of 80% and confidence of 95% (32).

6. Quality Control

6.1 Information Quality

Before the start of the study, the researcher and the research team of the participating site must be fully trained in the background, objectives and methodology of the study, as well as in their ethical and regulatory obligations.

A person responsible for quality control, verification of data collection, information analysis and transfer of the same to the case report form will be selected and assigned.

All the variables required by this study will be recorded in a CRF. After data capture, the missing or unlikely data will be raised as queries and the information will be validated. The study will be monitored according to Good Clinical Practices (GCP) to ensure the quality and validity of the data obtained. Details about monitoring (eg frequency, percentage of patients monitored) will be found in the Study Monitoring Plan (PM), available upon request.

At all times the laws on data protection, both national and international, as well as the regulations on clinical trials will be followed.

6.2 Quality assurance.

In a proportion of patients (at least 30% of all patients), a complete monitoring of the CRF will be carried out against the source documents, with the purpose of reviewing the documented information regarding integrity, plausibility and adherence to the protocol. To do this, the study monitors will have access to the clinical records of the study patients at the research site.

6.3 Record Storage and Archiving

The clinical records of the participating subjects will be kept at the research site, in accordance with its own procedures. The investigator must retain all study records and original documents for the maximum period required by applicable regulations and guidelines or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator should contact the sponsor prior to destroying any study-related records.

7. Protection of participating subjects

7.1 Ethical conduct of the study

The study will be carried out in accordance with the ethical principles established in the Declaration of Helsinki of 1964, Good Clinical Practices derived from the International Conference for Harmonization (ICH) and the applicable local regulations.

The study is an investigation with minimal risk: it is a prospective study that uses common procedures in physical examinations of diagnoses or routine treatments, among which are also considered the extraction of blood by venipuncture in adults in good health, with maximum volume of 12 ml in 8 days. It uses an antiparasitic drug in common use and widely studied, using the established indications, doses and routes of administration.

The patient selection criteria are designed so that no patient with possible contraindications to receive the drug enters the study, thus reducing the risk of adverse events.

Surveillance mechanisms have been established to promptly identify any patient who may suffer any adverse event.

7.2 Approval / authorization by regulatory authorities

This protocol will be submitted for review to the Federal Commission for Protection against Sanitary Risks (COFEPRIS). It will not be possible to start until it has the approval of this regulatory body. Any substantive amendment to the protocol must again be submitted for approval by COFEPRIS.

7.3 Research Ethics Committee

The principal investigator will submit to the Research Ethics Committee (IEC) the study protocol, informed consent, investigator manual, materials to be delivered to the patient, recruitment materials, and the documents requested in accordance with local requirements.

The study will not begin at the center without first having obtained the approval of the corresponding Research Ethics Committees. Where necessary, an extension, amendment,

or renewal of the approval of the REC must be obtained and forwarded to the sponsor. The IEC must provide the sponsor with a list of the voting members and a statement confirming that the Ethics Committee is organized and operates in accordance with the applicable laws and regulations.

7.4 Patient information and consent

An informed consent form will be provided to the patient containing all the information regarding the study. The investigator must have the written approval, from the CEI and COFEPRIS, of the written informed consent form, as well as any other written information given to the patients before starting the observation.

The informed consent will include permission for the collection and analysis of study data.

The informed consent will be signed by the patient, the researcher and two witnesses, in duplicate. One copy will be kept on site and the other will be delivered to the patient. In the event that a patient is illiterate, acceptance will be with their fingerprint, and in the event that the patient is unable to provide adequate written informed consent, a "legally authorized" patient representative may provide such consent by the subject in accordance with applicable laws and regulations.

7.5 Confidentiality

All records in which the patient is identified will be kept confidential and will not be made available to the public. The data is transmitted only in an encrypted format. No personal data will be shared with alternate contacts. NO ONE outside the research team will have access to the names or contact information of patients, and individual patient data will remain anonymous. Personal information and medical information will be recorded in different databases.

If the patient's name appears on any document, it must be erased before a copy of the document is delivered to any authority.

The monitoring database will maintain a contact list that allows the identification of patient records in case of consultations. In the case of an EAS report, the National Pharmacovigilance Center may request additional clarifications. In that case, the sponsor cannot contact the patient directly. The investigator will provide all additional information.

8. Management and reporting of adverse events

8.1 Definitions

An adverse event (AE) is any unfavorable medical event that occurs in a patient or in a patient participating in a clinical investigation who was administered a pharmaceutical product (here, the study drug) and that does not necessarily have a relationship of causality (association) with this treatment. The term also includes laboratory findings or results from other diagnostic procedures considered clinically relevant (eg requiring unscheduled diagnostic procedures or treatments or leading to withdrawal from the study).

All adverse events must be recorded on the Adverse Event Report Form attached to the CRF. Faced with each adverse event, the investigator must evaluate and record the severity, duration, relationship with the study drug, the measure taken, and the outcome of the event.

The adverse event can be:

• A new disease.

• The aggravation of a sign or symptom of the condition under treatment or a concomitant disease.

• An effect of the study drug (or comparator drug).

• Any combination of one or more of these factors.

As mentioned above, the use of the term “adverse event” does not imply that there is a causal relationship with a study drug.

A drug-related adverse event is an adverse event that, in the discretion of the investigator or sponsor, has a reasonable and presumed causal relationship with the treatment. It is defined as the harmful and unwanted response to a drug, which occurs when the doses that

are usually used for the prophylaxis, diagnosis or treatment of a disease or for the modification of a physiological function are administered.

Planned hospitalizations prior to study inclusion will not be considered adverse events. This also includes outpatient hospitalizations (lasting less than 12 hours) or part of routine treatment or study disease monitoring and not due to disease worsening.

An adverse event is serious if:

• produces death;

• endangers life;

• requires hospitalization of the patient or the extension of the existing hospitalization (see exceptions below);

• results in a persistent or significant disability or incapacity;

• results in a congenital anomaly or birth defect;

• It is an important medical event at the discretion of the investigated.

Death is usually the result of an underlying clinical event that causes it. Therefore, the cause of death is what should be considered a serious adverse event. The only exception to this rule is sudden death, where no cause of death has been determined. In this case, sudden death should be considered an adverse and “fatal” event, which is why it is serious.

Life risk: the term “life risk” in the definition of “seriousness” refers to an adverse event in which the patient was at risk of losing his life at the time of the event. It does not refer to an adverse event that could hypothetically have caused death if it had been more serious.

Hospitalization: Any adverse event that leads to hospitalization or the prolongation of a hospitalization will automatically be considered serious, unless it meets at least one of the following exceptions:

• the patient's admission results in a hospital stay of less than 12 hours, or

• admission has been pre-planned (ie elective or elective surgery that has been planned prior to the start of the study).

However, it should be noted that invasive treatment during any hospitalization may meet the criteria to be considered "medically relevant" and, as such, may be reported as a serious

adverse event, based on clinical judgment. Furthermore, in cases where local regulatory authorities specifically require a stricter definition, local regulation will take precedence.

Disability means a significant alteration in a person's ability to perform the functions of a normal life.

A congenital anomaly (birth defect), that is, any congenital anomaly observed in a baby or later when it is a child, should be considered a serious adverse event in the following cases:

• The mother was exposed to a medicinal product at any stage during conception, pregnancy or delivery; or

• The father was exposed to a medicinal product before conception.

Major Medical Event - Any adverse event can be considered serious because it can endanger the patient and may require intervention to prevent another serious condition.

Major medical events refer to or may indicate a serious disease state. Special attention should be paid to this type of report due to its possible link to a serious illness state.

8.2 Collection

Beginning with the first administration of ivermectin after inclusion in the study, all non-serious AEs must be documented in the Adverse Event Reporting Forms in the CRF and sent to the sponsor within 60 calendar days of detection. All EAS must be documented and shipped immediately (within one business day of detection). For each EA, the investigator must evaluate and document its seriousness, duration, relationship with the product, actions taken, and outcome of the event.

If a pregnancy occurs during the development of the study, it will be taken as EAS as described above. The outcome of the pregnancy will be monitored according to the applicable Sponsor Procedure. Any information on abnormal findings concerning the mother or the product will be collected as adverse events.

Documentation of any EA / EAS ends with the end of the patient's treatment period. However, any EA / EAS - regardless of their relationship and seriousness - that occurred up

to 30 days after the end date of the study treatment, which is made known to the investigator, must be documented and sent to the sponsor within the limits. set times.

8.3 Management and Report

Non-Serious Adverse Events

The outcomes of all EAs should be monitored and documented. The sponsor will prepare the reports that are presented to the competent authorities in accordance with national regulations; however, all participants must comply with local legal requirements. When required, the researcher may be contacted directly by the personnel responsible for the study to provide additional information.

Serious Adverse Events

Any SAE or pregnancy reported in the CRF should be immediately sent (within one business day from its detection) to the person in charge of pharmacovigilance of the sponsor. The outcome of all reported EAS (resolution, death, etc.) must be monitored and documented. When required, the investigator may be contacted directly by the person in charge of pharmacovigilance to provide additional information.

The presentation of the EAS to the local authorities according to the national regulations will be made by the sponsor; however, all researchers must obey local legal requirements.

8.4 Evaluation

When new relevant information on product safety is received, the reports are processed and captured in the sponsor's global safety and pharmacovigilance database. These reports will be reviewed on a regular basis. If a potential security risk is suspected, an investigation will be conducted according to the sponsor's standard internal operating procedures, for further evaluation within the risk-benefit context.

9. Planning for dissemination and communication of the results of the study

INVESTIGACIÓN BIOMÉDICA PARA EL DESARROLLO DE FÁRMACOS SA DE CV is the owner of the data obtained during the development of this research study. The results of this study are intended to be included as abstracts / presentations at medical conferences under the supervision of the sponsor. No investigator may publish the results of this study individually or on their patients without the prior authorization of the sponsor. This study will be registered at www.clinicaltrials.gov.

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