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Study to verify the effectiveness and safety of the modified isothymol or carvacrol compound against SARS-CoV-2 in COVID-19 patients

Submission date
22/06/2022

Recruitment status
No longer recruiting

Registration date
23/06/2022

Overall study status
Completed

Last Edited
07/10/2022

Condition category
Infections and Infestations

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
The general objective of this study is to verify the efficacy and safety of modified Isothymol as a therapeutic treatment against COVID-19 disease.

Who can participate?
Patients 18 years of age or older, with positive RT-PCR for SARS-CoV-2, who attend a medical center with an active primary care program, in the first hours after the onset of symptoms.

What does the study involve?
The study investigators will record the hospital course of patients including complications and derived treatments of the same, both pharmacological and non-pharmacological.

What are the possible benefits and risks of participating?
Participants will receive treatment for 15 continuous days for COVID-19 disease. Medications are guaranteed free of charge.
Product safety data confirms a positive benefit/risk ratio, no treatment-emergent toxicities attributable to isothymol or carvacrol are observed, in rare cases loose stools and yellow urine may occur after taking the drug. Drawing blood with the insertion of a cannula may cause minor and mild discomfort. Risks associated with blood draws include minor pain, bleeding, and bruising.

Where is the study run from?
Hospital Dr. Leopoldo Manrique Terrero - Periférico de Coche (Venezuela)

When is the study starting and how long is it expected to run for?
June 2020 to November 2020

Who is funding the study?
Instituto Venezolano de Investigaciones Científicas (IVIC) (Venezuela)

Who is the main contact?
Prof Raul Antonio Ojeda Rondon
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Contact information

Type(s)
Principal investigator

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT05445089

Protocol serial number
LAB-2020-01

Study information

Scientific Title
Multicenter, randomized, double-blind study with placebo to verify the efficacy, safety and tolerability of the modified isothymol or carvacrol compound against the SARS-CoV-2 agent in COVID-19 patients

Study objectives
The administration of modified Isothymol would reduce by 60% the possibility of cytokine storm (severe patients in phase 2b and 3) caused by hyperactivation of inflammatory mediators by the agent SARS-CoV-2 (COVID-19).

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 25/08/2020, Bioethics Committee, Hospital Dr. Leopoldo Manrique Terrero - Periférico de Coche (Av. Intercomunal de El Valle con Calle Zea – Parroquia Coche, Caracas, Venezuela; +5802126811133; no email provided), ref: G-20009444-3

Study design
Interventional randomized parallel double-blind multicenter study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
COVID-19 (SARS-CoV-2 infection)

Interventions
Experimental drug name: Carvativir 6 mg/ml diluted for oral solution.

Qualitative and quantitative composition: Each ml contains 6 mg of CARVATIVIR (2-Methyl-5-(1-methylethyl)-phenol modified) at 1% v/v. (Isothymol modified lipophilic GRAS).

Pharmaceutical form:
Oral solution (dispersion L/L). Dilute lipophilic aqueous solution of light or medium yellow.
Excipients q.s: cis-9-octadecenoic acid with Squalene (99% v/v).

Presentation: Carvativir (Modified Isothymol) comes in a 15 cc presentation in a plastic container, with label and sealed.

Dosage and method of administration: The recommended dose of Carvativir in patients over 18 years of age and weighing at least 45 kg is:
Five to fifteen loading drops of Carvativir 6mg/ml administered orally sublingually every 4 hours according to administration criteria.

Control type and design
Randomized, double-blind, multicenter study with blind evaluation of events, designed to compare the efficacy and safety of Isothymol modified with placebo in patients ≥18 years of age who meet the inclusion criteria.
Drug administration scheme: Randomized and parallel (modified isothymol and placebo).
Statistical design: Superiority. It will allow the detection of the difference between drug and placebo after parallel administration.

Masking techniques
The assigned treatment will not be known to the study subjects, the participating researchers and the evaluators of the criteria of study assessment. The placebo should contain the same technical specifications and physical appearance of modified Isothymol.

To ensure individual opening of the randomization code, sealed envelopes will be prepared for each subject, which will contain the specific treatment received by each. These envelopes can be controlled by the Clinical Researcher, the Nursing Staff or Pharmacy available 24 hours. In the

event that the opening of the envelope and the randomization code before the end of the test, said procedure must be documented and explained the causes of the opening.

Selection and initial management of patients
Immediately after the diagnosis of the COVID-19 disease and if the presence of criteria for inclusion and the absence of exclusion criteria, the informed consent.
Simultaneously, and in the absence of contraindications, will administer a dose of 6 mg/ml modified Isothymol, in case of who had not previously received it.
After obtaining informed consent, the treatment strategy uses centralized randomization, using a phone system. Eligible patients will be randomized to one of the following therapeutic strategies:
• Modified Isothymol Treatment Group: Immediately after randomization a dose of 6 mg/ml of modified isothymol.
• Placebo Treatment Group: Immediately after the randomization a placebo dose will be administered.
The sample will be stratified according to the risk of the disease in 4 risk groups from highest to lowest:
• Group 1: Diagnosed patients and performance of procedures that generate aerosols (e.g., tracheal intubation, bronchoalveolar lavage or manual ventilation).
• Group 2: Patients diagnosed, but without performing aerosol-generating procedures.
• Group 3: Undiagnosed patients, but with symptoms compatible with infection.
• Group 4: Asymptomatic undiagnosed patients.

The total duration of treatment should be at least 15 days.

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
Carvativir (carvacrol, isothymol)

Primary outcome(s)
1. Diagnosis of the presence of COVID-19 infection by RT-PCR: day 0 (start of treatment) and in case of withdrawal due to infection.
2. Diagnosis of COVID-19 infection due to absence of acute respiratory infection: day 0 (start of treatment), day +15 (end of treatment) and day 0 and +45 (end of follow-up).
3. Therapeutic compliance: day 0 and +15 (end of treatment).
4. Completion of the study (yes/no): day 0 and +45 (end of follow-up).

Key secondary outcome(s))
1. Vital signs (heart rate, respiratory rate, temperature, blood oxygen saturation (SpO2) and blood pressure): day 0 (beginning of treatment), +15 (end of treatment) and +45 (end of follow-up).
2. Basic analysis (Complete hematology (Hg, Hto, WCB, Neutrophils, Lymphocytes, Platelets), CRP, PT – PTT, Ferritin, Fibrinogen, D-dimer, IL-6, IgM and IgG, Chest CT): day 0 (start of treatment), +15 (end of treatment) and +45 (end of follow-up).

3. Adverse events: day +15 (end of treatment) and 45 (end of tracing).
4. Death: at the time of death.
5. Use of PPE: day +15 (end of treatment) and +45 (end of follow-up).

Completion date
01/11/2020

Eligibility

Key inclusion criteria
1. Positive test PDR, positive test RT-PCR, patients diagnosed with COVID-19
2. Chest pain or other symptom consistent with bilateral pneumonia atypical, with one of the following paraclinical alterations and imaging:
3. Oxygen saturation (SpO2) ≤93%.
4. Elevation of D-dimer ≥10 mg/mL.
5. Elevation of Ferritin ≥120 ng/mL.
6. Elevation of Fibrinogen ≥400 mg/dL
7. Elevation of Immunoglobulin M (IgM) ≥200 mg/dL.
8. Elevation of Interleukin 6 (IL-6) ≥1800 pg/mL.
9. Rx. chest and CT showing thickening of the bronchi, consolidation and ground glass opacities.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
600

Key exclusion criteria
Negative test PDR, negative test RT-PCR and Inadequate administration of antiviral (for non-compliance with indicated intervals or death of the patient before 15 days treatment indications).

Date of first enrolment
01/07/2020

Date of final enrolment
30/07/2020

Locations

Countries of recruitment
Venezuela

Study participating centre
Hospital Dr. Leopoldo Manrique Terrero - Periférico de Coche.
Calle Zea
Local S/N, parroquia Coche
Municipio Libertador
Caracas
Venezuela
1090

Sponsor information

Organisation
Instituto Venezolano de Investigaciones Científicas

ROR
https://ror.org/02ntheh91

Funder(s)

Funder type
Government

Funder Name
Instituto Venezolano de Investigaciones Científicas

Alternative Name(s)
Venezuelan Institute for Scientific Research, IVIC

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
Venezuela

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request
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IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	page 151	01/10/2021	22/06/2022	Yes	No
Results article		09/09/2022	07/10/2022	Yes	No
Protocol file	in Spanish	01/06/2020	17/08/2022	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes