

## Participant Information Sheet

### **Intervention: newly available and repurposed antiviral drugs and monoclonal antibodies only**

**In this information sheet, we will give you information about the study to help you decide whether or not you will agree for you to take part. You may discuss with relatives or your doctor to assist you in making a decision to take part in this study. If you have any questions or concerns, you will have a chance to discuss them with the study staff.**

<b><u>Study Title</u></b>	Finding treatments for COVID-19: A phase 2 multi-centre adaptive platform trial to assess antiviral pharmacodynamics in early symptomatic COVID-19 (PLATCOV)
<b><u>Short Title</u></b>	Finding treatments for COVID-19: A phase 2 platform trial of antiviral pharmacodynamics in early symptomatic COVID-19
<b><u>Co-Principal Investigators</u></b>	Professor Sir Nicholas White and Dr William Schilling
<b><u>Sponsor</u></b>	University of Oxford

### **Introduction**

We are inviting you to join a research study to see whether drugs given early in COVID-19 illness can decrease the amount of virus inside your body.

The study will look at drugs which already exist for other diseases, as well as new drugs designed to treat COVID-19, and study their effects on the virus which causes COVID-19. The results of this study will help determine the effects of different treatments on COVID-19, helping Governments and Healthcare professionals make better decisions about which treatments to acquire and use on patients infected with the virus.

The aim of this study is to see if these drugs increase the rate that your body gets rid of the virus (“viral clearance”). These drugs will be compared with receiving no specific drug treatment, and treatments which have already been shown to be effective at decreasing the amount of virus. For treatments that are shown to clear the COVID-19 virus, they can be studied further. If treatments do not clear the COVID-19 virus, this is also an important result, so the medical and scientific community can then focus attention instead on other treatments.

This study will recruit healthy adults who have symptoms of COVID-19 illness and a confirmed diagnosis. Most patients would be expected to have an uncomplicated, and fairly mild, COVID-19 illness. The study requires daily swabbing, done twice, to determine the effects of the drugs on the amount of virus in your body. Some patients will also give a saliva sample. Your participation in the study is expected to last about 1 month (28 days).

The study will last for about 3 years and is expected to take place at centres in up to six countries around the world.

### **What is natural disease progression?**

The natural disease process for COVID-19 infection is that when the virus gets into your body, it will multiply and grow rapidly at first, and naturally gradually decrease thereafter. This is because the human immune system eliminates the infection from the body. Most young and healthy infected patients have no or only mild symptoms and can fight the infection themselves without any specific antiviral therapy. In some infected persons, their body may not be able to control the infection, leading to more severe symptoms. These often include people who have risk conditions or underlying diseases such as chronic obstructive pulmonary disease, chronic kidney disease, cardiovascular disease, cerebrovascular disease, uncontrolled diabetes, obesity (BMI greater than or equal to 35 kg/m<sup>2</sup>), cirrhosis, and immunosuppressive conditions.

### **What is the main purpose of this research?**

The purpose of this study to find out if certain drugs can decrease the amount of coronavirus, known as SARS-CoV-2, in healthy adults with early COVID-19 infection.

Another goal is to design a study structure which can give information quickly for future research.

### **What is this study about?**

Currently there are only a few COVID-19 drugs for prevention or treatment which have been shown to decrease the amount of virus in the body. Although vaccination to prevent COVID-19 infections continues, vaccinated people can still get infected with newer variants. Antiviral drugs are, and will be, still very important for managing COVID-19 infection around the world.

### **What will happen to you if you participate in the study?**

Patients with a diagnosis of COVID-19 or symptoms of suspected COVID-19 who are otherwise eligible, will be invited to see if they are able to participate in the study. You may be contacted at the place where you may seek care for your symptoms, or had a COVID-19 test, or will be invited to come to the unit where the study is conducted.

You will be asked about how long you have had COVID-19 symptoms, and any medications you are taking.

If you are a woman you will be asked if you are pregnant, trying to become pregnant, or breastfeeding. You will be asked to take a urine test to check if you are pregnant.

A swab of the back of the throat will be performed by the study nurse and a rapid test for COVID-19 will be done. This test needs to be positive within four days of your symptoms for you to join the study.

A finger prick may also be conducted and a few drops of blood used for a rapid antibody test (this will tell us if you have previously had COVID-19). If you meet the inclusion and exclusion criteria of the study, and are willing to join the study, you will be eligible to enrol. You will be told the intervention arms which are currently available in the study (e.g. treatments currently being studied and the no study drug arm), as well as what the study entails before you consent to being part of the study. You will have your oxygen levels measured and may have other symptoms checked.

**Summary of first visit. If you can take part in the study and agree to do so, you will:**

Sign two copies of this consent form, one will be kept by the study team and one will be returned to you. You will provide information about yourself such as contact details, place of residence and telephone number.

You will have a brief physical examination by the study team and you will be asked some questions about your general health and COVID-19 symptoms.

You will have an electrocardiogram (ECG) to monitor your heart.

Further swabs will be taken by the study nurse from the back of the throat and some blood will be taken from a vein in your arm with a needle. The amount of blood is up to 20 mL (1.5 tablespoons). In addition, some patients may be asked to give a sample of saliva, either by spitting in a tube, or by sucking on a swab tip until it is saturated for example.

If there are abnormal results from the blood tests, which would prevent you from receiving one of the available drugs, you may be excluded from the study. Of note, not all drugs below will be used in the study at the same time (**please ask the investigator to indicate which of the full list are currently being investigated which you may receive**):

- **Favipiravir:** You will receive favipiravir for a total of 7 days. On the first day, you will receive 9 tablets in the morning and another 12 hours later. Thereafter, on the next day, you will receive 4 tablets in the morning and evening for a further 6 days.
- **Regeneron:** A synthetic antibody, injection medicine. The drug will be infused into your arm vein once on the first day.
- **Sotrovimab:** A synthetic antibody, injection medicine. The drug will be infused into your arm once on the first day.
- **Nitazoxanide:** You will take 3 tablets, then another three tablets 12 hours later, with food, this will be for a total of seven days.
- **Molnupiravir:** You will take four tablets in the morning, then another four 12 hours later, this will be for a total of five days.
- **Nirmatrelvir/ritonavir (e.g. Paxlovid):** Nirmatrelvir/ritonavir consists of 2 separate medications, taken orally - Nirmatrelvir and ritonavir. Nirmatrelvir is two tablets twice a day 12 hours apart. Ritonavir is one tablet twice a day taken 12 hours apart. They will be taken for 5 days.

- **Fluoxetine:** You will take two capsules of fluoxetine once a day in the evening for 7 days, it is a capsule.
- **Fluvoxamine:** You will take fluvoxamine 1 tablet three times a day for 7 days.
- **Evusheld:** You will receive two separate injections into your muscle at different sites consecutively once on the first day.
- **Ensitrelvir:** On the first day you will take 3 tablets, then 1 tablet a day for a total of 5 days.
- **Molnupiravir and Nirmatrelvir/ritonavir combined.** For molnupiravir you will take four tablets in the morning, then another four 12 hours later, this will be for a total of five days. For Nirmatrelvir/ritonavir you will be taking 2 separate medications, taken orally - Nirmatrelvir and ritonavir. Nirmatrelvir is two tablets twice a day 12 hours apart. Ritonavir is one tablet twice a day taken 12 hours apart. They will be taken for 5 days. In total you will be taking 3 separate medications for 5 days.
- **No antiviral treatment (also known as no study drug arm): You will not receive one of the above treatments but will receive otherwise the same standard supportive care for your infection.**

All groups will receive standard supportive treatment such as antipyretics (paracetamol), anti-tussives or cough suppressants, antihistamines/decrease runny nose, vitamins, etc., and you will be assessed for symptom assessment as an inpatient for any changes in symptoms throughout the treatment period.

There will be an equal chance of being randomly assigned to one of these study groups above, apart from the no antiviral treatment arm, which is set at a minimum of 20% throughout the study. Please follow the study procedures.

Whether you receive a study drug or not, you will remain in the study. Not all the drugs mentioned here will be available to you at the point of enrolment however the study team will inform you of the available drug at the site. The study may take place as an inpatient on the ward, at your own home, or at an outpatient centre. You will then be observed for 1 hour after your first dose of medication. You will be given the contact number of the study team should you need to contact them, and they will take your phone number should they need to contact you. You will also be given a diary card and thermometer to record symptoms and the study team will tell you how to take your temperature and record your symptoms each day. The study team will confirm your contact information for any questions.

If you are randomised to a treatment arm which has been shown to decrease the virus in the body in this study you will be asked to stay in the ward or treatment centre for more blood tests. These blood tests are to measure drug levels in the blood, and help improve the dosing. The exact schedule of blood tests will depend on the drug (the study team will give you more details of this). Most of these blood tests will occur on the same day, and be taken from a cannula (small tube) in your vein, although you will likely be called back for a further blood test for the following day if you are not staying as an inpatient. The amount of blood for these tests is up to 20 mL (1.5 tablespoons).

**Summary of visits after enrollment – Inpatient:**

After baseline tests and enrollment in the trial, you will be hospitalised for up to 8 days. All study procedures will be conducted while you are in the hospital.

You will be closely monitored by doctors and the study team throughout hospitalisation, including in case of allergic reactions from study drugs. You will have a throat swab for COVID-19 done twice (once on each tonsil) on the screening day (4 swabs are done on the first day), drug administration day, and every day, once daily, for 7 more days, on Day 10 and again on Day 14. You may also be asked to provide a saliva sample at the same time as each swab. If you become unwell you may require additional swabs.

As well as on days 3, 7 and 14 of the study, blood samples will be taken from the vein for health status assessment and some tests to assess your immune response (antibodies) to infection.

If the investigator needs to change your treatment group for safety concern during the first 7 days, you will have an extra set of throat swabs for COVID-19 test before starting a new treatment.

Additional blood samples may be collected by the study team to assess the amount of the drug in your blood and how the drug behaves in your body. If you received a study drug that has been shown to reduce the amount of virus in your body. The study team will make an appointment with you to collect additional blood samples by appointment and will notify you in advance.

**Summary of visits after enrollment – outpatient:**

For the next 7 days (Days 1-7) after baseline you will see the study nurse once a day

If you are getting a drug into the vein, arrangements will be made for you to return to the clinic to receive your medication. If the study medication can be taken by mouth or another way (inhaled, injected into muscle or below the skin) these may be given to you to take at your home or at the study site. The study nurse will agree with you how these should be taken each day and will arrange to observe you taking your medications.

The study team will also take two throat swabs from you each day to check your levels of the virus and ask you some questions about how you are doing, and record your temperature. You will also be asked to record how you are feeling and your temperature, as well as the time you take your drugs (if you are taking a drug which is given more than once a day).

You will have one more visit with the nurse on Day 14 after you complete the study medication.

On Days 3, 7 and 14 of the study, blood samples will be taken from the vein. If the investigator needs to change your treatment group for safety concern during the first 7 days, you will have an extra set of throat swabs for COVID-19 test before starting a new treatment.

Additional blood samples may be collected by the study team to assess the amount of medication in your blood, if you are assigned a study drug that has been shown in this study to be

effective. If you are chosen for these samples the study nurse will arrange to meet or admit you to take the samples at the scheduled time. The maximum blood draw for these drug measurement tests across all visits is not expected to be more than 20mls (1.5tablespoons).

### **Day 28**

For the final study visit on Day 28, you will have a phone call with the study team to check you have fully recovered, and record how you felt and whether you needed to consult any healthcare providers.

### **What do I do if I don't feel well or if I have any problems?**

There may be side effects from the drugs. If you have any side-effects or unexpected problems that may be related to your drug or study procedures, study you should inform the study doctor or study staff right away. We will treat these problems fully and with no charge to you. Treatments, and costs associated with treatments, which would have been required anyway, and are not related to the study procedures, will not routinely be provided by the study. The study team will however ensure that you receive appropriate medical management if you are hospitalised for your COVID-19 infection as per local care. The physician may decide that further study swabs of the back of the throat should be taken to see if the virus has come back.

### **Are there any risks or disadvantages to me of taking part?**

#### **Risk of study drugs**

In general, these drugs are well tolerated. There may be some common side effects, but they are not expected to last after you stop taking the medication. Of note not all drugs below will be used in the study at the same time (please ask the investigator to indicate which of the full list are currently being investigated). The side effects can be summarised as follows:

<b>Drug</b>	<b>Potential side effects</b>
Favipiravir	<ul style="list-style-type: none"> <li>• Diarrhoea (loose bowel movement), and less commonly;</li> <li>• changes to laboratory tests (such as enzymes produced by the liver and the uric acid).</li> </ul>
Nitazoxanide	<ul style="list-style-type: none"> <li>• Diarrhoea, nausea, stomach (tummy) pain</li> <li>• Headache</li> <li>• Change in urine colour</li> </ul>
Lopinavir - Ritonavir	<ul style="list-style-type: none"> <li>• Gastrointestinal upset, stomach pain, diarrhoea, nausea and vomiting (throwing up or feeling like you need to)</li> </ul>
Hydroxychloroquine	<ul style="list-style-type: none"> <li>• Gastrointestinal upset, stomach pain, diarrhoea, nausea and vomiting (throwing up or feeling like you need to)</li> </ul>
Nebulised unfractionated Heparin	<ul style="list-style-type: none"> <li>• N/A</li> </ul>

REGN-COV2	<ul style="list-style-type: none"> <li>• Nausea, headache, tachycardia (fast heart rate), palpitations and low blood pressure</li> </ul>
Miglustat	<ul style="list-style-type: none"> <li>• Sperm damage in males</li> <li>• Menstrual frequency (periods) in female</li> <li>• Nausea, stomach pain or upset feeling</li> <li>• Diarrhoea (loose bowel movement)</li> </ul>
Molnupiravir	<ul style="list-style-type: none"> <li>• Gastrointestinal upset, diarrhoea, nausea</li> </ul>
Nirmatrelvir/ ritonavir (e.g. Paxlovid)	<ul style="list-style-type: none"> <li>• Diarrhoea</li> <li>• Altered taste sensation</li> </ul>
Fluoxetine	<ul style="list-style-type: none"> <li>• Nausea, diarrhoea, anorexia</li> <li>• Insomnia, drowsiness, anxiety</li> </ul>
Fluvoxamine	<ul style="list-style-type: none"> <li>• Nausea, diarrhoea, anorexia</li> <li>• Insomnia, drowsiness, anxiety</li> </ul>
Evusheld	<ul style="list-style-type: none"> <li>• Pain at site of injection</li> </ul>
Ensitrelvir	<ul style="list-style-type: none"> <li>• Rash, nausea and diarrhoea.</li> </ul>
Molnupiravir and Nirmatrelvir/ri- tonavir com- bined*	<ul style="list-style-type: none"> <li>• Altered taste sensation, diarrhea, nausea and dizziness</li> </ul>

\* They are not known to interact with each other and you are not expected to have additional side effects taking both, but we will monitor you more closely for side effects. Side effects are specific to each medication as above.

There is also the unlikely possibility of a severe reaction to any study drug. Please ask the study team if you would like more information. The study team will be aware of whether there are any particular side effects that they should look out for, and may ask more questions about your health to confirm which treatments you can receive.

The study team will also keep you informed if some study drugs show more evidence to be effective than the other medications available.

**If any new information arises** about benefits and risks related to the study that may be relevant to your willingness to continue participation in this study, we will tell you as soon as possible.

**Risk of blood withdrawal from the arm or the finger prick and risk from drug administration procedure**

The risks of blood withdrawal from the arm or the finger prick include discomfort, occasional bleeding or bruising of the skin at the site of needle puncture, and, very rarely, an infection.

Some drugs will be administered into a vein in your arm. The risks from this procedure include pain, haematoma (bruise), rarely an infection, or bleeding in the site of the injection after the

needle is removed. If an infection of the skin occurs, these are often mild and resolve by themselves, but if required we will treat it.

#### **Risk of throat swab**

The throat swabs can be uncomfortable but take a short period of time (few seconds)

#### **Risk of saliva sample collection**

There is no risk associated with giving saliva

#### **Risk for pregnant or breastfeeding women**

Some drugs used in this study are not allowed to be used in pregnant women. Hence, women who are pregnant, actively trying to become pregnant, or breast feeding are not being enrolled in the study.

If you are a woman of childbearing age, you will be asked to use an effective contraceptive method e.g. contraceptive pills, condom, throughout the study and for up to 2 weeks after your last dose of study medication, depending on the medication you received. The study team will tell you if you have been allocated one of the study drugs requiring use of an effective contraceptive and the duration which this should be used.

#### **Risk for male fertility**

Miglustat may damage sperm based on a single animal experiment. However, damage to sperm did not occur in humans. If you would like to discuss further, please ask the study team for more information.

#### **Specific risks for those trying to have a baby treated with Molnupiravir**

Pregnant or lactating women are already excluded from the study.

As per USA FDA advice, those on molnupiravir need to be aware of avoiding pregnancy. The concern relates to this new drug, regarding the theoretical worry that it may adversely affect the genetic material of the sperm or the egg, or the fetus in the uterus. Females of child bearing potential need to use a reliable method of contraception for the duration of the treatment, and also for 4 days after the final dose of molnupiravir and you will be asked to take a urine pregnancy test on day 14 of the study. Males of reproductive potential, if they are sexually active with females of child bearing potential, should use a reliable form of contraception during the treatment and at least 3 months after the final dose.



### **What are the advantages of taking part in the study?**

We do not yet know if any of the treatments being tested will have additional benefits in the management of COVID-19 for you. Your study treatment may or may not help you personally, but this study should help future COVID-19 patients.

### **What will happen if you choose not to take part in the study, or if you change your mind after you agree?**

Your participation in this study is entirely voluntary. You are free to withdraw from the study at any time and it will not affect your care.

The study doctor and the study sponsor have the right to withdraw you from this study if it is considered that it is in your best interest.

If you decide not to participate in the study or withdraw, your COVID-19 infection and symptoms will be managed as per local care.

### **What will happen to my data?**

All of the information obtained during the study will be kept strictly confidential at study sites. Identifiable data will be removed whenever possible and any data transfer will be done securely.

The study records will be stored for at least 5 years after completion of the study, or according to local site regulation.

If you withdraw from the study before your last visit, the data and samples collected prior to withdrawal will be kept and used for analysis unless you tell us you don't want us to use this information.

### **What will the blood sample be used for?**

For all patients, the total blood volume that will be taken for the entire duration of the study is approximately 80 mL (around 5 tablespoons), but may be 100 mL (around 6 tablespoons) if you are given a treatment where we are checking drug levels. These samples will be used to check for general health at enrollment, look for potential markers which may affect your response to the study medication, measure the amount of study drug in your blood, and check your response to COVID-19 infection.

In some patients, additional blood samples will be collected if they receive a treatment that is effective at clearing their virus. This sample will measure the study drug in their blood and will be no more than 24 mL (around one and a half tablespoons).

Your blood sample will be stored for genetic tests related to the risk of coronavirus infection, and response to treatments.

All testing will be anonymised so there it cannot be traced to your personal details.

If you agree, some of your blood and swab may be shipped abroad for further research by groups working with the study team, and some of your blood samples will be stored and may be used for further studies related to susceptibility or response to the COVID-19 infection in the future.

**Will there be any financial cost to or compensation for you?**

For the time that you are enrolled in the study, you will be reimbursed for costs associated with travel and the inconvenience associated with being in the study, as allowed by local guidelines.

In case, you are experiencing any side effects or harms which are directly caused by the study, we will treat you according to the standard treatment free of charge. Treatments, and costs associated with treatments, which would have been required anyway, and are not related to the study procedures, will not routinely be provided by the study. The study team will however ensure that you receive appropriate medical management if you are hospitalised for your COVID-19 infection as per local care.

**Who has reviewed this study?**

This study has been reviewed by, and received ethics clearance through, the Oxford Tropical Research Ethics Committee (OxTREC) and the local Ethics committees.

**List of Study Member Contacts**

If you have any questions or concerns after reading this information sheet, you will have a chance to discuss them fully with a member of our team before you decide whether or not to take part in the study. We will also be available throughout the study to answer any questions or address any concerns that you may have later on.

If you have any questions while you are at home, you can contact the study staff by telephone as below.

*Name:*

*Telephone number:*

or

*Name:*

*Telephone number:*

If you haven't been treated as specified in this information sheet or you wish to know the participant's rights, contact the secretariat office of the Ethics Committee. (*Ethics committee contact information will be added per site*).

### **Confidentiality**

Your name will not be in any report or on any sample being shipped away from the hospital. We repeat that the information we collect from you and from analysing your blood samples will be kept confidential by the study team. We will not share personal information with anyone outside the study.

No one other than the study team, authorised personnel from the study sponsor, monitor, ethics committee and regulatory authorities such as Food and Drug Administration are allowed direct access to personally identified medical records.

When the study is completed, we will combine the test results with those of the other participants, and the overall results will be analysed.

The clinical data, genetic information and results from blood analyses that is stored in our database may be shared with other researchers to use in the future. The other researchers will not be given any information that could identify you.

### **Data protection**

The University of Oxford is responsible for ensuring the safe and proper use of any personal information you provide, solely for research purposes.

## Informed Consent Form

I would like to take part in a study, titled: **“Finding treatments for COVID-19: A phase 2 platform trial of antiviral pharmacodynamics in early symptomatic COVID-19”**

I have read the participant information sheet and have had the opportunity to ask questions about the study and any questions I have asked have been answered to my satisfaction.

I understand that I can withdraw or stop taking part in the research at any time without affecting further services and hospital care to which I am entitled to in the future. To consent to take part in this study, I allow the investigators to use my personal information obtained from this research. My information will be presented as part of research results without revealing my name or identity.

If I have doubts about the study procedures or I experience adverse side effects from the research, I will be able to contact study doctors or study staff at any time.

I fully understand the statements in the participant information sheet and this informed consent form.

I consent to participate in this study.

I agree to adhere to the study protocol.

I understand I am to not take any drugs during participation in this study other than the study drug assigned to me, unless agreed in advance by the study team (e.g. paracetamol).

If I do not feel well and need to see a healthcare professional, I will inform them that I am participating in this research study.

I allow my blood to be tested for genetic tests related to susceptibility or response to the COVID-19 infection, and treatments.

I allow my blood, swab and saliva to be shipped abroad.

I allow my blood to be stored for future studies related to susceptibility or response to the COVID-19 infection, and treatments.

I allow my anonymised clinical data, genetic information and results from blood analyses that is stored in the database to be shared with other researchers for use in the future. These data will be carefully and securely anonymised so it will not be possible to identify the individual.

Signature of Participant .....

Print name of Participant .....

Date .....

Signature of person conducting the informed consent .....  
Print name of person conducting the informed consent .....  
Date .....

**To sign 2 originals: 1 copy for participant, 1 copy for site file**

**For the participants who cannot read or sign in the consent form, the participant can thumb print in the following box.**

I cannot read but the investigator/study staff have read the information in this informed consent form to me and explain until I fully understand the given information. Therefore, I provide my thumbprint to voluntarily consent to joining this research study:

I consent to participate in this study.

I agree to adhere to the study protocol.

I understand I am to not take any drugs during participation in this study other than the study drug assigned to me, unless agreed in advance by the study team (e.g. paracetamol).

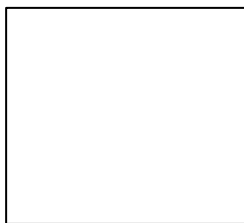
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I allow my anonymised clinical data, genetic information and results from blood analyses that is stored in the database to be shared with other researchers for use in the future. These data will be carefully and securely anonymised so it will not be possible to identify the individual.



Right thumb print of the Participant

Signature of person conducting the informed consent.....

Print name of person conducting the informed consent.....

Date .....

Signature of witness.....

Print name of witness.....

Date .....

**To sign 2 originals: 1 copy for participant, 1 copy for site file**