ISRCTN16254682 https://doi.org/10.1186/ISRCTN16254682

An open-label, multicenter, randomized, controlled adaptive study to evaluate the efficacy and safety of investigational therapeutics for the treatment of hospitalized patients with mild to moderate novel coronavirus disease (COVID-19) in Kinshasa, Democratic Republic of the Congo

Submission date
27/09/2023

Recruitment status
No longer recruiting

Registration date
24/10/2023

Overall study status
Completed

Last Edited
05/11/2024

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
At the start of the COVID-19 pandemic, the herbal medicine Doubase C derived from two plant species found in the Democratic Republic of Congo, Uvaria brevistipitata and Haroungana madagascariensis, received authorization for clinical trials in the DR Congo. This study aims to determine its efficacy and safety compared to hydroxychloroquine-azithromycin, the national standard treatment for COVID-19 at that time. This is a multicenter trial designed as a platform clinical study with interim monitoring to allow addition or drop of treatment arms that will include similar inclusion and non-inclusion criteria, same primary and secondary endpoints, common data entry procedures, shared database and single statistical plan for analysis of the primary endpoint.

Who can participate?
Patients with mild and moderate COVID-19

What does the study involve?
An open randomized clinical trial will be conducted with asymptomatic, severe and critical cases excluded. Each patient's parameters (NEW score, Ordinale scale, viral load, EKG tracing) will be sequentially evaluated and the proportion of change compared between two study arms on days 7 and 14.

The results in the different therapeutics arm will be compared with the control arm, which is the Standard of Care (SoC). The initial plan of this study will randomize (1:1) participants to (i)

Doubase C + SoC; (ii) Hydroxychloroquine plus azithromycin + SoC; If additional arms are added to or dropped from the trial, randomization will proceed with an equal probability of assignment to each of the remaining arms. Randomization will be stratified by Site and Severity of illness at enrolment (mild or moderate).

All study subjects will undergo pre-trial tests and also during treatment additional tests on days 1, 7 and 14 after treatment. The tests include heart, lung, kidney and liver functions, complete blood count and PCR assessment of viral load. SpO2 will be monitored on a daily basis. Patients reaching SpO2 < 90% will be withdrawn from the study and provided the best care for severe case management.

What are the possible benefits and risks of participating?
Doubase C exhibits a broad spectrum of antiviral activity, effectively targeting retroviruses like HIV and Herpes, enteroviruses such as Hepatitis B and C, and influenzaviruses. It is also anticipated to be effective against SARS-CoV-2. Furthermore, Doubase C possesses significant antitumor properties, proving beneficial for both benign and malignant tumors.

Doubase C contains diverse compounds with varying effects and precautions. Some of these compounds can be acidic and potentially cause stomach discomfort, especially in patients with a history of gastralgia or gastric ulcers, necessitating adjuvant antacid treatments. It also comprises compounds with hypoglycemic and hypotensive properties, requiring regular blood sugar and arterial pressure monitoring, with possible adjustments in diet or medication dosages for patients undergoing related therapies. Additionally, some compounds exhibit promising potential in restoring myocardial functions and hemodynamic parameters, while the medication's diuretic effects do not deplete essential ions. Furthermore, Doubase C includes compounds that stimulate appetite. It's essential to avoid combining Doubase C with external hormones or hormone-related products, as this can counteract its intended effects.

Where is the study run from?
University of Kinshasa (DR Congo)

When is the study starting and how long is it expected to run for?
January 2021 to January 2022

Who is funding the study?
Industry Promotion Fund (Le Fonds de Promotion de l’Industrie; FPI) (DR Congo)

Who is the main contact?
Prof Jean-Robert Makulo, makulo.rissasi@unikin.ac.cd

Contact information

Type(s)
Public, Scientific, Principal Investigator

Contact name
Prof Jean-Robert Makulo

ORCID ID
https://orcid.org/0000-0001-5517-3281

Contact details
123 Cliniques Universitaires de Kinshasa
Kinshasa XI
Congo, Democratic Republic
Kinshasa
+243990205367
makulo.rissasi@unikin.ac.cd

Type(s)
Public

Contact name
Prof Jean-Robert Makulo

Contact details
123 Cliniques universitaires de Kinshasa
Kinshasa XI
Congo
Kinshasa
+243 990205367
jrmakulo2016@gmail.com

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
444/MIN.RSIT/CABMIN/JMK/2020UNIKIN COVID 001

Study information

Scientific Title
An open-label, multicenter, randomized, controlled adaptive study to evaluate the efficacy and safety of investigational therapeutics for the treatment of hospitalized patients with mild to moderate novel coronavirus disease (COVID-19) in Kinshasa, Democratic Republic of the Congo

Acronym
DOUBASE C Clinical Trial

Study objectives
The null hypothesis being tested is:

Whether the risk of progression from the mild or moderate form to a severe form of the disease is the same for the 2 arms;

Whether the safety of organ damage is the same in the 2 arms.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 16/03/2021, University of Kinshasa, School Of Public Health Ethics Committee (L'université de Kinshasa, Ecole de Santé Publique Comite d'ethique) (Lemba, Kinshasa, 11850 Kin I, Congo, Democratic Republic; +243 817493194; espsec_unikin@yahoo.fr), ref: ESP/CE/038 /2021

Study design
Randomized open-label controlled adaptive study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment, Safety, Efficacy

Participant information sheet

Health condition(s) or problem(s) studied
COVID-19 patients with mild or moderate clinical stage/WHO classification followed up at university clinics in Kinshasa during the second and third waves of the COVID-19

Interventions
Two initial arms (all oral therapeutics):
1. Doubase C (30 mg Uvaria brevistipitata extract; 6 mg Haroungana madagascariensis extract)
< = 70 kg: 2 tablets thrice for 7 days
> 70 kg: 4 tablets thrice for 7 days
2. Chloroquine/hydroxychloroquine + Azithromycin
Hydroxychloroquine 2x200 mg for 10 days
PLUS
Azithromycin 500 mg Day 1 and 250 mg Day 2-5.

The present open-label randomized controlled clinical trial is an adaptation of the standard protocol validated by the WHO for clinical trials of herbal medicines used in the treatment of COVID-19 (WHO Master Clinical Study Protocol, 2021). The study site is the COVID-19 treatment center (CTCO) of the Kinshasa University Hospital (KUH). Patients diagnosed with SARS-CoV2 infection on the basis of a polymerase chain reaction (PCR) carried out at the KUH Laboratory are invited to participate in the study after signing an informed consent form.

The inclusion criteria are the consultation at KUH for symptoms suggestive of COVID-19, agreement for the collection of nasopharyngeal/oropharyngeal swabs and venous blood per

protocol, positive SARS-CoV2 test confirmed by PCR, agreement to not be enrolled in another trial for the full duration of the study, agreement to be randomized in one or the other arm following the draw, agreement to take the proposed treatment and to be monitored according to the study protocol, mild or moderate COVID-19 according to the WHO clinical classification (World Health Organization, 2020).

The non-inclusion criteria are asymptomatic and severe/critical COVID-19 according to the WHO clinical classification (World Health Organization, 2020); aged under 18 years old, pregnancy, comorbidities meaning that the serum creatinine > 1.5 mg/dL, estimating glomerular filtration rate (eGFR) < 60 mL/min / 1.73m2, ASAT and/or ALAT > 2 times the upper limit of normal (ULN), Total bilirubin > 2 × ULN, chronic kidney disease, liver disease, blood disease, heart disease, prolongation of the QTc interval on the EKG, cancer psychiatric illness; the use of medications that prolong the QTc interval; known allergy to drugs under study clinic and the history of COVID-19 or under current treatment.

Randomization
A random sampling table will be used for randomization. Once the group is known, the patient will continue the study according to the recommended protocol and their follow-up will be performed on an outpatient basis with determined appointment days.

Parameters of interest
All patients will have pre-trial tests and additional tests during treatment on Days 1, 7 and 14. The tests include SpO2, EKG, creatinine, ALAT, ASAT, complete blood count (hemoglobin = Hb, white blood cells = WBC, platelets = PLT) and PCR assessment of viral load. Patients reaching SpO2 < 90% will be withdrawn from the study and provided the standard of care for severe case management. The clinical evaluations before, on days 1, 7 and 14 systematically included the clinical examination (measurement of weight, blood pressure, heart rate, respiratory rate), the degree of illness of a patient and prompts critical care intervention determined by the NEWS 2, the ordinal scale for grading disease severity and responses to therapy of COVID-19, the COVID-19/WHO Clinical Classification as well as the search for adverse effects.

Presentation of products and methods of administration
Doubase C is a large-spectrum antiviral medication derived from 2 plant species found in DR Congo (Uvaria brevistipitata extract + Haroungana madagascariensis extract). It has been certified by the DR Congo Ministry of Health since 2017 (AMM: MS.1253/10/05/DEM/0314 /2017). Doubase C dosage, < 80 Kg: 2 tablets TID for 7 days; 80-99 Kg: 3 tablets TID for 7 days and ≥ 100 kg: 4 tablets TID for 7 days.
The DR Congo reference protocol at the start of the pandemic (Democratic Republic of the Congo, 2020) :
• Hydroxychloroquine 200 mg TID for 10 days
• Azithromycin 500 mg once the first day then 250 mg once a day for 4 days.
In addition to this optional treatment, all the patients included in the clinical trial will be treated with zinc sulphate (20 mg once a day for 10 days), vitamin C (500 mg once a day for 10 days), and vitamin D (400 UI TID for 10 days). Diabetic and hypertensive patients will continue their usual treatment at the same dose. Oxygen is given when SapO2 is below 95%.

Statistical analyzes
All data are entered with a tablet using the Survey CTO app. A double entry on Excel 2016 was carried out to check the consistency of the data entered. Data cleaning was then carried out. Continuous data were expressed as averages ± standard deviation and categorised data as percentages. Changes in the WHO clinical classification of COVID-19, the NEWS and the Ordinal scale, on Days 7 and 14 were summarized by proportions. The two-sample Student’s t-test and

Chi-squared test are used for comparisons of means and proportions where appropriate. Repeated measures analysis of variance is used to test the change of clinical and paraclinical parameters (Friedman test).

Ethical approval and consent to participate
The investigators agreed to conduct the present study in agreement with the principles of the Declaration of Helsinki. Access to patient medical records was granted by the Direction of the hospital and the Research Ministry of DR Congo (444/MIN.RSIT/CABMIN/JMK/2020). Our research projects on COVID-19 received the approval of the Ethics Committee of the Kinshasa School of Public Health of the University of Kinshasa (ESP/CE/038/2021). All data were fully anonymized before they have been accessed.

Intervention Type
Drug

Pharmaceutical study type(s)
Pharmacodynamic

Phase
Phase III

Drug/device/biological/vaccine name(s)
Doubase C (extracts of Uvaria sp 30 mg + Harungana sp 6 mg), chloroquine/hydroxychloroquine, azithromycin

Primary outcome measure
The proportion of patients with mild/moderate COVID-19 whose clinical condition worsened measured using SpO2 < 90 % (severe clinical COVID-19) from baseline up to days 7 and 14 from randomization

Secondary outcome measures
1. SARS-CoV2 viral load measured using PCR on days 7 and 14 of randomisation
2. EKG tracing (prolongation of the QTc interval), results of creatinine, ALAT, ASAT, hemoglobin, WBC and Platelets measured using standard medical laboratory methods at baseline and on the 7th and 14th day

Overall study start date
01/01/2021

Completion date
31/01/2022

Eligibility

Key inclusion criteria
1. Male or non-pregnant female adult ≥18 years of age at time of enrolment. Children > 12 years of age and pregnant women may be included if recommended by the DSMB
2. Laboratory-confirmed SARS-CoV-2 infection as determined by PCR at a Government approved lab. from nasopharyngeal or oropharyngeal swab, within 48 hours prior to screening
3. No severe acute respiratory syndrome (SARS), that is, not using mechanical ventilation

4. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures
5. Understands and agrees to comply with planned study procedures
6. Agrees to the collection of NP/OP swabs and venous blood per protocol
7. Agrees to not be enrolled in another trial for the full duration of the study
8. Creatinine ≤ 110 umol/L, creatinine clearance rate (eGFR) ≥ 60 ml / min / 1.73m2, AST and ALT ≤ 40 IU/L

Participant type(s)
Patient

Age group
Mixed

Lower age limit
18 Years

Sex
Both

Target number of participants
176 patients/arm

Total final enrolment
376

Key exclusion criteria
1. Asymptomatic subjects
2. Requiring mechanical ventilation
3. Creatinine > 110 umol/L, eGFR < 60 ml / min / 1.73m2, ALT/AST > 2 × ULN or TBIL > 2 × ULN
4. Pregnancy or breastfeeding
5. Anticipated transfer to another hospital which is not a study site within 72 hours
6. History of allergy to any investigational product ingredients
7. Shortness of breath in resting position
8. Known prolonged QT syndrome
9. Use of concomitant medications that prolong the QT/QTc interval
10. Subjects who have severe underlying diseases that affect survival including uncontrolled malignant tumor with multiple metastases that cannot be resected, blood diseases, dyscrasia, active bleeding and severe malnutrition
11. Subjects who in the opinion of the investigators after assessing all relevant parameters are unsuitable for the study

Date of first enrolment
20/05/2021

Date of final enrolment
31/01/2022

Locations

Countries of recruitment
Congo, Democratic Republic

Study participating centre
Cliniques universitaires de Kinshasa
Avenue de l'université
Kinshasa
Congo, Democratic Republic
Kinshasa

Sponsor information

Organisation
Creppat Laboratories SARL

Sponsor details
3526, Avenue Good Year
Limete
Kinshasa
Congo, Democratic Republic
None available
None available
Betty.nzovo@fpi-rdc.cd

Sponsor type
Government

Website
Betty.nzovo@fpi-rdc.cd

Funder(s)

Funder type
Government

Funder Name
Le Fonds de Promotion de l’Industrie

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact and peer-reviewed journal

Intention to publish date
26/09/2023

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Abstract results			18/10/2023	No	No
Statistical Analysis Plan			18/10/2023	No	No
Other publications		25/06/2024	05/11/2024	Yes	No