

Patient Information Sheet & Informed Consent Form

An open-label, multicentre, randomised, adaptive platform trial of the safety and efficacy of several therapies, including antiviral therapies, versus control in mild/moderate cases of COVID-19

Investigator: Dr Y (principal investigator)

Study site: XXXX

Sponsor: XXX

To the patient:

You are being asked to participate in a clinical study. You are entirely free to choose whether or not you want to participate in the study. This information sheet contains important information about the study for you to consider before you decide whether or not you want to take part in the study. Please take the time to read the information carefully. Ask any questions you like. If you want, you can talk to other members of your family or friends before you decide whether or not you want to participate in the study.

This document is divided into two parts.

Part 1: Information Sheet, which presents the reason why the study is being done, how the study will be done, the risks and benefits of the study and your rights if you choose to participate.

Part 2: Informed Consent Form, which is to certify that you agree to participate in the study.

Part 1: Information Sheet

Introduction

You are being asked to participate in the study because you have an infection with a new virus called SARS-CoV-2. The disease caused by the virus is called COVID-19. In most patients, the disease is usually mild, but in some patients it may progress, requiring admission to hospital. In patients with mild COVID-19, the treatment usually consists in treating the symptoms, such as fever, headache, pain and chills.

In [country], the standard treatment for patients with COVID-19 is [treatment].

At the present time, several medicines are being tested in patients with severe COVID-19, but so far none of them has clearly shown that it can cure the disease. You have been diagnosed with symptoms of the non-severe form of COVID-19. The purpose of the study is to see whether giving you a medicine will stop the disease from progressing to the severe form, which could require special care and hospitalisation.

Your participation in the study is entirely voluntary.

If you decide not to participate in the study, you will receive the standard treatment that is given to patients with COVID-19 in the hospital or clinic where you are.

If you decide to participate in the study, you will receive one of the treatments that are being tested in the study.

Why the study is being done

The study is being done to test whether giving you one of the treatments in the study will stop the disease from getting worse. All of the treatments in the study have already been given to a large

number of patients with other diseases and generally they have been found to be safe. We want to know whether the treatments are also effective against COVID-19.

During the study each patient will receive only one of the treatments. Some treatments may be added to the list of treatments, and others may be taken off the list.

If you are still under treatment and a treatment arm is dropped as ineffective the study personnel will inform you of this during your next visit or at the time your ethics/regulatory authorities will be informed. You have the choice at this time to stop your current treatment and to be treated under the current standard of care in [ENTER COUNTRY NAME]. If the treatment arm is dropped for safety reasons, your study investigator will inform you as soon as they have been informed by the Sponsor. The treatment will be stopped, and you will be treated under the standard of care in place in [ENTER COUNTRY NAME]

How the study is being done

If you decide to participate, you will be asked to sign a form to confirm that you have understood the risks and benefits and that you agree to take part in the study.

Next, information about you and your medical history (including your vaccination status for Covid-19) will be collected to be sure that there are no reasons why you cannot take the treatments in the study and that you are eligible to take part in the study.

If you are a non-pregnant woman with childbearing potential, a urine pregnancy test will be performed to confirm your pregnancy status.

Ivermectin/Artesunate-Amodiaquine (ASAQ) Arm:

Since the benefit of this tested treatment is not yet demonstrated in mild to moderate Covid-19 patients, and as there is potentially a risk during pregnancy and for breast-feeding child, we have taken the decision that pregnant or breast-feeding women, will not receive the ivermectin / ASAQ treatment. Initiation of pregnancy is not recommended during the trial for women who will receive this treatment. Should you become pregnant during the course of the study, please notify your study doctor immediately, the tested drug will be stopped. If you agree, we would like to follow the pregnancy until term to gather information regarding the pregnancy and the health of your newborn.

Other treatment arms:

Pregnant or breast-feeding women can be included in the study to receive the other drugs

For the other drugs tested in this trial, should you be already pregnant at time of participating or become pregnant during the course of the study you must notify your study doctor. We need to follow the pregnancy until term to gather information regarding the pregnancy and the health of your newborn, unless if you disagree.

The same day or the next day, the study personnel will examine you, measure your blood pressure and heart rate, the level of oxygen in your blood and so on, to be sure that you can participate in the study. If you are eligible, you will then be assigned to one of the study treatments. Neither you nor the study personnel can choose which of the treatments you will receive. A computer will assign you to a group by chance, like a roll of the dice. You will start taking the treatment and you will continue to take the treatment for maximum 14 days, depending on which treatment you are on.

You or your doctor can stop the treatment at any time before you reach the end of the treatment period, and you are free to change your mind and stop participating in the study at any time. All you have to do is tell your doctor.

The study treatments will be given to you at no cost. You will not be paid for your participation, but you may be reimbursed for any private transportation (according to local guidelines on Covid 19 pandemic) costs or for missed days of work related to your participation in the study. Ask the study doctor or a member of the study personnel for more information.

During the course of the study, you will have to return to the investigational centre three times: on Day 7, Day 14 and Day 21. On these days, the study personnel will examine you and do tests to see whether the disease is getting better or worse and to check that the treatment is safe for you. Some optional tests may include collection of a blood sample (5 millilitres or about 1 teaspoonful) to check that the treatment is safe, as well as chest x-ray and/or CT-scan at investigational centres that are equipped to do the tests and that do them as routine measures for patients with COVID-19. The study personal will call you a last time at Day 35 for a final follow-up on your health status.

In between the visits to the centre, you will have to fill out a questionnaire on your smartphone each day so your doctor can see whether the treatment is working and to check that it is still safe for you. If you do not have a smartphone, a member of the study personnel from the site will call you and ask you questions about your health. Based on your responses, your doctor may ask you to come at the site for additional visit.

At any time during the study, you can contact the study personnel if you have any questions or concerns or to inform them on any new symptoms or worsening of existing symptoms. Ask the study doctor or a member of the study personnel who you should contact and how.

Overall, your participation in the study is expected to last 22 days.

The study is also being conducted in other investigational centres in [ENTER COUNTRY NAME], and in more than 10 other countries in Africa. A total of 2000 to 3000 patients are expected to participate in the study. The first 300 patients will be adult men and women. Then, if the treatments are safe, children 12 years of age or older, may be allowed to participate.

Risks and Benefits of the Study

All of the treatments in the study are taken by mouth as tablets or capsules or inhalation. They are all well-known and have been used to treat other diseases for many years. They have been given to a large number of patients and have been found to be safe overall. A few patients may have side effects (described below). There is also the unlikely possibility of a rare unexpected severe reaction to a treatment. The study treatments are listed briefly below. If you are currently under treatment, your doctor will ensure this is compatible with the treatment below before your inclusion in the study.

Paracetamol

Paracetamol is used to treat patients with fever.

If you are in the group that receives paracetamol, you will take the drug up to 3 or 4 times a day with a maximum daily dose of 3 grams for no more than 14 days. Side effects with paracetamol are rare, but hypersensitivity including skin rash can occur.

Nitazoxanide/Ciclesonide

Nitazoxanide is used to treat patients with parasites and viral infections.

Ciclesonide is used to treat asthma and cold symptoms due to allergy.

If you are in the group that receives Nitazoxanide/Ciclesonide, you will take this combination for 14 days. You will receive 2 tablets of Nitazoxanide and you will have to inhale Ciclesonide 2 times, twice a day.

Nitazoxanide is usually well tolerated. The most common side effects are abdominal pain, headache, abnormal urine colour and nausea. Ciclesonide appears to be well tolerated. Rare adverse events were noted such as unpleasant taste in your mouth, nausea, vomiting, dry mouth or throat, mouth or throat burning sensation, infection in your mouth and changes in your voice, headache.

Although the 2 treatments have not been widely used in combination, given that the 2 individual treatments are safe, we do not expect any additional adverse effects with the combination of the 2 drugs.

Ivermectin/ASAQ

Ivermectin is used to treat patients with parasites (like intestinal parasites among others)

ASAQ is also used to treat patients with parasites (malaria).

If you are in the group that receives Ivermectin/ASAQ, you will be treated for 5 days:

- ASAQ: You will receive 2 tablets of ASAQ once a day during 3 days
- Ivermectin: You will receive this drug once a day during 5 days. The number of tablets will depend on your weight.

For both drugs, the tablets will be swallowed with water on **an empty stomach**.

ASAQ is usually well tolerated. The most common side effects are loss of appetite, abdominal pain, fatigue, difficulty to sleep, cough and dizziness (feeling of being lightheaded), abnormal urine colour and nausea.

Ivermectin appears to be well tolerated. The most common side effects are changes in your blood test measurements and rarely lesions your skin. Side effects to your eyes may also occur, such as reduction in visual acuity, blurred vision and sensitivity to bright light.

If you have parasite infection which are usually treated by ivermectin, you may have some specific adverse events depending on the parasite such as, constipation (difficulty to evacuate), diarrhoea, nausea, vomiting, dizziness, tremor, fever, headache, feeling of weakness, muscle and joint pain, sore throat, feeling of discomfort to breath, sweating, testicular pain, pruritus, rash, conjunctivitis, fever, increase of heartbeat and decrease in blood pressure in stand-up position.

Although the 2 treatments have not been widely used in combination, given that the 2 individual treatments are safe, we do not expect any additional adverse effects with the combination of the 2 drugs.

Fluoxetine/Budesonide

Fluoxetine is used to treat patients with severe depression.

Budesonide is used to treat asthma.

If you are in the group that receives Fluoxetine/Budesonide, you will take this combination for 7 days. You will receive 1 tablet of Fluoxetine and you will have to inhale budesonide twice a day.

Fluoxetine is usually well tolerated. The most common side effects are headache, nausea, difficulty to sleep, fatigue and diarrhoea.

In case of history of excessive vaginal bleeding disorders, you should inform your doctor before you start taking fluoxetine so s/he can advise you.

If you are pregnant and take fluoxetine near the end of your pregnancy, there may be a risk of vaginal bleeding shortly after birth, especially if you have a history of bleeding disorders.

If you are pregnant, there is also a potential risk of a rare heart and lung condition for your baby known as persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs when a newborn baby does not adapt to breathing outside the womb and might require intensive care. This risk has not yet been proven but it might exist.

However, if you are pregnant, you also have a higher risk to develop severe symptoms due to COVID-19, therefore early treatment is important to avoid the severe symptoms.

If you are breastfeeding, please discuss with your physician the benefit and risk related to your participation in the study.

Budesonide appears to be well tolerated. The most common adverse events are cold or flu symptoms, respiratory infection, changes in your voice, headache, pain, back and joint pain, fever, infection in your mouth, indigestion, stomach virus, nausea, cough..

Although the 2 treatments have not been widely used in combination, given that the 2 individual treatments are safe, we do not expect any additional adverse effects with the combination of the 2 drugs.

Another possible risk is that the treatment you receive may not help you personally to get better, but the information collected in the study could help patients with COVID-19 in the future.

There are also risks related to the examinations in the study. For example, to measure your heart rate, some patches will be attached to your chest, arms and legs to record your heartbeat. This can cause some discomfort or mild skin irritation. Collection of blood samples (optional) can cause pain, bruising, mild bleeding or light-headedness and, in rare cases, infection. Chest X ray and CT scans (both optional) will expose you briefly to a small, targeted amount of ionizing radiation. Ionising radiation may cause damage to the cells in your body. This is usually very minor and does not cause any serious damage,

The potential benefit of participating in the study is that the treatment you take may prevent progression of COVID-19, which could require your hospitalisation. There may also be benefits for the community since your participation in the study may help prevent transmission of the virus to other people and learn which treatment is effective for COVID-19.

Your Rights in the Study

The study has been reviewed and approved by the ethics committee and the regulatory agency in [ENTER COUNTRY NAME].

You have the right to refuse to participate in the study. If you decide not to participate in the study, this will not have any effect on the quality of the medical care you receive for COVID-19. If you decide to participate in the study, you are still free to withdraw from the study at any time without having to explain the reason.

If you withdraw from the study:

-you will be asked to rapidly come at the site for a full assessment visit to ensure that you are safe. In addition, the site will invite you to come back for a last visit at Day 21 or will call you to inquire about your health status. The study personal will call you a last time at Day 35 for a final follow-up on your health status.

-you have the right to ask that no more data be collected concerning you, except data on your health if you stop the study because of a side effect of treatment. We will keep the information about you that we have already obtained, unless you disagree.

During the study, you might be contacted by phone or visited at home at least 3 times on different days, if either you are not completing the questionnaire or not attending a planned visit.

You have the right to receive information on the results of the study once the study is finished. Ask the study doctor or a member of the study personnel how to arrange to receive this information.

Personal data concerning you will be collected by the study personnel, stored in a computer and sent out of [ENTER COUNTRY NAME] to analyse the results of the study. In [ENTER COUNTRY NAME], there may be laws on the protection of personal data and, if so, these laws will be respected. In the personal data used in the study, it will not be possible to identify you personally. All identifying details will be removed so that only the study personnel will know that you participated in the study. The only exception may concern your diagnosis of COVID-19 since, in some countries, it may be compulsory to report this information to government agencies.

Personal data concerning you will be shared with other international research teams, so that research efforts on COVID-19 around the world can be coordinated. The teams will not have any data that identifies you personally. If data concerning you are used in another study, you will not have to come back to the investigational centre or to fill out more questionnaires. Data concerning you, as well as information about the study will be kept for at least 25 years after the study ends. The sponsor of this study has obtained an insurance to cover any possible harm or injury that may be caused by participation in the study. If you get harmed or have questions about injuries as a result of being in the study, please inform study doctor or a member of the study personnel for more information.

CONTACT PERSON IN CASE OF QUESTIONS

If you have any questions concerning your participation in this study, your rights or if you think you have been harmed as a result of the study, you can contact, now, during, or after the study:

Study doctor/researcher name:

Study doctor/researcher e-mail:

Study doctor/researcher telephone:

Part 2: Informed Consent Form

Patient		Witness*	
I have read the information or, I have had it read to me. I was allowed to ask any questions I wanted, and I received satisfactory answers to my questions. I voluntarily consent to participate in the study. I agree to allow personal data concerning me to be collected during the study. I agree to allow personal data concerning me to be shared internationally as long as it is not possible to identify me personally.		I witnessed accurate reading of the consent form to the potential patient, who was able to ask any questions and received satisfactory answers. I confirm that the patient freely gave consent.	
First & last name		First & last name	
Signature		Signature	
Date		Date	
Thumbprint (if illiterate)		* For patients illiterate.	

Statement by the Investigator or designee taking consent

I have accurately read the information sheet aloud to the potential patient and made sure that, to the best of my knowledge, the patient understood what the study involves. I certify that the patient was given an opportunity to ask questions about the study and that all questions were answered satisfactorily. I certify that the patient freely and voluntarily gave consent and that a signed copy of this form was given to the patient.

Person taking consent	
First & last name	
Signature	
Date	

The information sheet and form were reviewed and approved by [*name of the local research ethics committee*], a committee responsible for ensuring that study patients are protected from harm. If you want to learn more about the committee, contact [*name, address, telephone number*]. They were also reviewed by the regulatory agencies in all the countries where the study is being conducted.