

Evaluation of the Effect and Safety of HeberFERON vs Heberon Alpha in Patients Infected with Corona Virus SARS-CoV-2 (Study ESPERANZA/HOPE): Study Protocol for a Randomized Controlled Trial.

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Study protocol

Keywords: SARS-Cov-2, Interferons, Cuba, Clinical trial

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Abstract

Background: As the outbreak of COVID-19 has accelerated, an urgent need for finding strategies to combat the virus is growing. Results from in vitro studies suggest that a combination of IFN type I and Type II may be effective against SARS-CoV. The aim of this study is to investigate the efficacy of treatment with a recombinant IFN alpha 2b and gamma, provided with standard protocol (Kaletra (lopinavir-ritonavir 200/50 mg; 200/100 mg every 12 hour for 30 days; Chloroquine (250 mg) every 12 hours for 10 days) for COVID-19 patients, compared to standard protocol (IFN alpha 2b/Kaletra/Chloroquine) for COVID-19 hospitalized patients, positive diagnosed for SARS-Cov-2.

Methods: Hospitalized adult patients with qPCR confirmed SARS-Cov-2 will be enrolled in this open-labeled, single center, prospective, randomized and controlled clinical trial. One hundred and twenty eligible patients with confirmed SARS-CoV-2 positivity by qPCR amplification in oropharyngeal/nasopharyngeal swab samples will be enrolled at “Luis Diaz Soto” Hospital, Havana, Cuba. The primary outcomes are the time to 2019-nCoV RNA negativity in patients and the time until progression to severe COVID-19.

Discussion: This will be the first randomized controlled trial of a potential treatment for SARC-Cov-2 using the combinations of IFNs.

Trial registration: The study is sponsored by Center for Genetic and Biotechnology and Ministry of Health of Cuba and was duly registered April 2020 at <http://registroclinico.sld.cu/en/trials/RPCEC00000307-En>. Enrolment for this study began in April 11, 2020, and has enrolled one hundred patients as of May-26-2020

Administrative Information

Title {1}	Phase II clinical, randomized, clinical trial of evaluation of the effect and safety of HeberFERON versus Heberon alfa in patients infected with the SARS-CoV-2 coronavirus (Study ESPERANZA/HOPE).
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Trial
registration
{2a and
2b}.

Title {1}	Phase II clinical, randomized, clinical trial of evaluation of the effect and safety of HeberFERON versus Heberon alfa in patients infected with the SARS-CoV-2 coronavirus (Study ESPERANZA/HOPE).	
	Trial ID	RPCEC00000307
	Last Refreshed on	18/05/2020
	Public title	ESPERANZA study
	Scientific title	Evaluation of the effect and safety of HeberFERON versus Heberon alfa R in patients infected with the SARS-CoV-2 coronavirus (COVID-19).
	Acronym	
	Primary sponsor	Center for Genetic Engineering and Biotechnology (CIGB), in Havana
	Date registration	14/04/2020
	Date registration	20200414
	Export date	5/19/2020 9:53:57 PM
	Source Register	RPCEC
	web address	http://rpcec.sld.cu/en/trials/RPCEC00000307-En
	Recruitment Status	Recruiting
	other records	No
	Inclusion age min	19 years
	Inclusion age max	None
	Inclusion gender	Male/Female
	Date enrollment	10/04/2020
	Target size	120
	Study type	Interventional
	Study design	Randomization: Randomized trial. Blinding: Open. Control group: Active. Assignment: Parallel. Purpose: Treatment
	Phase	2

Title {1}	Country: Cuba Phase II clinical, randomized, clinical trial of evaluation of the effect and safety of HeberFERON versus Heberon alfa in patients infected with the SARS-CoV-2 coronavirus (Study ESPERANZA/HOPE).	
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	Contact Affiliation	Center for Genetic Engineering and Biotechnology (CIGB).
	Inclusion Criteria	Inclusion criteria: 1) Positivity to SARS-CoV-2 by rapid or confirmatory test of qPCR. 2) ECOG functional status ≤ 2 (Karnofsky $\geq 70\%$). 3) Voluntariness of the patient by signing the informed consent.
	Exclusion Criteria	Exclusion criteria: 1) Patients with decompensated chronic diseases at the time of inclusion (severe arterial hypertension, ischemic heart disease, diabetes mellitus, etc.). 2) Patients with a history of autoimmune diseases. 3) Presence of hyperinflammation syndrome. 4) Serious coagulation disorders. 5) Known hypersensitivity to any of the components of the formulation under study. 6) Pregnancy or lactation. 7) Obvious mental incapacity to issue consent and act accordingly with the study.
	Condition	patients infected with the SARS-CoV-2 coronavirus.
	Intervention	Group A: HeberFERON (Recombinant Interferon Alpha Gamma, 3.5 MIU), subcutaneously, twice a week for three consecutive weeks. Group B (Control): Heberon Alfa R (Recombinant Interferon alfa 2b, 3.0 MIU), subcutaneously, three times per week for three consecutive weeks. All the patients included in the study (as part of the protocol of action foreseen in the country for cases of SARS-CoV-2 in nasopharyngeal exudates) receive basic treatment (in addition to interferon according to study group) with calettra, chloroquine, azithromycin or rocefin, depending on the magnitude of respiratory symptoms.
	Primary outcome	1) Virological evaluation: Time until the negativity of the SARS-Cov-2 RNA (absence of the virus according to the qPCR technique in real time) in positive patients after starting antiviral therapy (the percentage of patients negative for SARS will be calculated). VOC-2 by qPCR in tissue of nasopharyngeal exudate Measurement time: 48, 72 and 96 hours after starting treatment. 2) Clinical evaluation: Time to progression to severe COVID-19 (the percentage of patients who become severe will be calculated). Measurement time: 3rd week, after completion of the antiviral treatment under investigation.

Title {1}	Phase II clinical, randomized, clinical trial of evaluation of the effect and safety of HeberFERON versus Heberon alfa in patients infected with the SARS-CoV-2 coronavirus (Study ESPERANZA/HOPE).	
	results date posted	15/08/2020
	results date completed	30/07/2020
	results url link	
	Retrospective flag	No
	Bridging flag true false	FALSE
Cuban Public Registry of Clinical Trials(RPCEC), RPCEC00000307		
Protocol version {3}	Protocol version I, 01/04/2020 and IG/IAG/CV/2001	
Funding {4}	CIGB support the investigational products, and qPCR, FACS and other laboratory determinations. Ministry of Health support all the patient care, hospitalization, and clinical determinations (hematological, biochemical, microbiology, RX, electrocardiogram).	

Title {1}	Phase II clinical, randomized, clinical trial of evaluation of the effect and safety of HeberFERON versus Heberon alfa in patients infected with the SARS-CoV-2 coronavirus (Study ESPERANZA/HOPE).
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Name and contact information for the trial sponsor {5b}	Hector Santana Milian. MSc. Direction of Pharmaceutical Development at Center for Genetic Engineering and Biotechnology. Ave31e/158 and 190, Cubanacan, Playa, Havana, Cuba hector.santana@cigb.edu.cu
Role of sponsor {5c}	<p>The study sponsor and funders has no roles in collection, management, analysis, and interpretation of data; or writing of the report.</p> <p>The study sponsor and funders has no roles in the decision to submit the report for publication.</p>

Introduction

Background and rationale {6a}

As the SARS-Cov-2 infection has spread to more than 180 countries of the world and generated a significant number of deaths, more than 5% of lethality, with great social and economic consequences, it is very urgent to find and develop strategies to combat this new virus.

There are guides issued by expert committees of WHO, Singapore, South Korea and US institutions, that recommend the clinical use of interferon (IFN) for the treatment and prevention of COVID-19¹². Countries like China and Spain have incorporated this medicine in their protocols and national clinical guidelines for the care of this type of patient.

There are three types of Interferons (IFNs): type I (IFN- α and IFN- β), type II (IFN- γ) and type III (IFN- λ). IFNs are proteins created by nature for the first line defense against pathogens (viruses, bacteria, parasites), a function demonstrated in a group of species at different levels of the evolution chain, confirming their protective role.

Infection with mammalian cell viruses incites the innate immune system to establish a first line of defense. IFNs play a key role in these events, as they activate the innate immune system and help shape adaptive immunity. IFN- γ is the main modulator in establishing the relationship between these two types of immune responses.

IFNs possess pleiotropic effects that overlap on various cellular functions. IFNs- α and β have a greater antiproliferative and antiviral effect and IFN- γ a superior immunoregulatory activity¹³.

IFNs- α and - γ exercise their functions through different but related signaling pathways. Studies in animal models have shown that IFNs- α and - γ are essential for antiviral defense and are functionally non-redundant.

Viruses have developed mechanisms to evade the functions of the IFN system by simulating proteins that intervene in the synthesis mechanisms of IFNs, and intracellular signaling to establish the protection mechanisms by these (IFN receptor and other signaling cascade proteins)¹⁴.

Severe acute respiratory syndrome coronavirus (SARS-CoV)-2 is a positive-sense, enveloped, single-stranded RNA β coronavirus similar to Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) virus. This type of virus is susceptible to the antiviral action of IFNs, but variations have been developed to interfere with this activity.

Viruses have developed mechanisms to evade the functions of the IFN system by simulating proteins that intervene in the synthesis mechanisms of IFNs, and intracellular signaling to establish the protection mechanisms (IFN receptor and other proteins of signaling cascades)¹⁵.

SARS-Co, which emerged in 2003 and caused widespread human mortality, encodes at least five proteins that function as IFN antagonists¹⁶, suppressing signaling and production components. These proteins are

believed to be responsible for the pathogenesis of SARS-CoV.

The induction of IFNs plays a fundamental role in defending the body against CoV infections. Numerous studies have presented the effectiveness of direct administration of IFN to eliminate these viruses.

IFN- γ has been reported to have an antiviral effect in coronavirus infection. This effect is described mediated by the recruitment of monocytes and T lymphocytes to the area of the infected cells and the production of IFN- γ by them. In the absence of IFN-mediated signaling, infection leads to the death of infected animals.

The IFN- α e IFN- γ combination in the infection of coronavirus

The combination of IFN- γ and - λ has been described to synergistically inhibit the replication of SARS-CoV in vitro. Larkin et al. indicate that the combination of IFN- α and IFN- γ generates strong synergistic antiviral activity. Another study demonstrates that co-administration of IFN- α and IFN- γ causes hyperactivation of IRF-1 and STAT1, ultimately leading to a more robust antiviral response against viral replication. The combination of type I IFN (IFN- α , β) with IFN- γ synergistically inhibits virus replication in vitro²².

The effects of IFNs on the replication of SARS-CoV, showed that treatment of Vero E6 cells with 100 U / mL of IFN- β or IFN- γ marginally reduced viral replication. However, treatment with IFN- β and IFN- γ inhibited SARS-CoV plaque formation 30 times and replication 3000 times at 24 h, and $> 1 \times 10^5$ times at 48 and 72 h after the infection. This result demonstrates the synergistic inhibition of SARS-CoV replication by IFN type I and IFN- γ ²².

The higher mortality rate from COVID-19 in elderly patients has been associated with a greater delay between the time of infection and the response of the immune system, caused mainly by the inhibitory effects of the virus on it. Early administration of IFNs could reduce this window of antiviral inactivity and decrease SARS mortality. Combining IFN- γ and IFN- α synergistically could maximize this benefit.

Heberon alpha R®

Heberon Alfa R® (IFN alfa-2b) is a drug produced in Cuba by the Center for Genetic Engineering and Biotechnology (CIGB), which has remained a product with proven antiviral efficacy and an adequate safety profile for 34 years.

The evidences are different for preventive use and the treatment at early stage of the disease, so Heberon Alpha R is one of the interventions included in the Cuban protocol for the management of COVID-19 and about 76,900 doses have been supplied to the National Health System by the CIGB since March 2020. The current Cuban recommendation for patients is to use recombinant interferon alfa 2b (Heberon alfa 2b) 3 million of units intramuscular routes thrice a week at early stage.

Today there are several clinical studies with IFN alpha-2b in COVID-19 registered at clinicaltrials.gov and guideline issued by Expert Committees of WHO, Singapore, South Korea and US Institutions recommend the clinical use of IFN alpha for the treatment and prevention of COVID-19. However, the use of IFN in advance stages of the disease has been inconsistent.

HeberFERON®

HeberFERON® (IFN- α 2b + IFN- γ) is a drug produced in Cuba by CIGB, which was approved in Cuba by CECMED in 2016 for the treatment of basal cell carcinomas (BCC), and since then it has been routinely administered to more than 3,000 patients with advanced, high-risk or multiple BCC in the country.

HeberFERON® has been extensively studied through physicochemical studies, biological activity in vitro and in vivo, in studies of pharmacokinetics, pharmacodynamics in humans, animals and toxicology.

The proteins, enzymes and metabolites mediating the antiviral effect (2–5 OAS, β -2 microglobulin, Neopterin) of IFNs are synergistically stimulated by HeberFERON^{28,29}. The main intracellular signaling factor common to both IFNs, STAT-1⁷ has also been synergistically stimulated and has been shown to be a target of SARS-CoV antagonism on the IFN system¹².

These evidences support the use of this therapeutic candidate for the control of COVID-19 in the early stages of the disease and in patients positive for the virus.

We have decided to compare these two formulations of IFNs to define the antiviral of IFN formulations activity against SARS-CoV-2 in a controlled randomized clinical trial.

Objectives {7}

Taking into account that the pharmacodynamics of HeberFERON® is superior to that of the IFNs separately, based on the stimulation of the genes of antiviral activity involved in the defense of the organism against COVID-19, between 2–5 times more, and that both IFN alpha and IFN gamma demonstrate antiviral activity against coronavirus infection synergistically, it is expected that patients treated with HeberFERON® achieve a reduction in the time until the SARS-CoV-2 RNA negative (absence of the virus according to the technique of qPCR in real time) with 20% superiority over the group treated with Heberon alpha R®.

Trial Design {8}

The investigation was designed as an open-labeled, single center, prospective, randomized and controlled clinical trial. One hundred and twenty eligible patients with confirmed SARS-CoV-2 positivity by qPCR amplification in oropharyngeal swab samples will be enrolled at “Luis Diaz Soto” Hospital, Havana, Cuba, based on a power of 80%, and a level of confidence set at 95%, while also considering a dropout rate of

5%. Patients will be block randomized individually to one of two treatment arms by means of random computer-generated lists, with an allocation ratio of 1:1, with block sizes of six patients.

Blood, nasopharyngeal swab, sputum, stool, and urine samples will be collected for laboratory examinations, which also includes hematological analysis, urinalysis, hepatic and renal function test, test for serum amylase levels and myocardial enzyme levels, arterial blood gas analysis, thyroid function test, COVID-19 RNA qualification test, lymphocyte subsets test, coagulation test, and chest imaging examination.

Methods: Participants, Interventions And Outcomes

Study setting {9}

This is clinical trial in one center. The clinical site is the Central Military Hospital Luis Diaz Soto, in Havana, Cuba.

Eligibility criteria {10}

Eligibility criteria

Inclusion criteria

1. Patients to be enrolled must compline the following inclusion criteria:
2. Positive to SARS-CoV-2, symptomatic or not,
3. ≥ 19 years of age,
4. Functional state according to ECOG ≤ 2 (Karnofsky $\geq 70\%$),
5. Be willing to sign informed consent.

Exclusion criteria

1. Decompensated chronic diseases at the time of inclusion (severe arterial hypertension, ischemic heart disease, diabetes mellitus, etc.);
2. Patients with a history of autoimmune diseases;
3. Presence of hyper-inflammation syndrome,
4. Serious coagulation disorders;
5. Known hypersensitivity to any of the components of the formulation under study;
6. Pregnancy or lactation,
7. Obvious mental inability to issue consent and act accordingly on study.

Who will take informed consent? {26a}

1. Patients will be asked for written consent to participate after having been duly informed about the characteristics of the trial, objectives, benefits and possible risks. They will have the necessary time to decide (minimum 24 hours). Likewise, they will be informed of the right to participate or not and to withdraw their consent at any time, without exposing themselves to limitations for their medical care or other retaliation.
2. The investigator should obtain the patient's written consent only after making sure they understood all the information offered. The procedure will be provided by means of a standard writing; in language easily understood by the patient (it should not be technical, but practical). Neither the investigator nor the trial staff can influence the patient's decision to participate or continue in the trial.

All patients who provide informed consent will be randomly allocated into one of two study groups.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

The consent for collection and use of participant data and biological specimens is included in the informed consent

Interventions

Explanation for the choice of comparators {6b}

Intervention description {11a}

The comparator is IFN alpha 2b, a drug that is used as part of the CUBAN NATIONAL ACTION PROTOCOL FOR COVID-19^[1] in the country. Controversial points of view about the use of IFN in the treatment of SARS-CoV-2 have been published. Definitive data about the efficacy of IFN in the COVID-19 has not been released. Additionally, the study drug, HeberFERON®, contains IFN alpha 2b and gamma. We consider Heberon® alpha R the most appropriate comparator for the study.

Intervention group

The intervention group will receive the standard of care as well as, Kaletra and chloroquine as described³³, and HeberFERON. HeberFERON will be administered two times per week at 3.5 MIU for 3 weeks.

Control group

The control group will receive standard of care as well as Heberon Alpha R, Kaletra, and chloroquine. Heberon Alpha R will be administered three times per week at 3.0 MIU for 3 weeks, with Kaletra and chloroquine as described in the CUBAN NATIONAL ACTION PROTOCOL FOR COVID-19 Version 1.4.³³.

Criteria for discontinuing or modifying allocated interventions {11b}

In the event of serious adverse events (with proven causality) the administration of the product will be interrupted and the required measures will be taken depending on the event and the possible expedited report of the same will be considered. The occurrence of the event will be notified to the monitor within a period not exceeding 24 hours.

The person responsible for the investigation, the monitors and the team of investigators, will carry out the corresponding investigations in order to determine the component causing the undesired effect.

After recovery from the adverse event, the patient may restart treatment according to the treatment scheme has been received. If severe toxicity occurs again, treatment is permanently discontinued.

Strategies to improve adherence to interventions {11c}

Prior to the preparation of this protocol, a criteria unification workshop was held with the participation of clinical specialists and opinion leaders involved in the project, where the experimental evidence in animals and humans, as well as the elements of rationality, were presented and discussed. The analysis, discussion and mastery of the protocol will favor adherence and compliance with GCP by all researchers.

The trial monitors will make quality monitoring visits at all stages of its execution, ensuring strict compliance with the provisions of the protocol.

In the case report form (CRF) there is a table to control the use of the in study drugs that signs the doctor.

Relevant concomitant care permitted or prohibited during the trial {11d}

Rules for the use of concomitant treatments.

Medicines may be used concomitantly to prevent or mitigate adverse events of probable causation with the use of Heberon Alfa R and HeberFERON.

Indications for treatment with antihistamines and / or steroids

Drugs	Habitual doses (adults)
Diphenhydramine	20 mg c/8 h
Hydrocortisone	100 mg c/8 h
Prednisolone	20 mg c/8 h
Dexamethasone	8 mg c/8 h
Chlorpheniramine	4 mg c/8 h
Promethazine	25 mg c/4-6 h

Dipirone or acetaminophen will be indicated to relieve fever, headache, and pain if necessary, depending on the doses listed below, taken from the AHCPR "Guidelines for the Management of Acute Pain"^[ii].

Indications for treatment with antipyretics / analgesics

Drugs	Habitual doses (adults)
Dipirone	300-600 mg c/4-6 h
Paracetamol	500 mg a 1g c/6-8 h

In the event of nausea or vomiting, gravinol (1 ampoule; 50 mg) or metoclopramide (1 ampoule; 10 mg IM or I.V. every 8 hours) may be administered.

In case of need for other concomitant medication, this will be administered at the discretion of the investigator in charge of the patient. The conduct before any adverse event will be the decision of the responsible investigator and will depend on the type, magnitude and severity of the clinical manifestations in each case.

Provisions for post-trial care {30}

'Not applicable'

Outcomes {12}

Primary outcomes

Time to 2019-nCoV RNA negativity in patients and the time until progression to severe COVID-19.

Secondary outcomes.

1. The rate of patients with non-favorable evolution as measured by clinical evaluation (fever, unproductive cough or dyspnea, and their X-ray or CT scan imaging);
2. The increments of RNA and protein levels of IFN responses markers (2-5 OAS, β -2 microglobulin), and IFN signaling factors (STAT-1 and STAT-3);
3. Increments in the MHC-I and II and the activation of NK, T cytotoxic and memory cells;
4. Safety.

Virological evaluation:

1. Time to negativization of the SARS-Cov-2 RNA (absence of the virus according to the qPCR technique in real time) in positive patients after starting antiviral therapy. The percentage of patients negative

to SARS-COV-2 by qPCR in nasopharyngeal exudate tissue will be calculated at 48, 72 and 96 hours after starting treatment.

Clinical evaluation:

1. Time to progression to severe COVID-19. The percentage of patients who become severe after the end of the antiviral treatment under investigation (three weeks) will be calculated.

Participant timeline {13}

	Study period					
	Base line	Post allocation				
Time point (study day)	DO	Week 1	Week 2	Close-out		
Enrroment and assignment						
Elegibility assesment	X	Day 2	Day 4	Day 9	Day 11	Day 14
Informed consent	X					
Randomized subjets	X					
Baseline data collection	X					
Study drug administration						
Drug dispensing	X		X	X	X	
Adverse-drug reaction- assesment						
Serious-adverse-event- assesment						
Clinical-data-collection						
Vital parmeters	X	X	X	X	X	X
Body temperature						
Outcomes						X
Chest-X-ray	X	X	X	X	X	X
Electrocardiogram	X	X	X	X	X	X
Laborartory data collection		48h	72h	96h		
SARS-CoV-2 bucal swabs	X	X	X	X		X
Hematological determintions	X	X	X	X	X	
Chemestry	X	X	X		X	

Sample size {14}

We hope to enroll a sample size of one hundred and twenty patients for this study, based on a power of 80%, and a level of confidence set at 95%, while also considering a dropout rate of 5%.

Recruitment {15}

'Not applicable' . The source of patients is all the positive patients that are hospitalized at the study hospital

Assignment of interventions: allocation

Sequence generation {16a}

One hundred and twenty eligible patients with confirmed SARS-CoV-2 positivity by qPCR amplification in oropharyngeal swab samples will be enrolled at Luis Diaz Soto Hospital, Havana, Cuba. Patients will be block randomized individually to one of two treatment arms by means of random computer-generated lists, with an allocation ratio of 1:1, with block sizes of six patients.

Concealment mechanism {16b}

There will be a centralized randomization at CIGB. The randomization procedure will be carried out by the Supply Group of the Direction of Clinical Investigations at CIGB. Patients will be block randomized individually to one of two treatment arms by means of random computer-generated lists, with an allocation ratio of 1:1, with block sizes of six patients.

Implementation {16c}

The information of the treatment group (A or B) will only be known after the patient is included. At the time of inclusion (after the selection criteria have been verified and written informed consent has been obtained), the clinical investigator will give the information to the CIGB monitors (who will visit the hospital daily and remain at their posts command). After collecting the general patient information to include (initials, date and time), will assign the inclusion number and the corresponding treatment (consecutive, according to a random list in their possession).

Assignment of interventions: Blinding

Who will be blinded {17a}

'Not applicable'

Procedure for unblinding if needed {17b}

'Not applicable'

Data collection and management

Plans for assessment and collection of outcomes {18a}

'Not applicable'

Plans to promote participant retention and complete follow-up {18b}

'Not applicable'

Data management {19}

For the purposes of this study, a data entry system will be generated at OpenClinica, which is a free software platform for protocol configuration and CRF design, which allows the electronic capture, storage and management of data.

The data entry will be carried out in duplicate (independently by two operators) for the subsequent process of automatic comparison and correction of the bases, necessary for statistical analysis with accurate information from the trial. For debugging errors, the data that does not match the one registered in the original CRF will be corroborated to avoid confusion. The comparison will be repeated until no differences are found between the databases. This process will guarantee the cleanliness of the data included in the databases that will later be used in the statistical analysis. This activity will be recorded, so that it can be traced to national and foreign inspections and / or audits.

Confidentiality {27}

The protocol's medical specialists, the promoter, the monitors and auditors appointed by the promoter will guarantee that the personal data of the subjects included in the protocol are treated in accordance with the provisions established in Law 15/1999 on data protection personal nature and the regulations that develop it. Likewise, the anonymity of the subjects included and the protection of their identity will be maintained; no personal data of the subjects of the protocol will be transferred, except in those circumstances allowed by law.

Monitors and auditors appointed by the promoter may access clinical information and documentation on the subjects included, in order to verify the accuracy and reliability of the data, but must not collect the personal identification data of the subjects. Access to this data should also be provided to the inspectors of the competent health authorities.

The results of the clinical trial, as well as all the work and reports carried out and all the industrial property rights derived from it, are the exclusive property of the promoter. The latter is committed to disseminating them, once the protocol is finished and whether they are negative or positive, in public access media.

The publication of the results, by the medical specialists of the hospital institutions, in scientific magazines or books and the oral presentations or posters at scientific events, workshops or meetings, must be carried out in agreement with the promoting center.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

The promoter center will be in charge of transmitting, operationally, the procedure for the extraction, identification and conservation of the biological samples that will be transferred to the CIGB according to procedures 4.40.121.01 and 4.40.122.01 in force at the Direction of Clinical Research at CIGB.

The transfer of samples from the healthcare unit will be the responsibility of the promoter center, which will guarantee the transportation, specialized personnel and resources necessary to carry out these operations with the maximum quality and compliance with GCP, as established by the procedures. in force (4.40.120.01 and 4.40.123.07) and their biosafety protocols.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

We will compare the study endpoints among the two arms using time-to-event methods with the Cox proportional-hazards model. The different categorical variables will be analyzed using the one-way analysis of variance. To describe the efficacy and safety of the IFN regimens, Kaplan-Meier estimates and a multivariate Cox proportional hazards model will be used to compare severity of patients and adverse events among the two arms during the study period at week four. A p-value of <0.05 will be deemed to confer statistical significance.

Interim analyses {21b}

'Not applicable'

Methods for additional analyses (e.g. subgroup analyses) {20b}

'Not applicable'

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

'Not applicable'

Plans to give access to the full protocol, participant level-data and statistical code {31c}

'Not applicable'

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

Steering Committee

The Steering Committee, led by the principal investigator, will be responsible for overseeing the conduction of the trial, providing training for new sites, ensuring compliance with the study procedures,

addressing challenges that occur at all sites, reviewing serious adverse events and formulating the statistical analysis plan.

For clinical trials at CIGB, the function of coordinating centre is playing by the Direction of Clinical Research that is the responsible for design, endpoint adjudication, data management, statistical analysis and final report for the clinical trial.

Monitors from the Clinical Research Direction at CIGB, Havana, Cuba.

- Iván Campa Legrá. MSc. Monitor
- Yaquelin Duncan Roberts, MD, MSc. Monitor
- Claudia Martínez Lic. Monitor

Data managing.

- Marel Alonso Valdés. Ing. Informatics at Clinical Research Direction

Statically analysis

- José C. Cortiñas Porras. Lic. Mathematics at Clinical Research Direction

Supervisors

- Iraldo Bello Rivero, MSc, PhD. Project Manager at Clinical Research Direction
- Francisco Hernández Bernal. Methodological Assessor at Clinical Research Direction
- Verena Muzio Gonzalez. MD, PhD. Director of Clinical Research Direction

1. Laboratory of Genomic and Immunological determinations. Biomedical Research Direction (BRD) at CIGB, Havana, Cuba.

- Dania M. Vázquez Blomquist, PhD. Genomic evaluations at BRD
- Monica Bequet Romero. PhD. Immunological evaluations at BRD
- Gilda Lemos Perez. MSc. Immunoenzymatic evaluations at BRD
- Gerardo Guillen Nieto. Methodological and Scientific Assessor. Director of Biomedical Research Direction.

Composition of the data monitoring committee, its role and reporting structure {21a}

Monitors from the Clinical Research Direction at CIGB, Havana, Cuba.

- Iván Campa Legrá. MSc. Monitor
- Yaquelin Duncan Roberts, MD, MSc. Monitor
- Claudia Martínez Lic. Monitor

The trial monitors will carry out quality monitoring visits at all stages of its execution, ensuring strict compliance with the provisions of the protocol.

The flow of primary protocol information to and from health institution will be guaranteed by the CIGB.

The research product (HeberFERON), CRF and other models will be delivered / collected by the CIGB, directly by the study monitors. The monitors, in the quality monitoring visits, will collect the CRFs of those patients who concluded their participation in the trial. The Supply Group at CIGB is responsible for the adequate supply of medicines and medical supplies, as well as the collection of the product under investigation (dispensed and not dispensed).

The investigator should have a report of the number of patients included, the detected adverse events, the study departures and the causes of these, as well as any other relevant information during the course of the trial, for when they are requested during the quality monitoring visits.

Adverse event reporting and harms {22}

In this study, the occurrence of serious adverse events is not expected, due to short time of exposure and low doses of treatment. However, if they occur, treatment will be suspended and the required measures will be taken depending on the type of event.

Special attention should be paid to known adverse events for HeberFERON. The “Product Manual” (attached to the protocol) describes the behavior against the most significant adverse reactions (reported in other entities). The investigator responsible for the study at the participating institution will be responsible for the diagnostic evaluation and follow-up of patients with adverse events.

In the event of serious adverse events (with proven causality) the administration of the product will be interrupted and if this has not been concluded, the required measures will be taken depending on the event and the possible expedited report of the same will be considered.

The occurrence of the event will be notified to the monitor within a period not exceeding 24 hours. The person responsible for the investigation, the monitors and the team of investigators, will carry out the corresponding investigations in order to determine the component causing the undesired effect. After recovery from the adverse event, the patient may restart treatment according to the treatment scheme they were receiving, if the inclusion in their group had not been stopped due to exceeding the maximum level of toxicity. If severe toxicity occurs again, treatment is permanently discontinued

- Notification of adverse events

It will consist of two stages: the immediate notification of all serious adverse events and the reporting of serious and unexpected adverse events in relation to causation, which will be independent of each other.

Immediate notification will be made to the national regulatory agency in Cuba, Center for State Control of the Quality of Medicines (CECMED), within the first 72 hours after the Promoter becomes aware of the

serious (serious) and unexpected adverse event and will be mandatory.

The model of the report of serious (serious) and unexpected adverse events in relation to causation and the attached documentation regarding the adverse event presented must be submitted to CECMED, as soon as possible and never after seven calendar days if the adverse event is fatal or compromises the subject's life, if not, the reporting time will be 15 days.

- Expedited report of adverse events

To do the same, you must follow the instructions of procedure 4.40.039.01 in force at the CIGB Directorate of Clinical Investigations. Any serious unexpected adverse event that arises must be evaluated with a view to the expedited report.

For any serious unexpected adverse event, the causal relationship with the drug should be established to assess whether it is classified as an adverse reaction. According to the defined terms, an adverse reaction is any harmful and involuntary event that has a reasonable possibility of a causal relationship between the medicinal product and the adverse event, meaning as reasonable causal relationship the existence of evidence, facts and arguments that suggest a relationship of causality.

In the event that the investigator classified the adverse event as reasonably related to the medication as serious and unexpected, said specialist will proceed to the expedited report of said reaction. Its realization will include:

- The immediate report by the specialist to the monitor as representative of the promoter. This must within the first 24 hours of occurrence. The information may be communicated by phone, fax, email or in person.
- The immediate report by the promoter to the CECMED. This must occur in the following periods:

The monitor's expedited report to CECMED will be carried out using the corresponding model. This model will be filled DOUBLE.

Frequency and plans for auditing trial conduct {23}

'Not applicable'

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

- Check-up and quality control monitoring in compliance with Good Clinical Practices.

The actions to be completed in these visits will be described in procedures 4.40.006.07, 4.40.010.07, 4.40.016.04, 4.40.027.01, 4.40.028.00, 4.40.033.00 and 4.40.049.07 in force at Clinical Research Direction at CIGB.

Quality monitoring and control will be carried out by the monitors, quality control managers, consultants and specialists responsible for the test. These visits will also serve to discuss any aspect of the protocol that the researcher suggests.

Execution check visits will be made daily from the beginning of the study. The first Quality Control visit will be made immediately after the first patient is included.

Dissemination plans {31a}

'Not applicable'

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Discussion

For many emerging infectious diseases patients are often treated with therapeutics minimal evidences. Due to the urgency of COVID-19 pandemic, not only IFN alpha, but various drugs are being used as therapeutic tools, even though their efficacy has not been completely demonstrated for the treatment of SARS-CoV-2. If these patients had been included in a properly designed study, conclusive evidence might have been generated. Performing such a trial meets a critical need.

Some limitations to our study design should be noted. The blinding was not feasible, it will maintained for laboratory SARS-CoV-2 RNA detection by PCR, that is one of the endpoint of the study.

Trial status.

The HOPE trial has already been approved by the Institutional Review Boards at “Luis Diaz Soto” Hospital and Regulatory Authority for Medicines, CECMED. Enrollment for this study began in April 11, 2020, and has enrolled one hundred patients as of May 26, 2020. The recruitment will be completed will be completed in the second week of June 2020.

Abbreviations

<i>[Review for completeness prior to finalizing protocol – all abbreviations mentioned within the protocol must be included; some are provided below, use/modify as needed.]</i>	
AE	Adverse Event
BCC	Basal Cell Carcinoma
CECMED	Center for State Control of the Quality of Medicines
CIGB	Center for Genetic Engineering and Biotechnology
CRF	Case Report Form
CSF	cerebral spinal fluid
CTCEA	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IND	investigational new drug application
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
MERS	Middle East Respiratory Syndrome
MIU	Million international Units
PD	disease progression
PK	Pharmacokinetics
SARS	Severe Acute Respiratory Syndrome

Declarations

- **Acknowledgements**

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Authors' contributions {31b},

IBR, conception and design, analytical plan, drafting of the manuscript, critical revision of the manuscript for important intellectual content, approval of the final version to be published and agreement to be

accountable for all aspects of the work. FHB, critical revision of the manuscript for important methodologically content, approval of the final version to be published. HNC, drafting of the manuscript. YDR, analytical plan, approval of the final version to be published and agreement to be accountable for all aspects of the work. CMS, analytical plan. ICL, critical revision of the manuscript for important methodologically content. IEM, clinical research coordinator at the hospital, analytical plan. VMG, approval of the final version of the protocol. GNG, revision of the manuscript for important intellectual content.

Funding {4}

This work was supported by Center for Genetic Engineering and Biotechnology and Ministry of Health of Cuba.

Availability of data and material {29}

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate {24}

The HOPE study is approved by the Ethics Committee of “Luis Diaz Soto” Hospital in Havana, Cuba and by CECMED

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Council for Harmonization–Good Clinical Practice guidelines. Informed consent will be obtained from patients. Site investigators will explain the objectives of the trial and its potential risks and benefits to patients during the process of obtaining consent. No compensation is provided for enrollment in the trial. Patient personal data are de-identified.

Consent for publication {32},

The consent for publication is included in informed consent that signs the patient

Declaration of Informed Consent for the subject

I (name and surname)

.....

I have read the information sheet given to me.

I have been able to ask questions about the study.

I have received enough information about the study.

I have spoken with:

.....

(name of researcher)

I understand that my participation is voluntary.

I understand that I may withdraw from the study:

1st Anytime

2º Without having to give explanations.

3º Without this having an impact on my medical care.

I freely give my consent to participate in the study and **give my consent for the access and use of my data under the conditions detailed in the information sheet.**

- I agree that the blood or tissue samples obtained for the study may be used in the future for new analyzes related to the disease or study drugs not provided for in the current protocol (genetic analyzes are excluded, as long as they are not part of it of the study objectives):

Competing interests {28}.

Authors IBR, FHB, HNC, YDR, CMS, ICL, VMG and GGN, are employees of the Center for Genetic Engineering and Biotechnology, Havana network where Heberon Alpha R and HeberFERON are produced. The other authors have no competing interests.

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