PARTICIPANT INFORMATION LEAFLET AND INFORMED CONSENT

Each **participant** must receive, read and understand this document **before** any study-related procedure is performed

Study Number:	EZ-SS-029
Study Title:	**A randomised, multi-centre, double-blind, Phase 3 study to observe the effectiveness, safety and tolerability of molnupiravir compared to placebo administered orally to high-risk adult outpatients with mild COVID-19 receiving local standard of care in South Africa**
Protocol Version and Approval Date:	Version 1.0; 22 April 2022
Sponsor:	Ezintsha, a division of Wits Health Consortium Johannesburg, South Africa
Investigator (Principal & Site):	Dr. Simiso Sokhela
Institution:	Ezintsha, a division of Wits Health Consortium Address: Ground Floor, Building C Sunnyside Office Park 32 Princess of Wales Terrace Parktown, Johannesburg, South Africa
Daytime and After-Hours Telephone Number(s):	082 618 7851 064 052 3193

To the potential participant: *This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home* ***an unsigned copy of this consent*** *form to think about or discuss with family or friends* ***before making your decision.***

ICF administration starting time: _____ ICF administration finish time: _____

INTRODUCTION

Good day, my name is _____ *(INSERT NAME OF STUDY STAFF)*, I am a _____ *(INSERT DESIGNATION)* at _____ (*INSERT SITE).*
I would like to invite you to consider taking part in a research study called "**A randomised, multi-centre, double-blind, Phase 3 study to observe the effectiveness, safety and tolerability of molnupiravir compared to placebo administered orally to high-risk adult outpatients with mild COVID-19 receiving local standard of care in South Africa**"

- Before you decide if you want to be part of this study, we would like to give you information to help you decide if you would like to be part of the study.
- Please take the time to think through the following information and discuss it with others if you wish. Knowing what is involved will help you decide if you want to take part.
- If you have any questions, do not hesitate to ask me.
- You should not agree to take part unless you are happy about all the procedures involved.
- Please be open with me regarding your health history since you may otherwise harm yourself by taking part in this study.
- If you decide to take part in this study, you will be asked to sign this document to confirm that you understand the study. You will also be given a copy to keep and refer to.
- As COVID-19 infection is a notifiable disease we must by law report all cases of COVD-19 to the National Institutes of Communicable Disease (NICD) within 24 hours. Should you agree to take part in the study we will do so without revealing your study identity.

WHAT IS THE PURPOSE OF THE STUDY?

- COVID-19 is a new disease that spreads quickly between people. It is often a mild infection in healthy people, but severe disease and death may occur in some cases, particularly in high-risk groups including people 50 years or older and those with underlying chronic diseases such as heart disease, hypertension, and diabetes.
- There are currently few approved medications known to stop COVID-19 or help people who have it get better quicker.
- Given the quick spread of COVID-19, medical treatments that prevent serious effects of the disease, decrease its spread to others and reduce the burden on the health system are urgently needed.
- We will investigate how new medical treatments against the virus that causes COVID-19 will affect the duration and severity of your symptoms, how well you recover from the infection. In this study we will be using a drug called Molnupiravir which is an antiviral (it stops the virus from multiplying in your blood-thereby killing it).
- This study will compare a medical treatment for COVID-19 (Molnupiravir) with a placebo which does not contain any medicine in the early treatment of people with mild symptoms of the disease.
- This information may help improve the care of people with COVID-19 in the future and to prevent complications, and ultimately achieve the best health outcomes.

PLACEBO

- A **placebo is an inactive substance** and it does not contain any medicine.
- You will be randomly allocated to one or other treatment (i.e. like spinning a coin). Neither you nor I will know which treatment you are receiving during your participation in the study. This procedure helps to ensure that the information gathered during the study is accurate. In case of an emergency, it will however be possible to determine which treatment you have been receiving.

WHY HAVE I BEEN INVITED TO PARTICIPATE IN THIS STUDY?

- You have been invited to take part in this study because you have tested positive for the virus that causes COVID-19 (same day LumiraDx™ SARS-CoV-2 Ag testing or a lab COVID PCR no older than 2 days) and/or have mild symptoms of the disease for no more than 5 days.

WHAT IF I DON'T WANT TO TAKE PART OR IF I WANT TO WITHDRAW LATER?

- Participation in this study is voluntary. It is completely up to you whether to participate.
- If you decide not to take part, it will not affect any tests or treatment you receive now or in the future for COVID-19, or for any other illness. Whatever your decision, it will not affect your relationship with the staff caring for you.
- If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason and without affecting your medical care.
- If you do decide to take part, you will be given this Participant Information Sheet and Consent Form to sign and you will be given a copy to keep.
- The study doctor can also make the decision to withdraw you from the study.

WHAT IS THE LENGTH OF THE STUDY AND NUMBER OF PARTICIPANTS?

- The study will be performed multiple sites in South Africa and 4000 participants will be invited to take part in this study.
- The participants will be 50 years or older, and have other risk factors for progression to severe COVID disease.
- The total amount of time required for your participation in this study will be up to 1 month including the treatment period and safety follow-up.

WHAT DOES PARTICIPATION IN THIS RESEARCH INVOLVE?

- Before receiving your first dose of study medicine, you will be seen by both a nurse and a doctor who will ask you questions and examine you to see if you qualify for this study.
- This is important for us to make sure that you do not have any other medical problems or treatments that would potentially make it unsafe for you to be in this study.
- You are requested to provide the study team with the names of all medicines you are currently taking.

Screening/Enrolment visit:

Your study doctor or nurse will:

- Discuss the COVID-19 Treatment South Africa study with you, and if you choose to participate you will sign and date the Consent Form.
- Test you for COVID using LumiraDx™ SARS-CoV-2 Ag testing (if you have not already tested positive for COVID by LumiraDx™ SARS-CoV-2 Ag testing or a lab COVID PCR).
- You will also be offered optional HIV testing.
- Collect your demographic information such as your age, race and gender/sex .
- Review any medical notes and collect your medical and medication history.
- Record any symptoms you present with. It will be very important to tell your study doctor or nurse if you have any unusual symptoms (fever, tightness in the chest, cough, etc.)
- Perform a physical examination including assessment of your height, weight, vital signs, your blood oxygen level (pulse oximetry/Sp02).
- If you are a woman and able to have children, ask you to provide approximately 25 mL (about 5 teaspoons) of urine for pregnancy testing.

- The information collected about you at this visit will be used to decide if you will be included in this study.
- You will also be asked to provide your contact details as well as those of a close family member, to allow the study staff and/or laboratory personnel to contact you for visit reminders.
- If you qualify for the study, you will be randomly placed (selected like flipping a coin) into one of the available study medicine arms. You will receive only one type of treatment. The different medication arms of treatment are as follows:
  Arm A: Molnupiravir
  Arm B: Placebo
- You will be given a 5 day course of the drug and a monitoring kit containing a thermometer and a SpO2 monitor which measures the oxygen content in your blood. You will need to take the study medication as instructed from Day 1 until day 5.
- You will also be given a study diary that will need to be updated daily for 10 days. In it you will record what are your symptoms (daily survey/FluPro), your temperature/oxygen/heartrate measures, any side effects to the medication as well as any other medication taken. You will be asked to return this to the study site at your day 29 visit.
- Please note that as COVID-19 positive client, you are required by law to self-quarantine or self-isolate at home for at least 7 days from the time of receiving a positive COVID-19 test. Quarantine or self-isolation means you must live separately or restrict your movements and activities (even if you do not feel ill), to stop the spread of the disease.

Day 3, 6, 10

Study staff will contact you telephonically, via text/direct messaging or web-based conference to see how you are doing, and if you have taken any other medication besides the study drug.

Day 29 Safety Follow-up:

You will be asked to come to the study site to see the doctor/nurse. The following will be performed:

- Vital signs (temperature, SpO2, respiratory rate, pulse, blood pressure)
- Review of any other medication you may be taking and ask if you are experiencing any health issues.
- Adverse Event review. Please note that we might have to draw safety bloods to assess your adverse events. The amount of blood drawn will not exceed 100mL (about 20 teaspoons) per visit.
- Urine pregnancy test (women of childbearing potential)
- Collection of unused study medication or empty study medication containers.

You will be asked to visit the study site clinic or answer phone calls for the specified visits within the specified time periods and provide complete and accurate information about your health. These requirements are in place to protect your safety and should be followed. If you have any questions or concerns, you should discuss them with the study doctor or nurse.

You should seek medical care and/or contact study staff immediately at any time during this study if you experience worsening of symptoms or have difficulty breathing.

If you seek emergency medical care or if you need to go the hospital at any time during the study or up to 30 days after the last study visit, please tell the hospital staff that you are/were enrolled in this research study and contact study staff as soon as you can.

You can, at any stage during the study, contact study staff via telephone to discuss any health issues, or if you are unsure of any study procedures.

Should you become pregnant, please ensure to contact the study team immediately.

HOW IS THIS STUDY BEING PAID FOR?

This study is being sponsored and conducted by the Ezintsha research team.

WHAT ARE THE POSSIBLE RISKS AND DISADVANTAGES OF TAKING PART?

Risks associated with taking part in this study include:

Risks of nasal swabs

The swabs will be collected at screening by a trained study staff (if you have not already tested COVID positive by LumiraDx™ SARS-CoV-2 Ag testing or a lab COVID PCR). Some people may experience mild discomfort when the samples from their nose are taken. The study doctor or nurse will thoroughly explain how the sample will be collected with as little discomfort as possible. Very few major problems are reported but you may experience minor bleeding from the nose, coughing or sneezing.

Risks of study medication

Molnuparavir has been shown to be a well-tolerated drug in clinical trials/studies. Some mild side effects could include diarhea, dizziness, nausea and headaches. Taking the study medications will also be for a short period of time (up to 5 days) at amounts that in studies have been shown to be safe. The risks to you as a participant are expected to be minimal. However, safety of the medication used during pregnancy is not well known, because of a lack of research in this area. Because of this, the US Food and Drug Administration considers this drug part of "category X" – this means that they should not be used (are contraindicated) in women who are pregnant (see pregnancy precautions below).

COVID-19 and many medicines are known to be associated with liver injury - all participants will be advised of signs and symptoms to look out for, and you are requested to report these urgently if they do develop.

Pregnancy

If you are a woman and able to have children, you must have started birth control 14 days before being enrolled on this study and agree to continue to use birth control throughout the study until the last study visit. The study staff will discuss with you how to ensure this.

If you are a male participant you must wear a condom when engaging in any activity that allows for passage of ejaculate to another while taking the investigational product. It is also advised that your female partner use a highly effective method of contraception as condom may break or leak.

Precautions regarding COVID-19

Because you are confirmed to have COVID-19, the study staff may ask you to use a different path to enter and move around the study site to avoid contact with other people. They will also ask you to wear a mask to cover

your mouth and nose, to avoid direct contact with objects and regularly wash/sanitise your hands. This is to protect other patients and health care givers from any risk of being infected with COVID-19.

WHAT ARE THE UNFORSEEN RISK OF THE STUDY?

The study medicine is investigational and there may be other risks or side effects which are unforeseen or unknown. You should immediately contact the site staff if any side effects occur throughout your participation in this study.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART?

We cannot guarantee or promise that you will receive any benefits from taking part in this study.
By taking part in this study, you may contribute new information that may benefit other participants in the future. You may or may not improve while taking part in this study. Possible benefits include earlier identification of COVID-19 and improved management of the symptoms of the disease.

WILL TAKING PART IN THIS STUDY COST ME ANYTHING, AND WILL I BE PAID?

Participating in this study will not cost you anything. You will not be paid for participating in this study, but you will be compensated for time and inconvenience associated with the visits. A compensation amount of R305 will be given to you for only physical study visits such as screening, enrolment, end of study and any other additional visits which will require you to be at site.

HOW WILL MY CONFIDENTIALITY BE PROTECTED AND WHAT WILL HAPPEN TO INFORMATION ABOUT ME?

Your confidentiality will be protected as explained to you by the study staff and detailed in this study's Participant Information and Consent Form. We summarise the information below.

Of the people treating you, only the study doctor and research team involved in your care will know whether you are participating in this study. Any information collected that can identify your connection with this study will be kept confidential and will be shared only with your permission, or as required by law.

Your study records might also be reviewed by the National Health Research Ethics Council (NHREC), University of the Witwatersrand, Human Research Ethics Committee (HREC), the South African Health Products Regulatory Authority (SAHPRA) and/or the United States Food and Drug Administration (FDA), as well as your personal doctor (if you have given us permission to contact your personal doctor).

Your health records and any information gathered during the research project may be subject to inspection (to check the procedures and information gathered) by the relevant authorities, the Sponsor and/or authorised representatives of the Sponsor and the institution relevant to this Participant Information Statement at the study site or as required by law.

By signing the consent form, you consent to the research team collecting and using information about you for the research study.

The research team will store the data collected from you for this research project for a minimum of 15 years after the publication of research results. The information about you will be stored in a re-identifiable format where any identifiers such as your name, address, date of birth will be replaced with a unique code. Only the research team can match your name to the unique code if it is necessary to do so.

You will be asked to provide your consent for the research team to share or use the information collected from you in future research that will be an extension of, or closely related to COVID-19 infection; or is in the same general area of research. The future research will need to be approved by the University of Witwatersrand HREC Ethics committee, before proceeding. Your information will only be shared in a format that will not identify you.

Information collected from you in an electronic format will be stored in safe password protected databases only accessible to the approved research investigators. Information collected from you using paper records will be stored in a locked cabinet in Ezintsha clinical trial site, and only the approved research investigators will have access to this information.

You have the right to see, copy and correct your personal health information data related to the trial, as long as this information is held by the trial doctor or research institution. You may access your medical information as allowed by national law. Your data will be collected, processed and stored according to the South African Protection of Personal Information (POPI) Act of 2013.

WHAT WILL HAPPEN WITH THE STUDY RESULTS?
By signing the Consent Form, you agree to the study doctor and relevant research staff collecting and using personal information about you for this research project. Any information obtained in connection with this research project that can identify you will remain confidential. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified. Results of the study can be provided to you.

NEW FINDINGS
You will be provided with any additional information that becomes available during the study, which may affect your willingness to continue on the study.

DISCLAIMER
The Principal Investigator or sub investigator reserve the right to withdraw you from the study if it is considered to be in your best interest. If your participation is ended early, you may be asked to return for end-of-study tests and procedures for your safety. If you did not provide an accurate medical history or did not follow the guidelines of the study and the regulations of the study facility, you may be withdrawn from the study at any time.

INSURANCE:
Ezintsha, a division of Wits Health Consortium, also known as the Sponsor, has obtained insurance for you and the study staff in the event of study related injury or illness. A study related injury or illness is one that occurs as a direct result of the administration of the study medicine or of study-specific procedures.

ABPI STATEMENT ON COMPENSATION:
Ezintsha, a division of Wits Health Consortium (the Sponsor) will provide compensation for reasonable medical expenses incurred as a result of study- related injury or illness, or death determined according to the guidelines laid down by the Association of the British Pharmaceutical Industry (ABPI Compensation Guidelines Version 2014), and Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa.

- You must notify the study staff immediately of any complications, side effects and/or injuries during the study and the nature of the expenses to be covered.

- If a research related injury occurs, you have not waived any of the legal rights that you otherwise would have as a participant in this study by signing this form.

Further detailed information on the payment of medical treatment and compensation due to injury can be obtained from me. I have a copy of the ABPI Guidelines (version 2014) and the insurance Certificate, should you wish to review them.

The insurance does not cover, and Ezintsha, a division of Wits Health Consortium will not pay for:

- Medical treatment of other injuries or illnesses
- Injury caused by non-observance of the protocol

I am indemnified by Ezintsha, a division of Wits Health Consortium conditional upon:

- My compliance with the applicable requirements of the study protocol
- My compliance with the regulations of the South African Health Products Regulatory Authority **(**SAHPRA) and the University of the Witwatersrand, Human Research Ethics Committee (HREC).
- The handling and administration of the study medication in accordance with instructions and guidelines provided in the protocol, subsequent amendments and related documents.
- The indemnification is not intended to be and is not a substitute for my personal **malpractice insurance.**

Please note that if you have a life insurance policy you should enquire whether your insurance company requires notification of your intention to participate in a clinical study. Information to date is that it should not affect any life insurance policy taken out. Nevertheless, you are strongly advised to clarify it with the company concerned.

ETHICAL APPROVAL:

- This clinical study protocol has been submitted to the University of the Witwatersrand, **Human Research Ethics Committee (HREC)** and written approval has been granted by that committee.
- The study has been structured in accordance with the **Declaration of Helsinki** (last updated: October 2013), which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained from me should you wish to review it.

SOURCE OF ADDITIONAL INFORMATION:

- For the duration of the study, you will be under the care of qualified medical doctors and nurses. If at any time between your visits, you feel that any of your symptoms are causing you any problems, or you have any questions during the study, please do not hesitate to contact the study staff.
- **The 24-hour telephone number** through which you can reach me, or another authorised person is 082 618 7851 or 064 052 3193.
- If you want any information regarding your **rights as a research participant, or complaints regarding this research study**, you may contact Prof. Clement Penny, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at (011) 717 2301.
- For **research information** you can contact Dr Simiso Sokhela at 082 618 7851 or 064 052 3193.

South African Health Products Regulatory Authority

If you have questions about this trial, you should first discuss them with your doctor or the Ethics Committee (contact details as provided on this form). After you have consulted your doctor or the Ethics Committee and if they have not provided you with answers to your satisfaction, you should write to the South African Health Products Regulatory Authority (SAHPRA) at:

The Chief Executive Officer
South African Health Products Regulatory Authority
Department of Health
Private Bag X828
PRETORIA
0001
E-mail: Boitumelo.Semete@sahpra.org.za
Tel: 012 501 0300.

PERSONAL DOCTOR / SPECIALIST NOTIFICATION OPTION

Please indicate below with your signature next to the chosen option, whether you want the principal investigator to notify your personal doctor or your specialist of your participation in this study:

_____
Signature / Mark or Thumbprint

YES, I want you to inform my personal doctor / specialist of my participation in this study

_____
Signature / Mark or Thumbprint

NO, I do not want you to inform my personal doctor / specialist of my participation in this study

_____
Signature / Mark or Thumbprint

N/A, I do not have a personal doctor / specialist

PARTICIPANT QUESTIONS:

Did the participant raise any questions? **YES ☐ / NO ☐**

If YES – What were they and what was the answer provided:

_____

_____

_____

_____

_____

_____

INFORMED CONSENT

Declaration by the participant

- I understand I am being asked to provide consent to participate in this research study;
- I have read the Participant Information Sheet, or someone has read it to me in a language that I understand;
- I understand the purposes, study tasks and risks of the research described in the study;

- I provide my consent for the information collected about me to be used for the purpose of this research study only;
- I have understood that the researchers may contact my healthcare givers if I am isolated in hospital to collect data on my health status and I agree;
- I have had an opportunity to ask questions and I am satisfied with the answers I have received;
- I freely agree to participate in this research study as described and understand that I am free to withdraw at any time during the study and withdrawal will not affect my relationship with any of the named organisations and/or research team members;
- I understand that I will be given a signed copy of this document to keep;
- I understand that the global results of the research will be made available to me and may be published in various media, including on the Ezintsha website.

PARTICIPANT:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

INFORM CONSENT ADMINISTRATOR:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

INVESTIGATOR:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

WITNESS (If applicable)**:**

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time