

“The efficacy and safety of carrimycin treatment in patients with novel coronavirus infectious disease (COVID-19) : A multicenter, randomized, open-controlled study”

Informed Consent Form (ICF)

An acute novel coronavirus viral pneumonia (NCP)or novel coronavirus infectious disease (COVID-19”) in Wuhan in December 2019 has attracted great attention of people all over the world. The Chinese people all are contributing to the complete victory of the battle through mass prevention and control. As the COVID-19 is an emerging infectious disease not scientifically recognized and has no effective treatment means currently, we will launch a national emergency scientific project **“The efficacy and safety of carrimycin treatment in patients with novel coronavirus infectious disease (COVID-19) : A multicenter, randomized, open-controlled study”** to provide important basis for scientific treatment and further understanding of the COVID-19. Your case may be eligible for the study, so we would like to invite you to participate in the study.

This ICF will provide you with an overview of the purpose, procedures, benefits, risks, inconvenience or discomfort of the study. Please read carefully and make a conscious decision about whether to participate in the study. When the investigator explains and discusses the ICF with you, you are free to ask questions and have him or her explain to you what you do not understand. You can also discuss this with your family members, friends and your doctor before making a decision. Please also let us know if you are currently participating in other clinical studies.

This study is led by Director Jin Ronghua of **Beijing YouAn Hospital, Capital Medical University**.

Why is this study conducted?

The sudden COVID-19 is an emerging infectious disease not scientifically recognized. Where does the virus come from? What are the transmission routes? How can it be treated and prevented scientifically? And the like. All these problems require good clinical study and observation to provide scientific and reasonable suggestions for controlling the spread of COVID-19 and further understanding this emerging infectious disease.

Who will be invited to participate in the study?

Subjects shall meet the following criteria before being included:

- (1) Subjects or their legal representatives have signed the ICF; agree not to participate in other clinical studies within 30 days after the last administration from the first administration of the study drug.
- (2) Subjects are aged ≥ 18 and ≤ 75 ;
- (3) Meet the diagnostic criteria for 2019-nCoV pneumonia (V5.0);
- (4) SOFA score: 1 ~ 13 points.
- (5) A retreated patient or the relapsed patient meets any of the following criteria:
 - ① Have fever again or aggravated clinical symptoms;
 - ② 2019nCOVRNA in the throat swabs converts from negative to positive;
 - ③ The clinical symptoms don't improve or 2019nCOVRNA continues to be positive;
 - ④ The chest CT shows pneumonia or fibrosis progression.

Clinical stratification of cases:

1. Mild type: clinical symptoms mild or asymptomatic, no pneumonia performance in CT, but positive 2019-nCoV in throat swabs or gargle.
2. Ordinary type: fever, respiratory symptoms, etc., pneumonia performance visible in CT.

3. Severe type: meeting any of the following criteria:

- (1) Respiratory distress, $RR \geq 30$ times/min;
- (2) Finger oxygen saturation $\leq 93\%$ in rest state;
- (3) Arterial partial pressure of oxygen (PaO_2)/concentration of oxygen inhalation (FiO_2) ≤ 300 mmHg ($1 \text{ mmHg} = 0.133 \text{ kPa}$).

4. Critical type: meeting any of the following criteria:

- (1) Respiratory failure occurs and mechanical ventilation is required;
- (2) Patients go into shock;
- (3) ICU is needed for other organ failure.

Who should not participate in the study:

- (1) Other viral pneumonia
- (2) Patients who have received tumor immunotherapy (such as PD-1/L1, CTLA4, etc.) in the past 1 month, and inflammatory factor modulators such as Ulinastatin;
- (3) Patients who have taken anti-bacterial drugs such as macrolide in the past 1 week;
- (4) Patients who have received organ transplantation or surgery planning in the past 6 months;
- (5) Patients who can't take food or drugs due to coma or intestinal obstruction;
- (6) Patients who have severe underlying diseases that affects survival, including uncontrolled malignant tumor with multiple metastases that cannot be resected, blood diseases, dyscrasia, active bleeding, severe malnutrition, etc.
- (7) Women subjects that are pregnant or lactating, or subjects (including male subjects) having a pregnancy plan (including plans for sperm donation or egg donation), or subjects that may fail to take effective contraceptive measures within the next 6 months;

- (8) Patients with allergic constitution, or patients allergic to macrolides and lopinavir/ritonavir tablets;
- (9) Patients with contraindications to lopinavir/ritonavir tablets who plan or are using drugs that interact with the drug (including: drugs that are highly dependent on CYP3A clearance and whose elevated plasma concentrations can be associated with severe and/or life-threatening events [with a narrow therapeutic index], CYP3A inducer [see instruction for details]) and cannot stop using or use other drugs instead;
- (10) Patients whose ALT/AST levels are 5 times higher than the normal upper limit and total bilirubin is 3 times higher than the upper limit of normal, or patients with child-Pugh grade C cirrhosis.
- (11) ECLS (ECMO, ECCO2R, RRT)
- (12) Critical patients with expected life < 48 hours
- (13) Patients who have participated in any other clinical study within 1 month;
- (14) The investigators conclude that the patients not suitable for the study.

How is the study conducted?

1. Before you are enrolled in the study, your doctor needs to know your condition in detail and make sure that you are a suitable candidate. You may participate in the study voluntarily and sign the ICF. You will be randomly assigned to two treatment groups:

(1) Trial group: basic treatment + Carrimycin

Mild type: 0.4g of Carrimycin tablets, p.o. after meal once a day for 7 consecutive days.

Ordinary type: 0.4g of Carrimycin tablets, p.o. after meal once a day for 10 days.

Severe and critical: 0.4g of Carrimycin tablets, p.o. after meal once a day for 14 consecutive days. If oral administration is not possible, the drug should be administered through a nasal feeding tube.

For the drug combination and treatment method of basic treatment according to the

the *Diagnosis and Treatment Program for 2019-nCoV* (V5.0,Chinese)

(2) Control group: any of basic treatment + lopinavir/ritonavir tablets or Arbidol or chloroquine phosphate:

Mild and ordinary type : 400mg/100mg, bid of lopinavir/ritonavir tablets each time; or 500mg bid of chloroquine phosphate; or 200mg tid of Arbidol for 7 consecutive days, followed up for observation after the end of treatment.

Severe and critical type: 400mg/100mg, bid of lopinavir/ritonavir tablets each time; or 500mg bid of chloroquine phosphate; or 200mg tid of Arbidol for 10 consecutive days, followed up for observation after the end of treatment.

For the drug combination and treatment method of basic treatment according to the the *Diagnosis and Treatment Program for 2019-nCoV* (V5.0,Chinese)

(3) Interrogation and physical examination for symptoms of discomfort and abnormal signs.

(4) **Take your morning gargle (throat swabs), urine, stool (anytime), and peripheral blood** and improve your routine examinations, including blood routine and lung CT according to your condition.

(5) Your samples will be used for 2019-nCoV RNA determination and 2019-nCoV antibody testing. Other specimens will be kept in the -80°C cryo freezer for scientific research. Based on these results, the doctor will make an accurate assessment of your disease and physical status and make scientific recommendations. We do not provide these study reports.

2. The study does not affect your treatment of other diseases, and we will provide you with quality medical and counseling services.

What are the risks and adverse reactions of participants in this study?

Drug risks: Carrimycin is already marketed for therapeutic indications including acute pharyngitis, acute suppurative tonsillitis, acute tracheitis - bronchitis, mild pneumonia, acute sinusitis, suppurative otitis media, and acute skin and soft tissue infection.

Safety results showed that 5 of 125 subjects in the Carrimycin group had adverse reactions, with the incidence rate of 4.00% (5/125), featuring ALT increased (3 cases), TBIL increased (1 case), and upper abdominal discomfort (1 case); 9 of 125 subjects in the Azithromycin group had adverse reactions, with the incidence rate of 7.20% (9/125), featuring ALT increased (3 case, 1 case of which is accompanied by AST increase and WBC increase in urine), upper abdominal or gastric discomfort (4 cases, with 1 accompanied by nausea), stomachache (1 case, accompanied by diarrhea) and headache (1 case). Lopinavir/ritonavir tablets are antiviral drugs recommended by the National Health Commission of the PRC and also have adverse reactions in this regard. **Risk of blood drawing:** the risk of blood drawing from the arm includes temporary discomfort and/or bruises, which usually go away on their own. There is also a slim chance of infection, bleeding, or syncope.

What are the potential benefits for participants in this study?

1. Get free examinations related to this study, including blood routine and CT, unless you don't need them.
2. Information obtained from this study will benefit other patients with the same disease in the future.
3. You can get routine observation and free consultation from a doctor with rich clinical experience.

Is it necessary to participate in and complete the study?

You are entirely volunteer to participate in the study. If you do not wish to, you may refuse to participate, which will not have any negative impact on your current or future medical treatment. Even if you agree to participate, you may change your mind at any time and tell the investigator to withdraw from the study. You will not face discrimination or retaliation for withdrawing from the study, nor will it affect your access to normal medical care. If you decide not to participate in this study, please inform your study doctor in time and the study doctor may provide advice and

guidance on your health status.

Under what circumstances will the subject cease to participate in the study?

Participation in the study will be terminated on one of the following conditions:

1. Re-hospitalization for another or the same disease
2. Aggravation or death of any cause.
3. Serious complications closely related to follow-up, such as anxiety, confirmed by the medical panel.

We may terminate the regular follow up with you during the study. We will promptly inform you if the study is terminated in advance. After subject withdrawal, we shall make it clear that no new data related to the subject will be collected in the future. We shall also make detailed instructions to the subject on how to deal with the previously collected study data and the data withdrawn due to adverse reactions.

Expenses for participation in the study

You may have access to free examinations related to this study during studying and follow-up. Every time you go to the hospital for collection blood and other samples.

What do I need to do to participate in the study?

1. Provide accurate medical history and current condition information.
2. Tell the study doctor about any health problems you have during the study.
3. Attend follow-up regularly.
4. Follow the instructions of investigators and medical staff.
5. Please feel free to ask if you have any questions.

Will the subject's personal information be kept confidential?

If you decide to participate in the study, your participation in the study and your personal data in the study will be kept confidential. Your blood specimens will be identified by the study number, not your name. Information that identifies you will not be disclosed to members outside the study group. To ensure that the study is carried out in accordance with the regulations, members of the government administration or ethics committee may, as required, access your personal data at the study site. No personal data of you will be disclosed when the results of this study are published. Your personal information will be kept strictly confidential.

Who should I contact if I have a problem or difficulty?

For any question regarding this study, please contact the doctor: _____ ,

Tel: _____

This study has been approved by the ethics committee of Beijing YouAn Hospital. If you need help, please contact:

Doctor Sheng 8610-83997028 Doctor Meng 8610-83997022

Compensation may be required for any damage related to the study. Please contact

Responsible person of compensation: Ding Huiguo

Tel:8610-83997155

Email:dinghuiguo@ccmu.edu.cn

Subject's informed consent statement

I have been informed of the study background, purpose, procedures, risks and benefits of the project "**The efficacy and safety of carrimycin treatment in patients with novel coronavirus infectious disease (COVID-19) : A multicenter, randomized, open-controlled study**". I have enough time and opportunity to ask questions, and I am satisfied with the answers. I has also been informed who to contact when I have questions or want further information. I have read this ICF and agree to participate in the study. I know that I can withdraw from the study at any time without any reason during the study. I'm informed that I would receive a copy of this ICF, which contains my and the investigator's signatures.

Name of subject in regular script:

Signature of subject:

Tel:

Date:

Investigator's informing statement

I have informed the subject of the study background, purpose, procedures, risks and benefits of the project "**The efficacy and safety of carrimycin treatment in patients with novel coronavirus infectious disease (COVID-19) : A multicenter, randomized, open-controlled study**", given him/her enough time to read the ICF and discuss with others, and answered the questions about the study; I have informed the subject of the contact information for any problem; I have informed the subject that he/she may withdraw from the study at any time during the study without any reason.

Name of investigator in regular script:

Signature of investigator:

Tel:

Date: