EZ-SS-029

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

Short Title:	COTeT
Phase:	3
Protocol Version and Approval Date:	Version 1; 22 April, 2022
Sponsor:	Ezintsha, Faculty of Health Sciences University of the Witwatersrand Building C, Sunnyside Office Park 32 Princess of Wales Terrance Parktown, Johannesburg 2193
Funder:	Bill and Melinda Gates Foundation
Principal Investigator:	Dr Simiso Sokhela University of the Witwatersrand Ground Floor, Building C Sunnyside Office Park 32 Princess of Wales Terrace Parktown, Johannesburg

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that:

- I agree to personally conduct or supervise the study.
- I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, as per any approved protocol amendments, as per ICH Good Clinical Practice (GCP) and all applicable Regulatory Authority requirements and national laws.
- I will not deviate from the protocol without prior written permission from the Sponsor and prior review and written approval from the Institutional Review Board or Ethics Committee, and Regulatory Authority, except where necessary to prevent immediate danger to the participant.
- I have read and understand the information in the relevant Summary of Product Characteristics, and I am familiar with the Investigational Medicinal Product (IMP); I also understand the IMP use, including its potential risks and side effects.
- I agree to inform all participants that the IMPs are being used for investigational purposes and I will ensure that the requirements related to obtaining informed consent are in accordance with ICH Guidelines for Good Clinical Practice (GCP) Section and local requirements.
- I agree to report adverse events that occur in the course of the study to the Sponsor, to maintain adequate and accurate records and make those records available, in accordance with ICH Guidelines for Good Clinical Practices (GCP), South African Good Clinical Practice and other local requirements. I agree to promptly report to the Ethics Committee (EC) all changes in the research activity and all unanticipated problems involving risk to the participants.
- I have sufficient time to properly conduct and complete the trial within the agreed trial period, and I will ensure that any qualified staff at my site(s) who are involved in the trial conduct are adequately trained regarding the IMP, the protocol, and their responsibilities for the foreseen duration of the trial to conduct the trial properly and safely. If I delegate any of my trial activities, I will provide the Sponsor with a Delegation of Activities Form. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- I understand that the study may be terminated, or enrolment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interest of the participants.

Dr Simiso Sokhela Date

FUNDER/SPONSOR SIGNATORY APPROVAL PAGE

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

I, the undersigned have read this protocol and I approve the design of this trial:

_____ _____
Shirley Chen Date
Deputy Director, Innovation Introduction
Global Health Program
Bill and Melinda Gates Foundation

_____ _____
Nonkululeko Mashabane Date
Head: Research Operations/Sponsor Representative
Ezintsha, University of the Witwatersrand

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ABBREVIATIONS AND TERMS

Term	Definition
ADR	Adverse drug reaction
AE	Adverse event
AUC	Area under the curve
BMGF	Bill and Melinda Gates Foundation
BMI	Body mass index
C_{max}	Maximum concentration
COVID-19	Coronavirus disease
DAIDS	Division of Allergy and Infectious Diseases
DSMB	Data Safety and Monitoring Committee
EC	Ethics Committee
EFD	Embryofoetal development
EOS	End of study
eCRF	Electronic case report form
FLU-PRO©	InFLUenza Patient-Reported Outcome
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GD	Gestation day
HIV	Human immunodeficiency virus
HREC	Human Research Ethics Committee
IATA	International Air Transport Association
ICF	Informed consent form
IMP	Investigational medicinal product
IRB	Institutional Review Board
LRTI	Lower respiratory tract infection
MedDRA	Medical Dictionary for Regulatory Activities
NHC	β-D-N4-hydroxycytidine
NHC-TP	NHC 5'-triphosphate
PPE	Personal protective equipment
RHD	Recommended human dose
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SAHPRA	South African Health Products Regulatory Authority
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOE	Schedule of Events
SpO2	Oxygen saturation
SmPC	Summary of Product Characteristics
SRT	Safety Review Team
T_{max}	Time to maximum concentration
TB	Tuberculosis
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary

SYNOPSIS

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
Short Title	COTeT
Rationale	Recurring waves and outbreaks of COVID-19 driven by the highly transmissible Delta (B.1.617.2) variant and most recently by the Omicron variant first described in South Africa, are exacerbating the global public health crisis. Vaccines have substantially reduced the morbidity and mortality rates in those infected with SARS-CoV-2, and several therapeutic agents, including steroids, have been shown to impact on severe disease[1–3]. However, individuals who have been infected or vaccinated still run the risk of recurrent infection. These infections are often symptomatic, with occasional severe morbidity and even mortality in those with similar risk factors for severe disease to those without immunity. Several oral, injectable and infusion agents have been tested for use as early treatment, and several promising oral agents have recently emerged. These include fluvoxamine, molnupiravir and nirmatrelvir, and all have an impact on hospitalization and severe outcomes. Multiple other agents are being investigated. While study design varied for these new agents, all appear to have maximum impact if administered soon after symptom onset (within 3-5 days), and for several days. This aligns with the current understanding of the development of SARS-CoV-2 infection: an initial viral infection and dissemination phase is followed by an immunological phase (during which immunomodulation contributes significantly) in certain high-risk patients with associated severe morbidity and mortality. Current thinking is that new agents play a role in early disease by limiting viral replication and potentially preventing or limiting the subsequent immunological phase. The effectiveness of these agents relies on early presentation of patients to a relevant health care facility, rapid confirmation of SARS-CoV-2 infection, and prompt initiation of therapy. South Africa, like many countries, has endured several waves of SARS-CoV-2, with some estimates suggesting that 80% of the population have been infected. Excess mortality due to the virus is recorded at just over 300 000 since the first cases in March 2020 [4], in a population of 50 million. Currently, only 48% of the population have been vaccinated (68% in those over 60 years)[5]. Accurate comparisons with elsewhere on the continent, or even with high income countries are difficult, although there are some suggestions that South African mortality is particularly high. This may be due to the very high levels of obesity and diabetes, both significant risk factors for poor COVID-19 outcomes, as well as high levels of HIV, also somewhat associated with poorer outcomes[6,7]m. Access to agents with a demonstrated ability to impact hospitalisation and severe outcomes related to COVID-19 will have clear benefits in the South African context but is limited by the time to registration of new drugs, or caveats attached to the use and monitoring of unregistered products through the Section 21 mechanism. Rapid access to molnupiravir in South Africa will be facilitated for a large number of COVID-19 patients through this Phase 3 clinical trial while awaiting registration applications and procedures. The LumiraDx™ point of care diagnostic platform for diagnosis of SARS-CoV-2 infection through antigen detection, will enable rapid confirmation of COVID-19 in patients with recent onset of symptoms and mild disease. Patients who meet the enrolment criteria will have same-day initiation of a five-day treatment course of molnupiravir, and will be followed to monitor tolerability, adverse

	drug reactions, effectiveness through time to resolution of symptoms and progression to severe disease (requiring hospitalisation and/or resulting in death), and adherence.
Design	This is a multi-centre, double-blind, Phase 3 study to observe the effectiveness, safety, and tolerability of molnupiravir 800 mg administered 12-hourly for five days to adult patients with mild COVID-19 at the time of enrolment who are at risk of progression to severe disease, compared to a placebo. Patients with recent onset of COVID-19 symptoms will be screened to assess eligibility for enrolment. Confirmation of SARS-CoV-2 infection will be performed through rapid antigen detection using the LumiraDx™ point of care diagnostic platform. Eligible patients will be enrolled and will be randomised in a 1:1 manner to start treatment with either molnupiravir or a placebo on the same day. Patients will record their symptoms (through a self-administered questionnaire) and self-observed vital signs daily for 10 days from the time of enrolment and will be contacted by study team personnel on Days 3, 6 and 10 to monitor their well-being. Adverse event and concomitant medication data will be collected. A final end-of-study follow-up visit will be conducted on Day 29. An independent Data and Safety Monitoring Board (DSMB) will be convened for this study with expertise in COVID-19 or respiratory viruses, and emerging epidemics. The purpose of the DSMB is to monitor the study for safety and operational futility. In addition to the usual, regular, required reporting to SAHPRA, we anticipate that additional reporting may be required, noting the severity of the 3rd and 4th waves, the level of ''breakthrough'' infections in the context of high background comorbidities, and the urgent interest in this class of drugs.
Population	Adults ≥50 years of age with self-reported symptoms of COVID-19 for no more than five days prior to screening, and who test positive for SARS-CoV-2 antigen on the day of screening or have a documented positive SARS-CoV-2 RT-PCR within 2 days prior to screening, and who are at risk of progression to severe disease, will be enrolled. The following eligibility criteria will be used to select study participants. Inclusion criteria: 1. Able and willing to provide written or electronic informed consent prior to any study-specific procedure. 2. Age ≥50 at the time of signing the informed consent form. 3. Women of reproductive potential must have a negative pregnancy test at screening and be using a highly effective method of contraception. Highly effective methods of contraception include: a. Hormonal methods of contraception for at least 14 days prior to screening (including oral contraceptive pills, injectables, or implants) b. Intrauterine devices from at least 7 days prior to screening (including hormone-releasing, and non-hormone-releasing devices) c. Bilateral tubal ligation d. Engaging exclusively single-sex relationships e. Sexual abstinence 4. A male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another while taking the investigational product. Male participants should also be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak 5. Self-reported symptoms of COVID-19 with onset no more than five days prior to screening informed consent including at least one of, fever or chills, cough, sore throat, rhinorrhoea or rhinitis or sinusitis, shortness of breath, headache, myalgia, new onset anosmia or ageusia, nausea, diarrhoea, or extreme fatigue,

	or other symptoms recognized in local and international guidelines as typical of mild COVID-19. 6. SARS-CoV-2 infection confirmed through a positive LumiraDx™ rapid antigen test on the day of screening or a positive RT-PCR within two days prior to screening. 7. Participant is at high risk for progression to severe COVID-19, this defined as either: a. Age ≥50 with at least one of the following background or medical conditions: diabetes mellitus, obesity (BMI ≥30 kg/m^2), hypertension, HIV, or active or previous TB. b. Age ≥65 8. Participant agrees to comply with study procedures, including the completion of a daily diary for 10 days from the time of enrolment, and to be available for study contacts and visits. Exclusion criteria: 1. Pregnant or breastfeeding women, or women planning/desiring to become pregnant during the 28 days following enrolment into the study. 2. Duration of self-reported symptoms of COVID-19 for more than five days prior to screening. 3. Signs of respiratory distress or severe disease prior to enrolment, including: a. respiratory rate >24 breaths/min b. SpO2 <95% in room air c. heart rate ≥120 bpm d. abnormal mental status e. inability to walk due to COVID-19 symptoms f. inability to talk in full sentences due to COVID-19 symptoms g. a requirement for hospitalisation. 4. Inability/unlikely to be in the study area for the duration of the 28-day follow-up period. 5. Inability to tolerate oral medications. 6. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the safety of the patient or the objectives of the study. The Investigator should make this determination in consideration of the volunteer's medical history. 7. The volunteer is assessed to be clinically unstable in the Investigator's opinion. 8. Participation in another investigational study involving an investigational product within 30 days, or 5 half-lives, whichever is longer, prior to screening. 9. Personnel (e.g., investigator, sub-investigator, research assistant, pharmacist, study coordinator or anyone mentioned in the delegation log) directly involved in the conduct of the study. 10. Any physical, mental, or social condition, drug/alcohol use, history of illness or laboratory abnormality that, in the Investigator's judgment, might jeopardise the safety of the patient in the context of this study, or might interfere with study procedures or the ability of the subject to adhere to and complete the study. The Investigator should make this determination in consideration of the volunteer's medical history. Volunteers may be re-screened if they are found not to have COVID-19 at the time of the initial screening, but develop a further, and distinct, acute illness suggestive of COVID-19 at a later stage.
Investigational Medicinal Product	Molnupiravir 800 mg 12-hourly or placebo administered orally for five days.

Objectives and Endpoints	**Primary Objectives**	**Primary Endpoints**
	• To evaluate the effectiveness of molnupiravir compared to placebo in preventing severe disease progression in adults with mild COVID-19	• Combination of incidence of COVID-19-related hospitalisation (≥24 hours of care in a hospital or similar acute care facility) and COVID-19-related mortality to Day 29
	• To evaluate the safety of molnupiravir in adults with mild COVID-19	• Adverse events (including serious adverse events and adverse drug reactions) • Self-assessed vital signs to Day 10
	Secondary Objectives	**Secondary Endpoints**
	• To facilitate same-day COVID-19 diagnosis and treatment initiation in adults with mild COVID-19 and comorbid conditions	• Proportion of enrolled patients for whom diagnosis and same day treatment initiation was facilitated through use of a LumiraDx™ rapid antigen test
	• To assess the tolerability of molnupiravir in adults with mild COVID-19	• Severity of adverse events • Adverse event-related study drug discontinuations
	• To describe time to symptom resolution in adults with mild COVID-19 treated with molnupiravir compared to placebo	• Time to sustained resolution of symptoms as reported in the Flu-PRO© Plus
	• To evaluate maximum COVID-19 disease severity in adults treated with molnupiravir compared to placebo	• Maximum score on the WHO Clinical Progression Scale from Day 1 to Day 29
	• To evaluate the relationship between effectiveness of molnupiravir and time between onset of symptoms and initiation of treatment	• Number of days from symptom onset to initiation of treatment • Incidence of hospitalisation (≥24 hours of care in a hospital or similar acute care facility) and/or death to Day 29 in patients with co-morbid conditions • Time to sustained resolution of symptoms as reported in the Flu-PRO© Plus • Maximum score on the WHO Clinical Progression Scale from Day 1 to Day 29
	• To describe adherence to a 5-day course of molnupiravir in adults with mild COVID-19	• Proportion of patients completing the course of molnupiravir as prescribed
	• To describe the utilisation of health care services by adults with mild COVID-19 treated with molnupiravir compared to placebo	• Rate of hospital, emergency facility, clinic, health care practitioner or home visits to Day 29
	• To report the incidence and outcome of pregnancies in female participants who received molnupiravir	• Incidence of pregnancy in female participants to Day 29 • 20-week gestational age ultrasound findings • Pregnancy complications • Pregnancy outcome • Infant wellbeing to three months of age

	Exploratory Objectives • To describe the proportions of eligible patients from different sites of screening • To describe the proportion of women failing screening due to pregnancy • To describe COVID-19 disease severity in adults who receive molnupiravir with different at-risk indicators • To describe the symptoms of COVID-19 in male compared to female adult participants • To describe COVID-19 disease severity in vaccinated compared to unvaccinated adults who receive molnupiravir
Sample Size	4000 patients will be enrolled into this study (2000 per treatment arm).
Duration	29 days per participant.

1. SCHEDULE OF EVENTS

Procedure / assessment	Screening/ Enrolment	Treatment and Follow-Up (including self-quarantine as required in accordance with local guidelines)						EOS
	Day 0[a]	Day 1-2	Day 3	Day 4-5	Day 6	Day 7-9	Day 10	Day 29 (±3)[b]
Informed consent	X							
Demography	X							
Duration of COVID-19 symptoms	X							
Pregnancy and lactation status[c]	X							
Urine pregnancy test[d]	X							
LumiraDx™ SARS-CoV-2 Ag testing[e]	X							
Point of Care HIV test[f]								
Past and current medical conditions (including COVID-19 vaccination status)	X							
Concomitant medications, including contraception	X		X		X		X	X
Physical examination, including weight and height[g]	X							X
Vital signs (temp., pulse, BP, RR, SpO2)[h]	X							X
Eligibility criteria	X							
WHO Clinical Progression Scale[i]	X		X		X		X	X
Study treatment[j]		X	X	X				
Patient reported vital signs (temp., pulse and SpO2)[k]		X	X	X	X	X	X	
Completion of daily survey and FLU-PRO© Plus questionnaire[l]		X	X	X	X	X	X	X
Adverse event review[m]			X		X		X	X
Return of unused IMP and empty containers								X[m]
Contact with study staff[n]	X		X		X		X	

EOS: end of study; temp.: body temperature; BP: blood pressure; RR: respiratory rate; SpO2: oxygen saturation; WHO: World Health Organization.

Note: Participants who stop study product should continue study participation off study product with continued evaluations as per the schedule of activities. The reason for study product discontinuation should be recorded.

[a] A window period of -1 day may apply in cases where COVID-19 symptoms have not already been present for 5 days at the time of screening. Screening/enrolment (Day 0) and initiation of study treatment and follow-up (Day 1) are anticipated to occur on the same day for most participants.

[b] For participants who are hospitalized at the time of the scheduled Day 29 visit, the EOS visit will be approximately 3 days after discharge.

[c] Female participants only.

[d] Urine pregnancy test for women of reproductive potential only.

[e] Participants with same-day LumiraDx SARS-CoV-2 Ag from another vendor or a laboratory confirmation of an RT-PCR positive for SARS-CoV-2 within 2 days prior to screening will not require an additional rapid antigen test.

[f] Optional HIV point of care testing will be offered to participants at screening. Newly diagnosed patients will be referred appropriately for care.

[g] An abbreviated, symptom-directed physical examination including at least a general examination and chest auscultation will be performed. Height will be measured at screening only.

[h] Body temperature will be measured. Pulse, RR and SpO2 will be measured after at least 5 minutes resting.

[i] To be performed via telephone call or text/direct messaging or web-based conference, or in person as necessary. For the Day 3, 6 and 10 contact sessions, a window period of ±1 days is permitted. This window period will also apply to the assessment of the WHO Clinical Progression Scale score by the study team personnel, and the review of adverse event and concomitant medication data to be performed during these contact sessions.

[j] Molnupiravir 800 mg will be taken approximately 12-hourly, with a glass of water, with or without food, for five days (10 doses).

[k] The Day 1 assessments will be performed by enrolled participants under observation of the study personnel. Assessments will be recorded utilizing a mobile phone/tablet application, or other device, or diary, or during a telephonic or in person interaction with the site personnel. Assessments may be performed by study personnel if an in-person visit is conducted after completion of the quarantine period.

[l] The FLU-PRO© Plus questionnaire and daily survey will be recorded daily for 10 days by participant utilizing a mobile phone/tablet application or diary. The daily survey will consist of the FLU-PRO© Plus Global Additional Daily Diary Items (related to general well-being, overall severity of symptoms, and ability to perform usual daily activies) as well as other general daily diary questions related to study drug administration, recording of vital signs and SpO2 measurements, review of concomitant medications, and information related to possible adverse events.

[m] Serious adverse events, adverse events resulting in treatment discontinuation, and all other AEs, including those judged by the site Investigator to be related to the administered treatment regimens.

[n] Or anytime from Day 6 if an earlier contact visit takes place.

2. INTRODUCTION

2.1 Background

Recurring waves and outbreaks of COVID-19 driven by the highly transmissible Delta (B.1.617.2) variant and most recently by the Omicron variant first described in South Africa, are exacerbating the global public health crisis. Vaccines have substantially reduced the morbidity and mortality rates in those infected with SARS-CoV-2, and several therapeutic agents, including steroids, have been shown to impact on severe disease[1–3]. However, individuals who have been infected or vaccinated still run the risk of recurrent infection. These infections are often symptomatic, with occasional severe morbidity and even mortality in those with similar risk factors for severe disease to those without immunity.

Several oral, injectable and infusion agents have been tested for use as early treatment, and several promising oral agents have recently emerged. These include fluvoxamine, molnupiravir and nirmatrelvir, and all have an impact on hospitalization and severe outcomes. Multiple other agents are being investigated. While study design varied for these new agents, all appear to have maximum impact if administered soon after symptom onset (within 3-5 days), and for several days. This aligns with the current understanding of the development of SARS-CoV-2 infection: an initial viral infection and dissemination phase is followed by an immunological phase (during which immunomodulation contributes significantly) in certain high-risk patients with associated severe morbidity and mortality. Current thinking is that new agents play a role in early disease by limiting viral replication and potentially preventing or limiting the subsequent immunological phase. The effectiveness of these agents relies on early presentation of patients to a relevant health care facility, rapid confirmation of SARS-CoV-2 infection, and prompt initiation of therapy.

South Africa, like many countries, has endured several waves of SARS-CoV-2, with some estimates suggesting that 80% of the population have been infected. Excess mortality due to the virus is recorded at just over 300 000 since the first cases in March 2020[4], in a population of 50 million. Currently, only 48% of the population have been vaccinated (68% in those over 60 years)[5]. Accurate comparisons with elsewhere on the continent, or even with high income countries are difficult, although there are some suggestions that South African mortality is particularly high. This may be due to the very high levels of obesity and diabetes, both significant risk factors for poor COVID-19 outcomes, as well as high levels of HIV, also somewhat associated with poorer outcomes[6,7]. Access to agents with a demonstrated ability to impact hospitalisation and severe outcomes related to COVID-19 will have clear benefits in the South African context but is limited by the time to registration of new drugs, or caveats attached to the use and monitoring of unregistered products through the Section 21 mechanism.

2.2 Molnupiravir

The broad-spectrum antiviral agent, molnupiravir, is a prodrug of the nucleoside analogue β-D-N4-hydroxycytidine (NHC). NHC distributes into cells where it is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHC-TP acts by a mechanism known as viral error catastrophe. NHC-TP incorporation into viral RNA by the viral RNA polymerase, results in an accumulation of errors in the viral genome leading to inhibition of replication[8].

The drug is orally bioavailable (and is indicated for treatment of mild to moderate COVID-19 in adults with a positive SARS-COV-2 diagnostic test and who have at least one risk factor for developing severe illness. The recommended dose is 800 mg (four 200 mg capsules) taken orally 12-hourly for five days, and should be administered as soon as possible after diagnosis of COVID-19 has been made and within five days of symptom onset[8,9].

2.2.1 Summary of findings from non-clinical studies

Preclinical data in cell culture revealed a dose-dependent increase in G to A and C to U transition mutations that correlated with increased antiviral effects against coronaviruses[10,11]. NHC was active in cell culture assays against SARS-CoV-2 with 50% effective concentrations (EC50) ranging between 0.67 to 2.66 µM in A-549 cells and 0.32 to 2.03 µM in Vero E6 cells. NHC had similar activity against SARS-CoV-2 variants B.1.1.7 (Alpha), B.1351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) with EC50 values of 1.59, 1.77 and 1.32 and 1.68 µM, respectively. No impact was observed on the *in vitro* antiviral activity of NHC against SARS-CoV-2 when NHC was tested in combination with abacavir, emtricitabine, hydroxychloroquine, lamivudine, nelfinavir, remdesivir, ribavirin, sofosbuvir, or tenofovir[8].

2.2.1.1 General toxicity

Reversible, dose-related bone marrow toxicity affecting all haematopoietic cell lines was observed in dogs at ≥17 mg/kg/day (0.4 times the human NHC exposure at the recommended human dose (RHD)). Mild decreases in peripheral blood cell and platelet counts were seen after 7 days of molnupiravir treatment progressing to more severe haematological changes after 14 days of treatment. Neither bone marrow nor haematological toxicity was observed in a 1-month toxicity study in mice up to 2000 mg/kg/day (19 times the human NHC exposure at the RHD) and a 3-month toxicity study in rats up to 1000 mg/kg/day (9.3 and 15 times the human NHC exposure at the RHD in females and males, respectively).

Bone and cartilage toxicity, consisting of an increase in the thickness of physeal and epiphyseal growth cartilage with decreases in trabecular bone was observed in the femur and tibia of rapidly growing rats in a 3-month toxicity study at ≥500 mg/kg/day (5.4 times the human NHC exposure at the RHD). There was no bone or cartilage toxicity in a 1-month toxicity study in rapidly growing rats up to 500 mg/kg/day (4.2 and 7.8 times the human NHC exposure at the RHD in females and males, respectively), in dogs dosed for 14 days up to 50 mg/kg/day (1.6 times the human NHC exposure at the RHD), or in a 1-month toxicity study in mice up to 2000 mg/kg/day (19 times the human NHC exposure at the RHD). Growth cartilage is not present in mature skeletons; therefore, the bone and cartilage findings are not relevant for adult humans. The clinical significance of these findings for paediatric patients is unknown.

2.2.1.2 Carcinogenesis

Carcinogenicity studies with molnupiravir have not been conducted.

2.2.1.3 Mutagenesis

Molnupiravir and NHC were positive in the in vitro bacterial reverse mutation assay (Ames assay) with and without metabolic activation. In 2 distinct in vivo rodent mutagenicity models (Pig-a mutagenicity assay and Big Blue® [cII Locus] transgenic rodent assay) molnupiravir did not induce increased mutation rates relative to untreated historical control animals, and therefore is not mutagenic *in vivo*. Molnupiravir was negative for induction of chromosomal damage in in vitro micronucleus (with and without metabolic activation) and *in vivo* rat micronucleus assays. Based on the totality of the genotoxicity data, molnupiravir is of low risk for genotoxicity or mutagenicity in clinical use[8].

2.2.1.4 Fertility

There were no effects on fertility, mating performance or early embryonic development when molnupiravir was administered to female or male rats at NHC exposures approximately 2 and 6 times the human NHC exposure at the recommended human dose (RHD), respectively[8].

2.2.1.5 Development

In an embryofoetal development (EFD) study in rats, molnupiravir was administered orally to pregnant rats at 0, 100, 250, or 500 mg/kg/day from gestation days (GDs) 6 to 17. Molnupiravir was also administered orally to pregnant rats at up to 1000 mg/kg/day from GDs 6 to 17 in a preliminary EFD study. Developmental toxicities included post-implantation losses, malformations of the eye, kidney, and axial skeleton, and rib variations at 1000 mg/kg/day (8 times the human NHC exposure at the RHD) and decreased foetal body weights and delayed ossification at ≥500 mg/kg/day (2.9 times the human NHC exposure at the RHD). There were no developmental toxicities at ≤250 mg/kg/day (0.8 times the human NHC exposure at the RHD). Maternal toxicities included decreased food consumption and body weight losses, resulting in the early sacrifice of individual animals at 1000 mg/kg/day, and decreased body weight gain at 500 mg/kg/day.

In an EFD study in rabbits, molnupiravir was administered orally to pregnant rabbits at 0, 125, 400, or 750 mg/kg/day from GDs 7 to 19. Developmental toxicity was limited to reduced foetal body weights at 750 mg/kg/day (18 times the human NHC exposures at the RHD). There was no developmental toxicity at ≤400 mg/kg/day (7 times the human NHC exposures at the RHD). Maternal toxicities included reduced food consumption and body weight gains, and abnormal faecal output at 750 mg/kg/day.

2.2.2 Summary of findings from clinical studies

2.2.2.1 Pharmacokinetic properties

Following twice daily oral administration of 800 mg molnupiravir, the median time to peak plasma NHC concentrations (T_{max}) was 1.5 hours with a C_{max} of 2970 ng/mL in healthy subjects. NHC is not bound to plasma proteins. AUC_{0-12} at steady state after 12-hourly administration of molnupiravir 800 mg was 8260 ng·hr/mL with C_{12} of 31.1 ng/mL (derived from population PK analysis in patients). The effective half-life of NHC is approximately 3.3 hours. The fraction of dose excreted as NHC in the urine was ≤3% in healthy participants[8].

In healthy subjects, the administration of a single 200mg dose of molnupiravir with a high-fat meal resulted in a 35% reduction in NHC peak concentrations (C_{max}). AUC was not significantly affected[8].

Molnupiravir was evaluated in a clinical Phase 3 trial (MOVe-OUT) for the treatment of SARS-CoV-2 infections[12]. Analysis of the Phase 3 trial data demonstrated that monulpiravir reduced the risk of hospitalisation and death in patients with mild to moderate COVID-19 and at least one risk factor linked to reduced outcomes by 30% (relative risk 0.70; 95% CI: 0.49, 0.99)[13].Clinical efficacy

Clinical data are based on an interim analysis of data from 775 randomised subjects in the Phase 3 MOVe-OUT trial. MOVe-OUT was a randomised, placebo-controlled, double-blind clinical trial evaluating molnupiravir for the treatment of non-hospitalised patients with mild to moderate COVID-19 who were at risk for progressing to severe COVID-19 and/or hospitalisation. Eligible subjects were 18 years of age and older and had one or more pre-defined risk factors for disease progression: 60 years of age or older, diabetes, obesity (BMI >30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer. The study included symptomatic subjects not vaccinated against SARS-CoV-2 and who had laboratory confirmed SARS-CoV-2 infection and symptom onset within 5 days of enrolment. Subjects were randomised 1:1 to receive 800 mg of molnupiravir or placebo orally twice daily for 5 days.

At baseline, in all randomised subjects, the median age was 44 years (range: 18 to 88 years); 14% of subjects were 60 years of age or older and 3% were over 75 years of age. Forty-nine percent (49%) of subjects received molnupiravir or placebo within 3 days of COVID-19 symptom onset. The most

common risk factors were obesity (77%), 60 years of age or older (14%), and diabetes (14%). Overall, baseline demographic and disease characteristics were well balanced between the treatment arms.

Results of the primary endpoint (the percentage of subjects who were hospitalised or died through Day 29 due to any cause) are summarised in Table 1. Treatment with Lagevrio resulted in a 3.0 percentage point reduction in the risk of hospitalisation or death (30% relative risk reduction). 10 deaths were reported through Day 29; one death was reported in the molnupiravir group and 9 in the placebo group and all were hospitalised prior to their death. Efficacy results were consistent across sub-groups including age (>60 years), at-risk medical conditions (e.g., obesity, diabetes), and SARS-CoV-2 variants[14].

Table 1: Interim Efficacy Results in Non-Hospitalised Adults with COVID-19

	Monulpiravir [N=385] n (%)	**Placebo [N=377] n (%)**	**Risk difference[a] (95% CI)**	**p-value**
All-cause hospitalisation or death through Day 29[b]	28 (7.3)	53 (14.1)	-6.8 (-11.3, -2.4)	0.0012
Hospitalisation	28 (7.3)	52 (13.8)		
Death	1 (0.1)	9 1.3)		

[a] Risk difference of molnupiravir-placebo based on Miettinen and Nurminen method stratified by time of COVID-19 symptom onset (≤3 days vs. >3 [4-5] days).

[b] Defined as ≥24 hours of acute care in a hospital or an acute care facility (e.g., emergency room).

[c] Subjects with unknown status at Day 29 are counted as having an outcome of all-cause hospitalisation or death in the efficacy analysis.

Note: All subjects who died through Day 29 were hospitalised prior to death.

2.2.2.2 Safety

In an interim analysis of a Phase 3 trial of subjects with mild to moderate COVID-19 treated with molnupiravir (n=386), the most common adverse reactions (≥1% of subjects) reported during treatment and during the 14 days after the last dose were diarrhoea (3%), nausea (0.7%) and dizziness (0.7%) all of which were Grade 1 (mild) or Grade 2 (moderate)[14].

The safety and efficacy of molnupiravir when administered for periods longer than 5 days have not been established

2.2.2.3 Special populations

No dose adjustment of molnupiravir for required for patients with renal or hepatic impairment or based on age.

The safety and efficacy of molnupiravir in patients below 18 years of age have not been established. No data are available.

There are no data from the use of molnupiravir in pregnant women. Studies in animals have shown reproductive toxicity and molnupiravir is not recommended during pregnancy. Women of childbearing potential should use effective contraception for the duration of treatment and for 4 days after the last dose of molnupiravir.

It is unknown whether molnupiravir or any of the components of molnupiravir are present in human milk, affect human milk production, or have an effect on the breastfed infant. Animal lactation studies with molnupiravir have not been conducted. Based on the potential for adverse reactions in the infant

from molnupiravir, breast-feeding is not recommended during treatment and for 4 days after the last dose.

2.2.2.4 Resistance

No amino acid substitutions in SARS-CoV-2 associated with resistance to NHC have been identified in Phase 2 clinical trials evaluating molnupiravir for the treatment of COVID-19[8]. Studies to evaluate selection of resistance to NHC with SARS-CoV-2 in cell culture have not been completed.

2.2.3 Drug-drug interactions

No drug interactions have been identified based on the limited available data. No clinical interaction studies have been performed with molnupiravir. Molnupiravir is hydrolysed to NHC prior to reaching systemic circulation. Uptake of NHC and metabolism to NHC-TP are mediated by the same pathways involved in endogenous pyrimidine metabolism. NHC is not a substrate of major drug metabolising enzymes or transporters. Based on *in vitro* studies, neither molnupiravir nor NHC are inhibitors or inducers of major drug metabolising enzymes or inhibitors of major drug transporters. Therefore, the potential for molnupiravir or NHC to interact with concomitant medications is considered unlikely[8].

2.2.4 Summary of known and potential risks and benefits

Theoretically, mutagenic drugs could cause both birth defects and cancer. A recent study found that NHC displays host mutational activity in an animal cell culture assay, consistent with RNA and DNA precursors sharing a common intermediate of a ribonucleoside diphosphate. These results indicate highly active mutagenic ribonucleosides may hold risk for the host[15]. Preclinical studies with molnupiravir, however, have demonstrated that the compound is neither mutagenic nor *genotoxic in vivo* mammalian systems.

Molnupiravir has been shown to reduce the risk of hospitalisation and death related to COVID-19 in patients at risk for severe disease progression by approximately 50%. In the Phase 3 trial of the drug, the adverse effects of COVID-19 appear worse than those of molnupiravir since patients in the placebo group were more likely to withdraw early (3.4%) than recipients of the active drug (1.3%)[13].

2.3 Study Rationale

Rapid access to molnupiravir in South Africa will be facilitated for a large number of COVID-19 patients through this Phase 3 clinical trial while awaiting registration application and procedures. The LumiraDx™ point of care diagnostic platform for diagnosis of SARS-CoV-2 infection through antigen detection, will enable rapid confirmation of COVID-19 in patients with recent onset of symptoms and mild disease. Patients who meet the enrolment criteria will have same-day initiation of a five-day treatment course of molnupiravir, and will be followed to monitor tolerability, adverse drug reactions, effectiveness through time to resolution of symptoms and progression to severe disease (requiring hospitalisation and/or resulting in death), and adherence.

3. OBJECTIVES AND ENDPOINTS

Primary	
Objectives	**Endpoints**
• To evaluate the effectiveness of molnupiravir compared to placebo in preventing severe	• Combination of incidence of COVID-19-related hospitalisation (≥24 hours of care in a hospital

disease progression in adults with mild COVID-19	or similar acute care facility) and COVID-19-related mortality to Day 29
• To evaluate the safety of molnupiravir in adults with mild COVID-19	• Adverse events (including serious adverse events and adverse drug reactions) • Self-assessed vital signs to Day 10
Secondary	
Objectives	**Endpoints**
• To facilitate same-day COVID-19 diagnosis and treatment initiation in adults with mild COVID-19 and comorbid conditions	• Proportion of enrolled patients for whom diagnosis and same day treatment initiation was facilitated through use of a LumiraDx™ rapid antigen test
• To assess the tolerability of molnupiravir in adults with mild COVID-19	• Severity of adverse events • Adverse event-related study drug discontinuations
• To describe time to symptom resolution in adults with mild COVID-19 treated with molnupiravir compared to placebo	• Time to sustained resolution of symptoms as reported in the Flu-PRO© Plus
• To evaluate maximum COVID-19 disease severity in adults treated with molnupiravir compared to placebo	• Maximum score on the WHO Clinical Progression Scale from Day 1 to Day 29
• To evaluate the relationship between effectiveness of molnupiravir and time between onset of symptoms and initiation of treatment	• Number of days from symptom onset to initiation of treatment • Incidence of hospitalisation ((≥24 hours of care in a hospital or similar acute care facility) and/or death to Day 29 in patients with co-morbid conditions • Time to sustained resolution of symptoms as reported in the Flu-PRO© Plus • Maximum score on the WHO Clinical Progression Scale from Day 1 to Day 29
• To describe adherence to a 5-day course of molnupiravir in adults with mild COVID-19	• Proportion of patients completing the course of molnupiravir as prescribed
• To evaluate the utilisation of health care services by adults with mild COVID-19 treated with molnupiravir compared to placebo	• Rate of hospital, emergency facility, clinic, health care practitioner or home visits to Day 29

• To report the incidence and outcome of pregnancies in female participants who received molnupiravir	• Incidence of pregnancy in female participants to Day 29 • 20-week gestational age ultrasound findings • Pregnancy complications • Pregnancy outcome • Infant wellbeing to three months of age
Exploratory	
Objectives	
• To describe the proportions of eligible patients from different sites of screening • To describe the proportion of women failing screening due to pregnancy • To describe COVID-19 disease severity in adults who receive molnupiravir with different at-risk indicators • To describe the symptoms of COVID-19 in male compared to female adult participants • To describe COVID-19 disease severity in vaccinated compared to unvaccinated adults who receive molnupiravir	

4. STUDY DESIGN

4.1 Overall Design

This is a multi-centre, double-blind, phase 3 study to observe the effectiveness, safety, and tolerability of molnupiravir 800 mg administered 12-hourly for five days in adult patients with mild COVID-19 at the time of enrolment, who are at risk of progression to severe disease, compared to a placebo.

Patients with recent onset of COVID-19 symptoms will be screened to assess eligibility for enrolment. Confirmation of SARS-CoV-2 infection will be performed through rapid antigen detection using the LumiraDx™ point of care diagnostic platform. Approximately 4000 eligible patients will be enrolled and will be randomised in a 1:1 manner to start treatment with either molnupiravir or a placebo on the same day. Patients will record their symptoms (through a self-administered questionnaire) and self-observed vital signs daily for 10 days from the time of enrolment and will be contacted by study team personnel on Days 3, 6 and 10 to monitor their well-being. Adverse event and concomitant medication data will be collected. A final end-of-study follow-up visit will be conducted on Day 29.

An independent Data and Safety Monitoring Board (DSMB) will be convened for this study with expertise in COVID-19 or respiratory viruses, and emerging epidemics. The purpose of the DSMB is to monitor the study for safety and operational futility.

In addition to the usual, regular, required reporting to SAHPRA, we anticipate that additional reporting will be required by the Clinical Trials Committee, noting the severity of the 3rd and 4th waves, the level of ''breakthrough'' infections in the context of high background comorbidities, and the urgent interest in this class of drugs.

4.2 Dose Selection

A dose of 800 mg of molnupiravir twice daily has been demonstrated to be safe and well-tolerated in participants with SARS CoV-2 infection. The plasma concentrations attained are within the target range based on scaling from animal models[16,17].

The recommended dose of molnupiravir is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days[8].

4.3 Study Pausing Rules

The occurrence of any serious adverse event (SAE) considered related to the study drug will prompt a halt to further enrolment into the trial pending a formal safety review by the DSMB.

Dosing of on-study participants, and follow-up of participants previously enrolled and dosed, will not be altered unless, for example, additional safety measures are judged to be required following the safety review.

The DSMB will provide recommendations to the Sponsor regarding study stopping or continuation or amended circumstances under which the study may proceed as detailed in the DSMB Charter. Additional investigations or assessments may be recommended to establish causality or ensure ongoing safety of enrolled participants.

4.4 Individual Participant Withdrawal

A participant may be withdrawn from the study for any of the following reasons:

- At the request of the participant (withdrawal of informed consent), irrespective of the reason for this
- At the request of the primary care provider if he or she thinks the study is no longer in the best interest of the participant
- At the discretion of the Investigator if he or she believes that continuation in the study would be detrimental to the participant's well-being in any way
- At the discretion of the Institutional Review Board (IRB)/Ethics Committee (EC), Regulatory Authority, Funder or Medical Monitor if they believe that continuation in the study would be detrimental to the participant's well-being in any way, or
- Any protocol non-conformance that results in a significant risk to the participant's safety.

Participants will be considered withdrawn if they state an intention to withdraw, fail to return for visits, or are lost to follow-up for any other reason. The Investigator will make every effort to determine the primary reason for a participant's withdrawal from the study and record this information in the electronic case report form (eCRF). For participants who are lost to follow-up, the Investigator will attempt to trace the participant, and will demonstrate "due diligence" by documenting all steps taken to contact the participant (e.g., dates of telephone calls, home visit, etc.) in the source documents.

If a participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such withdrawal of consent.

If a participant withdraws from the study, he or she may request destruction of any samples taken and not tested. This must be documented by the Investigator in the site study records.

If possible and agreed to by the participant, assessments detailed for the Day 29 EOS visit (Section 1, Schedule of Events), should be completed at the time of study discontinuation if a participant withdraws from the study.

Participants who withdraw or are withdrawn will not be replaced.

5. STUDY POPULATION

Four thousand (4000) adults ≥50 years of age with self-reported symptoms of COVID-19 for no more than five days prior to screening, and who test positive for SARS-CoV-2 antigen at screening or have a

positive SARS-CoV-2 RT-PCR within 2 days prior to screening, and who are at risk of progression to severe disease, will be enrolled.

Interested volunteers will be invited to participate in the informed consent process as described in Section 12.2. Written informed consent will be obtained prior to any screening procedures.

Volunteers may be re-screened if they are found not to have COVID-19 at the time of the initial screening, but develop a further, and distinct, acute illness suggestive of COVID-19 at a later stage.

The following eligibility criteria will be used to select study participants.

5.1 Inclusion criteria:

1. Able and willing to provide written or electronic informed consent prior to any study-specific procedure.
2. Age ≥50 at the time of signing the informed consent form.
3. Women of reproductive potential must have a negative pregnancy test at screening and be using a highly effective method of contraception. Highly effective methods of contraception include:
    a. Hormonal methods of contraception for at least 14 days prior to screening (including oral contraceptive pills, injectables, or implants)
    b. Intrauterine devices from at least 7 days prior to screening (including hormone-releasing, and non-hormone-releasing devices)
    c. Bilateral tubal ligation
    d. Engaging exclusively single-sex relationships
    e. Sexual abstinence
4. A male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another while taking the investigational product. Male participants should also be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak.
5. Self-reported symptoms of COVID-19 with onset no more than five days prior to screening informed consent including at least one of, fever or chills, cough, sore throat, rhinorrhoea or rhinitis or sinusitis, shortness of breath, headache, myalgia, new onset anosmia or ageusia, nausea, diarrhoea, or extreme fatigue, or other symptoms recognized in local and international guidelines as typical of mild COVID-19.
6. SARS-CoV-2 infection confirmed through a positive LumiraDx™ rapid antigen test on the day of screening or a positive RT-PCR within two days prior to screening.
7. Participant is at high risk for progression to severe COVID-19, this defined as either:
    a. Age ≥50 with at least one of the following background or medical conditions: diabetes mellitus, obesity (BMI ≥30 kg/m^2), hypertension, HIV, active or previous TB.
    b. Age ≥65
8. Participant agrees to comply with study procedures, including the completion of a daily diary for 10 days from the time of enrolment, and to be available for study contacts and visits.

5.2 Exclusion criteria:

1. Pregnant or breastfeeding women, or women planning/desiring to become pregnant during the 28 days following enrolment into the study.
2. Duration of self-reported symptoms of COVID-19 for more than five days prior to screening.
3. Signs of respiratory distress or severe disease prior to enrolment, including:

a. respiratory rate >24 breaths/min
b. SpO2 <95% in room air
c. heart rate ≥120 bpm
d. abnormal mental status
e. inability to walk due to COVID-19 symptoms
f. inability to talk in full sentences due to COVID-19 symptoms
g. a requirement for hospitalisation.

4. Inability/unlikely to be in the study area for the duration of the 28-day follow-up period.
5. Inability to tolerate oral medications.
6. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the safety of the patient or the objectives of the study. The Investigator should make this determination in consideration of the volunteer's medical history.
7. The volunteer is assessed to be clinically unstable in the Investigator's opinion.
8. Participation in another investigational study involving an investigational product within 30 days, or 5 half-lives, whichever is longer, prior to screening.
9. Personnel (e.g., investigator, sub-investigator, research assistant, pharmacist, study coordinator or anyone mentioned in the delegation log) directly involved in the conduct of the study.
10. Any physical, mental, or social condition, drug/alcohol use, history of illness or laboratory abnormality that, in the Investigator's judgment, might jeopardise the safety of the patient in the context of this study, or might interfere with study procedures or the ability of the subject to adhere to and complete the study. The Investigator should make this determination in consideration of the volunteer's medical history.

5.3 Justification of the Inclusion and Exclusion Criteria

The eligibility criteria have been selected to minimise risk to the well-being of participants in this study. The criteria are also set to ensure that the study population closely approximates the real-life target population of molnupiravir (i.e., intended recipients of a therapeutic agent known to reduce the risks of severe progression of mild COVID-19 in the South Africa setting).

5.4 Participant Identification

All volunteers who are screened for eligibility to participate in the study will be allocated a unique sequential screening number which will be used as the primary identifier for the duration of the study for enrolled participants.

5.5 Co-enrolment Guidelines

Participants may be co-enrolled in other research studies if these are observational in nature or include behavioural interventions only. Any other exception requires approval by the Principal Investigator in consultation with the Medical Monitor.

6. STUDY TREATMENTS

6.1 Molnupiravir

Molnupiravir is a broad-spectrum antiviral that is an orally bioavailable prodrug of the nucleoside analogue NHC. NHC distributes into cells where it is phosphorylated to form the pharmacologically active NHC-TP. NHC-TP acts by a mechanism known as viral error catastrophe. NHC-TP incorporation into viral RNA by the viral RNA polymerase, results in an accumulation of errors in the viral genome leading to inhibition of replication.

6.1.1 Packaging, labelling, storage, and accountability

Adequate quantities of molnupiravir will be supplied in pre-packaged quantities (each sufficient for a five-day treatment course for one patient) to the study site once approvals from the South African Health Products Regulatory Authority (SAHPRA) and relevant IRB/EC(s) have been obtained. The drug will be packed, labelled, and shipped together with the respective Certificates of Analysis containing the batch numbers.

The label content will be in accordance with South African legal requirements.

The Principal Investigator is responsible for ensuring that the study drug is stored in a secure location with restricted access to unauthorised personnel. Molnupiravir should be stored at room temperature. Storage conditions must be adequately monitored, and appropriate temperature logs maintained throughout the study.

Upon receipt of the molnupiravir shipment, the study pharmacist (or designee) must immediately inspect the shipment for damage, acknowledge receipt and confirm the shipment condition and content. Any damage or discrepancies from the packing list must be documented and promptly discussed with the supplier and study monitor to determine the appropriate action.

The study pharmacist (or designee) is responsible for maintaining accurate study drug accountability records. Instructions and the necessary forms for completion will be detailed in the Pharmacy Manual. Study drug accountability records will be reviewed by the study monitor during interim site visits and upon completion of the study. On study completion, copies of all study drug management records will be provided to the Sponsor. The originals must be maintained at the study site with the rest of the study records.

6.1.2 Cohorts

Eligible participants will be randomised in a 1:1 manner to receive either molnupiravir 800 mg orally approximately 12-hourly for five days or a placebo for the equivalent amount of time.

6.1.3 Blinding

The study will be double-blind. Neither the participants nor the principal investigator (or designee) who will be assessing AEs, will know the treatment group. A participant's treatment assignment may only be unblinded when knowledge of the treatment is essential for the safety of the participant and following consultation with the medical monitor. The process for unblinding will be documented in a Study Unblinding Plan.

6.1.4 Dispensing

Study drug (and home monitoring kits) will either be dispensed to participants at the site or delivered to participants at their homes.

6.1.5 IMP administration

Molnupiravir capsules can be taken with or without food. Each dose should be swallowed whole with fluid (e.g., a glass of water). The capsules should not be opened, crushed or chewed.

Participants will be provided with dosing instructions at the time of enrolment and when study drug is dispensed. They will self-administer the study treatment approximately 12-hourly for five days (10 consecutive doses).

6.1.6 Treatment compliance

All participants will be asked to complete a daily survey to gather information regarding treatment compliance.

If the participant notices that they have missed a dose of molnupiravir within 10 hours of the time that it was scheduled, they should take the missed dose as soon as possible and resume the normal dosing schedule thereafter. If a participant misses a dose by more than 10 hours, they should not take the missed dose and instead take the next dose at the regularly scheduled time. The participant should not double the dose to make up for a missed dose.

6.1.7 Overdose

There is no human experience of overdosage with molnupiravir. Treatment of overdose should consist of general supportive measures as required, including the monitoring of the clinical status of the patient. Haemodialysis is not expected to result in effective elimination of NHC.

6.1.8 Returns and destruction

After study completion and on the receipt of written authorisation from the Funder, any remaining study drug supplies will either be returned to Dr Reddy's Pharmaceutical company or will be destroyed at a defined location. Details of the final disposition of unused study drug, including a copy of the destruction certificate as relevant, will be documented in the Trial Master File.

6.2 Concomitant Therapy and Lifestyle and Dietary Restrictions

6.2.1 Concomitant treatments

Participants will be asked about concomitant medications at the screening evaluation visits. At each contact, the Investigator should question the participant about any medication taken (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements). All concomitant medications, vaccines, dietary supplements and herbal or traditional preparations taken from 28 days prior to study vaccine administration until the final safety follow-up visit will be detailed in the eCRF.

No concomitant treatments are prohibited during the study.

6.2.2 Lifestyle restrictions

The following lifestyle restrictions apply for participants enrolled in the study:

- Female participants should avoid becoming pregnant for the duration of the study.

- Women of reproductive potential must continue to use a highly effective method of contraception (as detailed in Section 5.1) during the study.
- Male participants will be advised to wear a condom when engaging in any activity that allows for passage of ejaculate to another while taking the investigational product. Male participants should also be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak.
- Female participants should not breast-feed during the study.

6.3 After Study Treatment

No additional treatment (prophylactic or therapeutic) will be provided at the end of the study.

7. STUDY VISITS

The planned visit schedule, associated visit window periods, and assessments and procedures to be conducted at each visit are detailed in the Section 1 (Schedule of Events [SOE]). Details regarding each assessment and procedure are described in Section 8.

Contact between study participants and study personnel will be limited as far as is possible. Study personnel will be instructed to wear appropriate PPE during all interactions, and participant and study personnel will be instructed to adhere to national and regional guidance for COVID-19-related safety measures.

For this study, data collection will be self-conducted where possible to minimize the impact of non-ill participants within the healthcare system and the risks of SARS-CoV-2 transmission. If the participant is assessed as eligible during the screening visit, contact between study participants and study personnel will occur via telephone, text/direct messaging, or tele-medicine, as far as is possible.

Participants will be instructed to seek clinical care should they manifest any signs or symptoms of a lower respiratory tract infection (LRTI) requiring medical intervention and notify their physician about trial participation. Any participant whose clinical condition deteriorates during the study, will be hospitalised if required in accordance with the national guidelines for clinical management of patients with COVID-19[18].

8. STUDY ASSESSMENTS AND PROCEDURES

No study-specific assessments will be performed, or information gathered, until the potential participant has given written, informed consent (Section 12.2) for screening procedures and (if found to be eligible) for procedures and assessments to be conducted during the study period.

The timing of all assessments and procedures is detailed in the SOE (Section 1).

8.1 Screening and Baseline Assessments

Screening evaluations must be completed, and the results reviewed by the Investigator to confirm eligibility of participants. A maximum of 1 calendar day is permitted between screening evaluations and the initiation of study drug, although in most cases, it is anticipated that these will be performed on the same day.

8.1.1 Demographics and social habits data

Demographic and baseline characteristic data to be collected for all participants includes age, sex, reproductive potential, self-reported race and predominant ethnicity.

8.1.2 Relevant medical and surgical history/current medical conditions including treatment

Information related to past and current relevant medical conditions and surgical procedures will be collected, including previous COVID-19, pregnancy and/or lactation status. In addition to the age of the participant, the presence of the following risk factors for disease progression will be noted:

- Obesity (BMI $\geq$30.0 kg/m^2)
- Diabetes mellitus
- Hypertension
- HIV
- Active or previous TB.

COVID-19 vaccination history, and current and previous medication usage, including contraception as relevant, will be ascertained and interpreted as relevant to the study-specific eligibility criteria.

Collection of information regarding illicit drug and alcohol consumption will be collected to enable assessment of eligibility.

8.1.3 Screening-specific special investigations

8.1.3.1 Rapid antigen test

Anterior nasal or nasopharyngeal swabs will be collected from all potentially eligible volunteers at screening on Day 0 for qualitative detection of SARS-CoV-2 nucleocapsid protein antigen. Swabs from other anatomical sites may be used based on emerging recommendations detailed in the LumiraDx™ SARS-CoV-2 Antigen [Ag] test specifications.

Details regarding sample collection, handling and processing, the assays and interpretation of the results, will be documented in the Laboratory Manual.

Patients that have tested positive by same-day LumiraDx™ SARS-CoV-2 Ag from another vendor or have a laboratory confirmation of an RT-PCR positive for SARS-CoV-2 within 2 days prior to screening, will not require an additional rapid antigen test at screening.

8.1.3.2 Pregnancy test

A point-of-care high sensitivity β-HCG urine pregnancy test will be conducted for all women of reproductive potential at screening to assess eligibility, at the EOS visit, and during unscheduled visits if deemed necessary by the Investigator.

Women are considered post-menopausal and/or not of reproductive potential if they have had at least 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with local laboratory serum follicle stimulating hormone (FSH) levels (performed as standard of care i.e., not a study-specific procedure) commensurate for post menopause; or have had surgical bilateral oophorectomy or bilateral salpingectomy (with or without hysterectomy) at least six months prior to screening.

8.1.3.3 Optional HIV Test

An optional point-of-care HIV antibody test will be offered to all participants at screening. All participants who test positive will be referred to their local clinics for care.

Participants who test negative for COVID antigen, or are pregnant, will be screen failed, and no further screening study procedures will be done (except for the collection of patient demographics).

8.2 Safety Assessments

8.2.1 Physical examination

Abbreviated, symptom-directed physical examinations will be performed at screening, at the EOS visit, and during unscheduled visits if deemed necessary by the Investigator. At a minimum these examinations will include:

- general appearance
- skin
- heart / circulation
- chest and lungs.

Significant findings present at screening will be recorded in the relevant medical history/current medical conditions section of the participant's eCRF. Significant findings, or worsening of pre-existing findings, detected after dosing will be recorded as adverse events in the participant's eCRF.

8.2.2 Height and weight

Height in centimetres (cm) and body weight (to the nearest 0.1 kg in light indoor clothing, but without shoes) will be measured.

Body Mass Index (BMI) will be calculated using the formula: BMI = weight (kg) / height $(m)^2$.

8.2.3 Vital signs

Vital signs include body temperature, pulse rate, blood pressure assessments and SpO2. Blood pressure, pulse rate and SpO2 will be measured after the participant has been at rest for at least 5 minutes in accordance with the timepoints detailed in the SOE (Section **Error! Reference source not found.**). An appropriately sized cuff will be used to ensure accurate blood pressure determination.

8.2.4 Laboratory evaluations

8.2.4.1 Safety laboratory assessments

No scheduled safety laboratory assessments are planned. *Ad hoc* laboratory evaluations may be conducted for participants requiring specific safety monitoring of emergent adverse events.

8.3 Efficacy Assessments

8.3.1 Patient Reported Outcomes

Participants will be asked to complete the following surveys during the study:

- The FLU-PRO© Plus questionnaire[19–21] to assess the symptomatic extent of their illness (Appendix 2)
- The daily survey (Appendix 3) that includes:

- The FLU-PRO© Plus Global Additional Daily Diary Items (related to general well-being, overall severity of symptoms, and ability to perform usual daily activities)
- General daily diary items (related to study drug administration, recording of vital signs and SpO2 measurements, review of concomitant medications, and information related to possible adverse events).

These surveys will be completed electronically or using a participant diary. Participants will be contacted via telephone call or text/direct messaging or web-based conference on day 3/6/10 by a staff member to confirm any AE occurrence, general well-being and update the WHO clinical progression scale. The participants will fill in the surveys daily themselves for 10 days, these will be collected at EOS or if electronically captured, before then.

8.3.2 WHO Clinical Progression Scale

A study team member will complete the WHO Clinical Progression Scale (Appendix 4) during participant contact sessions via telephone, text/direct messaging, web-based conference, or in person on relevant study days as detailed in the SOE (Section 1).

8.4 Biohazard Containment

Precautions will be employed by all personnel in the handling of specimens collected during this study.

All dangerous goods and materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by national and regional regulations.

Details of these procedures will be described in the Laboratory Manual and will comply with relevant IATA Dangerous Goods Regulations.

9. SAFETY MONITORING

9.1 Responsibilities for Ensuring the Safety of Study Participants

9.1.1 Principal Investigator

The Principal Investigator has a personal responsibility to closely monitor study participants and an inherent authority to take whatever measures necessary to ensure their safety, including ensuring that procedures and expertise are available to cope with medical emergencies during the study. The Principal Investigator has the authority to terminate, suspend or require changes to a clinical study for safety concerns and may pause or delay the administration of the study drug to an individual or across the study if they have concerns that the study drug may place participants at significant risk.

9.1.2 Study Sponsor

The Sponsor has an institutional responsibility to ensure participant safety and undertakes to promptly notify the concerned Investigators, IRB/EC(s) and the Regulatory Authority of findings that could adversely affect the safety of participants included in the study, impact the conduct of the study, or alter the IRB/EC's approval of, or favourable opinion to continue, the study. This includes the expedited reporting to these parties of all adverse drug reactions that are both serious and unexpected.

9.1.3 Study Funder

The Funder (BMGF) and/or Dr Reddy's Pharmaceutical company has a responsibility to immediately inform the Sponsor and Principal Investigator of any new information related to the study drug or its

intended use which could alter the existing risk assessment of the study or could adversely affect participant safety.

9.1.4 Medical Monitor

The Medical Monitor, in consultation with the Safety Review Team (SRT), will provide medical review during the execution of the study. This oversight will include the review of safety information and the provision of applicable recommendations to both the Investigator and the Sponsor. This review is intended to facilitate the early detection of safety signals and to maximise the chances for the continued appropriateness of the study and the protection of the study participants. Medical review of data will be specified in detail in the medical section of the Medical Monitoring Plan to be finalised prior to enrolment of the first participant.

In addition to routine review of medical data, the Medical Monitor will also support the site and provide advice on protocol clarifications, assessment of eligibility and required follow-up procedures as and when requested by the Investigator.

The Medical Monitor, in conjunction with the Principal Investigator, will be responsible for adjudication of the primary endpoint events of hospitalisations and deaths to ascertain if these are/were COVID-19 related.

9.1.5 Safety Review Team

The SRT will comprise at least the following personnel:

- the Principal Investigator
- the Medical Monitor
- the Safety Physician
- another medically qualified physician, virologist, or immunologist.

The members of the SRT are responsible for decisions relating to participant safety and study continuation.

The timing of other SRT data reviews and a detailed description of the operational aspects of the SRT will be documented in the SRT Charter.

9.1.6 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be convened for this study with expertise in COVID-19 or respiratory viruses, and emerging epidemics. A biostatistician will also form part of the DSMB. The purpose of the DSMB is to monitor the study for safety and operational futility. The board will provide recommendations to the Sponsor regarding ongoing study conduct.

In addition to meeting at pre-determined, scheduled time points, the DSMB will also be called upon to perform evaluations of relevant data should any of the study pause criteria be met at any stage, and to make recommendations about study stopping or continuation, or amended circumstances under which the study may proceed.

The objectives and responsibilities of the DSMB, and the DSMB operational procedures will be detailed in the DSMB Charter which will be ratified by the DSMB members prior to study start.

9.2 Adverse Events

9.2.1 Definitions

The following definitions are based on those described in the SAHPRA Safety Reporting Guidelines for Clinical Trials conducted in South Africa[22].

An **adverse event (AE)** is any untoward medical occurrence in a patient or clinical trial participant administered an investigational product that may present during treatment with that investigational product, but which does not necessarily have a causal relationship with this treatment.

A **treatment emergent adverse event (TEAE)** is any new AE that begins, or any pre-existing condition that worsens in severity, after at least one dose of study product has been administered.

An **adverse drug reaction (ADR)** is a response to a medicine in humans which is noxious and unintended, and which occurs at any dose, and which can also result from overdose, misuse, or abuse of a medicine. “Response” in this context means that a causal relationship between a medicine and an adverse event is at least a reasonable possibility.

A **serious adverse event (SAE)** is defined as any untoward medical occurrence that:

- Results in death (including from COVID-19)
- Is life-threatening (the term "life-threatening" in the definition of "serious" refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation (including for COVID-19) unless this is for:
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the trial and has not worsened since the start of the investigational product
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission
    - cosmetic surgery or for social reasons or respite care in the absence of any deterioration in the participant’s general condition
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is medically significant or important event or reaction.

An **Unexpected Adverse Drug Reaction** is one in which the nature, specificity, severity, and outcome is not consistent with the applicable product information (i.e., with the Summary of Product Characteristics [SmPC] or the Investigator’s Brochure). An expected ADR with a fatal outcome should be considered unexpected.

A **suspected unexpected serious adverse reaction (SUSAR)** is an unexpected adverse drug reaction which also meets the criteria for a serious adverse event.

9.2.2 Assessment and recording of adverse events

All AEs regardless of seriousness or relationship to the study drug are to be recorded in the eCRF. AEs can be spontaneously reported by the participant, observed by the Investigator (either directly, or through an objective assessment) or elicited by general questioning. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis.

The following information should be recorded for each AE:

- a description of the adverse event (verbatim term)
- the dates of onset and resolution of the event (and whether the event started prior to or after start of study drug)
- the characteristics of the event (seriousness, severity)
- the action taken in response to the event (including treatment required)
- the outcome of the event
- the relationship of the event to the study drug (causality assessment).

Vital signs abnormalities are to be recorded as AEs only if they are considered clinically significant, are symptomatic, require corrective treatment or fulfil a seriousness criterion. Day-to-day fluctuations in pre-existing conditions that do not represent a clinically significant change in the participant's status (including fluctuation in symptoms of mild COVID-19) will not be reported as AEs.

9.2.2.1 Reporting time period

For the purpose of this study, all non-serious AEs will be reported from the time of granting main study informed consent until the participant's EOS visit (Day 29). Events reported prior to this will be recorded as medical history unless the symptoms worsen during the follow-up period.

SAEs will be reported for the same period. SAEs occurring after the reporting period that the Investigator becomes aware of will only be reported to the Sponsor if the Investigator suspects a causal relationship with the study intervention.

9.2.2.2 Severity grading

The medical assessment of AE severity will be recorded in accordance with the classification detailed in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events Version 2.1, Jul 2017[23]..

AEs not specifically referenced in the DAIDS classification will be graded in accordance with the following general guidelines detailed in the classification document:

- Grade 1: Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated
- Grade 2: Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated
- Grade 3: Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalisation indicated
- Grade 4: Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death
- Grade 5: Death related to the AE.

9.2.2.3 Relationship to study drug

The Investigator must assess the relationship of each event to the study drug and decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the study drug. This should be documented in the participant's source documentation and eCRF.

The following may guide this assessment:

- Related:
    - The event has a reasonable temporal relationship to study drug administration
    - The event is more likely to be explained by the study drug than by another cause
    - This includes events considered possibly related to the study drug
- Not related:
    - Events not meeting the "related" criteria.

Where possible, a distinction should be made between events considered related to the study drug and those related to study-specific procedures.

9.2.2.4 Outcome

The Investigator will follow up all AEs wherever possible until they have attained an acceptable outcome (Section 9.2.2.5).

The date of the outcome will be recorded, and the course of the AE will be assessed in accordance with the following classification:

- Recovered/resolved: the AE has resolved, and the participant returned to their condition prior to onset
- Recovered/resolved with sequelae: the AE resolved, but the participant has sequelae
- Recovering/resolving: the AE has almost resolved, and the participant is returning to his condition prior to onset
- Death: the participant died
- Not recovered/not resolved: the AE had not resolved, and the participant's condition remained unchanged at the last time of observation. In case of death from a different cause, events ongoing at the time of death will be classified as such.

9.2.2.5 Action taken and follow-up of events

All adverse events must be followed up by the Investigator until:

- the event is resolved, or
- no further medically relevant information in relation to the event can be expected, and
- the Investigator considers it justifiable to terminate the follow-up.

Events that are ongoing at the time of the participant's EOS visit should be indicated as "not recovered/not resolved" or "recovering/resolving" (whichever applicable) if considered unrelated to the study drug. AEs that are considered related to the study drug and are ongoing at the time of the participant's EOS visit should continue to be followed up by the Investigator until the event has resolved or the Investigator, Sponsor and Medical Monitor consider it justifiable to terminate the event follow-up.

All AEs should be treated appropriately. The Investigator will decide upon the appropriate action to be taken in response to an AE, which may include one or more of the following:

- no action taken (i.e., further observation only)
- administration of a concomitant medication or other treatment

- hospitalisation or prolongation of current hospitalisation (event to be reported as an SAE)
- other.

9.2.3 Reporting of serious adverse events

The Investigator will report all SAEs to the Sponsor (or their pharmacovigilance vendor) within 24 hours of the site personnel becoming aware of the event in accordance with the procedures described in the Safety Management Plan. The report should be in writing by email with the Medical Monitor on copy and documented on a standard SAE Reporting Form. In addition to this, fatal or life-threatening SAEs must be reported immediately to the Sponsor (or their pharmacovigilance vendor) and the Medical Monitor, irrespective of the extent of available AE information.

For all SAEs, the Investigator is obligated to pursue and provide information in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE case report form. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a participant death, a summary of autopsy findings (if available) must be submitted as soon as possible to the Sponsor.

All SAEs will be followed up until resolution, or until in the opinion of the Principal Investigator and the Medical Monitor, no further improvement can be reasonably expected on medical grounds.

The IRB/EC(s) and Regulatory Authority will be notified of all SAEs in accordance with their requirements.

Reporting and follow-up procedures are described in the Safety Management Plan.

9.2.4 Pregnancy

All women of reproductive potential will agree to remain on effective contraception for the duration of the study. While all efforts will be undertaken to prevent pregnancy among participants during this time, should a participant become pregnant during the study (at any stage), she will be counselled regarding the unknown risks associated with administration of molnupiravir, and will undergo a further informed consent process to confirm her continued participation in the study, and willingness to be followed through the pregnancy and for three months thereafter.

Pregnancies occurring in participants enrolled in this study must be reported. Follow-up will include, but is not limited to, the following:

- Ultrasound at approximately 20 weeks' gestation
- Pregnancy complications
- Outcome ascertainment
- Information related to live births
- Follow-up of infants to approximately 3 months of age.

Reporting will be performed using a standard Pregnancy Reporting Form. The reporting procedure follows that described for SAEs in Section 9.2.3.

Pregnancy alone is not regarded as an AE. Elective abortions without complications should not be considered AEs unless they were therapeutic abortions. Hospitalisation for normal delivery of a healthy newborn should not be considered an SAE. Pregnancy is not considered an SAE unless there

is an associated outcome that meets one or more of the SAE criteria. Spontaneous abortions should always be reported as SAEs.

Any pregnancy outcome considered to be an SAE should be reported within the timelines and using the procedures described in Section 9.2.3.

10. STATISTICAL CONSIDERATIONS

This section describes the planned analysis of study objectives as envisioned at the time of writing the protocol. Details of these analyses and their presentation, and any substantive changes to these planned analyses, will be documented in a detailed Statistical Analysis Plan (SAP) developed and approved prior to enrolment of the first participant.

10.1 Sample Size Determination

This study has been powered around a reduction from 6% to 4% in hospitalisation/death rates between the arms. This would give a 33% reduction, the approximate effect size seen in the registration MOVe-OUT trial[12].

With 1863 patients per arm, there would be 80% power to detect a reduction in hospitalisations from 6% to 4% in a single final analysis. A 5% overage to account for loss to follow up has been added, resulting in a total sample size of 2000 patients per arm. The interim (e.g., at 1000/arm) would need to use a Peto rule ($p<0.001$) to preserve statistical power for the final analysis.

10.2 Analysis Populations

For analysis purposes, the following populations are defined and will be described in greater detail in the trial Statistical Analysis Plan (SAP):

Population	Description
Full Analysis Set (FAS)	All enrolled participants.
Safety Analysis Set (SAF)	All enrolled participants who received a dose of the study drug.
Intention to Treat (ITT)	All enrolled randomized participants.
Per Protocol (PP)	All enrolled participants completing the study without major protocol deviations.

10.3 Analysis and Presentation of Data

10.3.1 General

10.3.1.1 Data summaries

All endpoints will be summarised overall and by risk factor. Continuous data will be summarised using descriptive statistics as appropriate (e.g., N, mean, standard deviation, median, range) and categorical data will be summarised using frequency tables (counts and percentages).

Baseline will be defined as the last available, valid measurement taken prior to initiation of the study drug.

Only data from protocol scheduled visits/time points will be included in “by visit” summary tables. Details of how data from unscheduled or out-of-window visits will be presented will be described in the SAP.

10.3.1.2 Handling of dropouts or missing data

No data imputation will be performed unless otherwise stated in the SAP.

10.3.2 Participant disposition

Participants enrolled, dosed, and completing the study will be summarised for the FAS, as well as reasons for withdrawal for all early withdrawals.

10.3.3 Participant demographics, baseline characteristics and concomitant medications

Demographic data, other baseline characteristics, prior (started prior to study drug administration) and concomitant medications (taken at the time of study drug administration or at any stage during the follow-up period thereafter) will be summarised for the SAF and ITT.

Some medications may be included in both the prior and concomitant medications summaries. Concomitant medications will be coded using the WHO Drug Dictionary (WHO-DD). The most recent released version at the time of study start will remain in effect throughout the study.

Medical and surgical history will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) and summarised by system organ class and preferred term.

10.3.4 Efficacy data

Details of efficacy data analyses to be performed will be included in the SAP.

10.3.4.1

10.3.5 Safety data

All safety analyses will be performed for the SAF.

An overall summary of the number of participants with any AE, AEs considered related to study drug, SAEs, SAEs considered related to study drug, AEs leading to withdrawal of study drug, and AEs leading to withdrawal from the study will be presented.

AEs will be coded in accordance with MedDRA. The most recent released version of MedDRA at the time of study start will remain in effect throughout the study.

AEs will be summarised by MedDRA primary system organ class and preferred term. Summaries will be presented for overall incidence (number of participants and number of events), as well as by severity and relatedness to study drug.

Vital signs will be summarised. Absolute values and change from baseline will be presented.

All safety data will be listed.

10.3.6 Exploratory analyses

Details of exploratory endpoints and analyses to be performed will be included in the SAP.

11. STUDY MONITORING

Study conduct will be monitored by an independent monitor. Monitors will conduct remote monitoring and will visit the site as required. Review of individual participant records, including

consent forms, eCRFs, supporting data, laboratory specimen records, and endpoints through medical records (physicians' progress notes, nurses' notes) will be performed as detailed in the Clinical Monitoring Plan, to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect the site regulatory files to ensure that regulatory requirements are being followed, and the pharmacy to review product storage and management.

The Clinical Monitoring Plan will describe these activities and will take into consideration necessary adaptations to be made if physical access to the site is limited at any stage due to pandemic restrictions.

12. ETHICAL CONSIDERATIONS

12.1 Regulatory and Ethical Considerations

The study will be conducted according to GCP (including South African GCP Guidelines[24]), the Belmont Report, the Declaration of Helsinki, and South Africa legal requirements regarding clinical trials. The study protocol and relevant supporting documents will be submitted for review and approval by the South African Health Products Regulatory Authority (SAHPRA) and the Human Research Ethics Committee (HREC) responsible for oversight of research conducted at the study site. The study protocol will be registered with the South African National Clinical Trial Registry (www.sanctr.gov.za), National Human Research Ethics Committee (www.ethicsapp.co.za) and www.ClinicalTrial.gov. Six-monthly progress reports will be submitted to SAHPRA and HREC for the duration of the study, and as requested. Upon completion or premature termination of the study, the Investigator will provide HREC and SAHPRA with a summary of the study's outcome, and any reports required.

12.2 Informed Consent Process

The principles of informed consent in the current edition of the Declaration of Helsinki will be implemented before any protocol-specified procedures or interventions are carried out. The screening consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. In the event of a female participant becoming pregnant, consent for follow-up of the pregnancy and outcome thereof will be requested.

Participants will be counselled about the available data regarding the efficacy of molnupiravir in preventing severe progression of COVID-19, and that there are only limited data from previous studies at this time.

Potential participants will have the opportunity to have any questions answered before and after signing the informed consent forms (ICFs). The informed consent process and all questions raised will be documented.

The study staff who conduct the informed consent process will also sign the ICFs. A copy of the consent form(s) will be given to the participant, and this fact will be documented in the participant's record.

Any participant who is rescreened should be reconsented and eligibility for the study must be re-checked prior to enrolment with regard to all other screening procedures.

12.3 Study Records and Confidentiality

The study site will establish a standard operating procedure for confidentiality protection. The site will ensure that study records including administrative documentation and regulatory documentation as well as documentation related to each participant enrolled in the study, including ICFs, locator forms, case report forms, notations of all contacts with the participant, and all other source documents are stored in a secure manner.

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. The exceptions are SARS-CoV-2 testing results, which are subject to local and national reporting. This may be name-based depending on local requirements. Local public health may contact participants diagnosed with SARS-CoV-2 for the purpose of surveillance and contact notification. Prior to SARS-CoV-2 testing, participants will be informed that results are reportable and may lead to contact by local public health officials if results are positive for infection.

All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring, and auditing by the Regulatory Authority or the IRB/EC(s).

The Principal Investigator or designee and all employees and co-workers involved with this study may not disclose or use, for any purpose other than performance of the study, any data, record, or other unpublished confidential information disclosed to those individuals for the purpose of the study.

All computers used during the study conduct will be password-protected, and records will only be accessible to authorised study staff.

12.4 Compensation for Injury

The Sponsor will ensure that compensation is provided for reasonable medical expenses incurred because of study-related injury, illness, or death, as 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[24].

12.5 Participant Remuneration

For each day of protocol-related study procedures, the participants will receive compensation for travel costs to and from the clinic and inconvenience incurred, as per local regulating body recommendations.

13. ADMINISTRATIVE CONSIDERATIONS

13.1 Protocol Amendments

Any protocol amendments will be prepared by the Sponsor and submitted to the IRB/EC(s) and SAHPRA in accordance with local requirements.

Approval must be obtained from the IRB/EC(s) and SAHPRA (as required) before the implementation of any changes, except for changes necessary to eliminate an immediate hazard to participants, or changes that involve logistical or administrative aspects only (e.g., change in contact information).

13.2 Clinical Data Records

A log of names, signatures and initials of all staff authorised to enter data into a participant's clinic file and eCRF will be kept.

The Investigator will maintain paper or electronic source documentation for all study participants. Protocol-specific participant information will be captured in an eCRF. The Clinical Data Management System will comply with regulatory guidelines and requirements for electronic systems.

Data validation and quality control procedures will be detailed in the Data Management Plan.

All deviations from this study protocol will be documented in the Trial Master File and included in the final study report. An assessment of the significance of each protocol deviation will be presented in the clinical study report.

13.3 Record Retention

All source data, clinical records and laboratory data relating to the study will be archived for a minimum period after completion of the study in accordance with South African GCP guidelines, Sponsor and Funder requirements. Data will be available for retrospective review or audit by arrangement with the appropriate representative at the archiving organisation (e.g., Sponsor Head). Written agreement from Dr Reddy's and BMGF, must precede destruction of the same.

13.4 Discontinuation of the Study

Dr Reddy's, the Sponsor, the Funder, the Principal Investigator, IRB/EC(s) and Regulatory Authority independently reserve the right to discontinue the study at any time for safety or other reasons. This will be done in consultation with the Funder, Sponsor and Principal Investigator where practical. In the event of premature termination or suspension of the study, the above-mentioned parties will be notified in writing by the terminator/suspender stating the reasons for early termination or suspension (with the exception of the Sponsor's responsibility for notifying the Regulatory Authority). Following such a decision, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the participants' interest and safety. All ongoing participants will be followed up for a minimum of 28 days post initiation of the study drug and will be scheduled for an EOS visit. At this visit all assessments scheduled in accordance with the SOE (Section 1) will be performed (with the addition of safety laboratory samples if considered necessary due to safety considerations).

13.5 Publication Policy

A dissemination plan will be developed with all project partners prior to study completion. After study completion, results will be disseminated using the following strategies: written methods (i.e., publications in peer reviewed scientific journals), presentations at scientific conferences and workshops, in person dissemination of results to the research participants, and using electronic methods such as the project website and electronic media to publish results.

13.6 Study Audits

Audits may be carried out by the Sponsor quality assurance representatives, local authorities, or authorities to whom information on this study has been submitted. All documents pertinent to this study must be made available for such inspections after adequate notice of the intention to audit is provided.

14. REFERENCES

1. Benfield T, Bodilsen J, Brieghel C, et al. Improved Survival Among Hospitalized Patients With Coronavirus Disease 2019 (COVID-19) Treated With Remdesivir and Dexamethasone. A Nationwide Population-Based Cohort Study. *Clin Infect Dis*. 2021;73(11):2031-2036. doi:10.1093/cid/ciab536

2. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med*. 2021;384(8):693-704. doi:10.1056/NEJMoa2021436

3. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. *N Engl J Med*. 2021;384(6):497-511. doi:10.1056/NEJMoa2023184

4. South African Medical Research Council. Report on Weekly Deaths in South Africa. Published 2022. Accessed February 14, 2022. https://www.samrc.ac.za/reports/report-weekly-deaths-south-africa

5. South African Department of Health. South African Department of Health COVID-19 Online Resource and News Portal. Published 2022. Accessed March 14, 2022. https://sacoronavirus.co.za/latest-vaccine-statistics/

6. Pillay-van Wyk V, Msemburi W, Laubscher R, et al. Mortality trends and differentials in South Africa from 1997 to 2012: second National Burden of Disease Study. *Lancet Glob Heal*. 2016;4(9):e642-e653. doi:10.1016/S2214-109X(16)30113-9

7. Venter WDF, Nel J. Coronavirus Disease 2019: First Data From Africa. *Clin Infect Dis*. 2021;73(7):e2016-e2017. doi:10.1093/cid/ciaa1293

8. Merck Sharp & Dohme Limited. Summary of Product Characteristics: Lagevrio 200 mg hard capsules. SmPC. Published 2021. Accessed November 4, 2021. https://www.medicines.org.uk/emc/product/13044/smpc%0A

9. Painter WP, Holman W, Bush JA, et al. Human Safety, Tolerability, and Pharmacokinetics of Molnupiravir, a Novel Broad-Spectrum Oral Antiviral Agent with Activity against SARS-CoV-2. *Antimicrob Agents Chemother*. 2021;65(5). doi:10.1128/AAC.02428-20

10. Agostini ML, Pruijssers AJ, Chappell JD, et al. Small-Molecule Antiviral β- <scp>d</scp> - *N* ^{4} - Hydroxycytidine Inhibits a Proofreading-Intact Coronavirus with a High Genetic Barrier to Resistance. Gallagher T, ed. *J Virol*. 2019;93(24). doi:10.1128/JVI.01348-19

11. Sheahan TP, Sims AC, Zhou S, et al. An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. *Sci Transl Med*. 2020;12(541). doi:10.1126/scitranslmed.abb5883

12. Merck Sharp & Dohme Limited. Efficacy and Safety of Molnupiravir (MK-4482) in Non-Hospitalized Adult Participants With COVID-19 (MK-4482-002). ClinicalTrials.gov. Published 2021. Accessed November 25, 2021. https://clinicaltrials.gov/ct2/show/NCT04575597

13. Merck Sharp & Dohme Limited. Merck and Ridgeback's Investigational Oral Antiviral Molnupiravir Reduced the Risk of Hospitalization or Death by Approximately 50 Percent Compared to Placebo for Patients with Mild or Moderate COVID-19 in Positive Interim Analysis of Phase 3 Study. Published 2022. Accessed March 15, 2022. https://www.merck.com/news/merck-and-ridgeback-biotherapeutics-provide-update-on-results-from-move-out-study-of-molnupiravir-an-investigational-oral-antiviral-medicine-in-at-risk-adults-with-mild-to-moderate-covid-19

14. Andrews N, Stowe J, Kirsebom F, et al. Covid-19 Vaccine Effectiveness against the Omicron (B.1.1.529) Variant. *N Engl J Med*. Published online March 2, 2022. doi:10.1056/NEJMoa2119451

15. Zhou S, Hill CS, Sarkar S, et al. β-d-N4-hydroxycytidine Inhibits SARS-CoV-2 Through Lethal Mutagenesis But Is Also Mutagenic To Mammalian Cells. *J Infect Dis*. 2021;224(3):415-419. doi:10.1093/infdis/jiab247

16. Wahl A, Gralinski LE, Johnson CE, et al. SARS-CoV-2 infection is effectively treated and prevented by EIDD-2801. *Nature*. 2021;591(7850):451-457. doi:10.1038/s41586-021-03312-w

17. Rosenke K, Hansen F, Schwarz B, et al. Orally delivered MK-4482 inhibits SARS-CoV-2 replication in the Syrian hamster model. *Nat Commun*. 2021;12(1):2295. doi:10.1038/s41467-021-22580-8

18. National Institute for Communicable Diseases. Clinical Management of Suspected or Confirmed COVID-19 Disease. Published 2021. Accessed November 25, 2021. https://www.nicd.ac.za/diseases-a-z-index/disease-index-covid-19/covid-19-guidelines/clinical-management-of-suspected-or-confirmed-covid-19-disease/

19. Powers JH, Guerrero ML, Leidy NK, et al. Development of the Flu-PRO: a patient-reported outcome (PRO) instrument to evaluate symptoms of influenza. *BMC Infect Dis*. 2015;16(1):1. doi:10.1186/s12879-015-1330-0

20. Powers JH, Bacci ED, Guerrero ML, et al. Reliability, Validity, and Responsiveness of InFLUenza Patient-Reported Outcome (FLU-PRO©) Scores in Influenza-Positive Patients. *Value Heal*. 2018;21(2):210-218. doi:10.1016/j.jval.2017.04.014

21. Powers JH, Bacci ED, Leidy NK, et al. Performance of the inFLUenza Patient-Reported Outcome (FLU-PRO) diary in patients with influenza-like illness (ILI). Ortiz JR, ed. *PLoS One*. 2018;13(3):e0194180. doi:10.1371/journal.pone.0194180

22. South African Health Products Regulatory Authority. *Safety Reporting During Clinical Trials in South Africa*.; 2021. https://www.sahpra.org.za/wp-content/uploads/2021/10/Safety-Reporting-During-Clinical-Trials_-August-2021_V4.pdf

23. National Institute of Allergy and Infectious Diseases. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. Published 2017. https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

24. South African Department of Health. *South African Good Clinical Praactice: Clinical Trial Guidelines*.; 2020. https://www.sahpra.org.za/wp-content/uploads/2021/06/SA-GCP-2020_Final.pdf

APPENDICES

APPENDIX 1: STUDY GOVERNANCE

The following Investigators and Institutional Affiliations are established. Designees may be provided, as appropriate.

Name	**Role**	**Institution**
Dr Simiso Sokhela	Principal Investigator	Ezintsha, University of the Witwatersrand Building C Sunnyside Office Park 32 Princess of Wales Terrace Parktown, Johannesburg South Africa
Prof Francois Venter Dr Joana Woods	Co-Investigator Site Investigator	Ezintsha, University of the Witwatersrand Building C Sunnyside Office Park 32 Princess of Wales Terrace Parktown, Johannesburg South Africa

APPENDIX 2: THE INFLUENZA PATIENT-REPORTED OUTCOME INSTRUMENT (FLU-PRO© Plus)

To be completed on D1-10, and D28:

FLU-PRO Plus©

People experience viral respiratory tract infections in different ways. We would like to know about the symptoms you have been experiencing during the past 24 hours. For each symptom, please mark one box ☐ under the response that best matches your experience. Mark the "Not at all" box, if you did not have that symptom in the past 24 hours.

What time is it?_____AM / PM (please circle)

Please rate the extent to which you had each symptom during the past 24 hours.

	Not at all	A little bit	Somewhat	Quite a bit	Very much
Runny or dripping nose	☐	☐	☐	☐	☐
Congested or stuffy nose	☐	☐	☐	☐	☐
Sinus pressure	☐	☐	☐	☐	☐
Scratchy or itchy throat	☐	☐	☐	☐	☐
Sore or painful throat	☐	☐	☐	☐	☐
Difficulty swallowing	☐	☐	☐	☐	☐
Teary or watery eyes	☐	☐	☐	☐	☐
Sore or painful eyes	☐	☐	☐	☐	☐
Eyes sensitive to light	☐	☐	☐	☐	☐
Trouble breathing	☐	☐	☐	☐	☐
Chest congestion	☐	☐	☐	☐	☐
Chest tightness	☐	☐	☐	☐	☐
Dry or hacking cough	☐	☐	☐	☐	☐
Wet or loose cough	☐	☐	☐	☐	☐
Felt nauseous (feeling like you wanted to throw-up)	☐	☐	☐	☐	☐
Stomach ache	☐	☐	☐	☐	☐
Felt dizzy	☐	☐	☐	☐	☐
Head congestion	☐	☐	☐	☐	☐
Headache	☐	☐	☐	☐	☐

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Please rate the extent to which you had each symptom during the past 24 hours.

	Not at all	A little bit	Somewhat	Quite a bit	Very much
Lack of appetite	☐	☐	☐	☐	☐
Sleeping more than usual	☐	☐	☐	☐	☐
Body aches or pains	☐	☐	☐	☐	☐
Weak or tired	☐	☐	☐	☐	☐
Chills or shivering	☐	☐	☐	☐	☐
Felt cold	☐	☐	☐	☐	☐
Felt hot	☐	☐	☐	☐	☐
Sweating	☐	☐	☐	☐	☐

In the past 24 hours, how often have you had any of the following symptoms?

	Never	Rarely	Sometimes	Often	Always
Sneezing	☐	☐	☐	☐	☐
Coughing	☐	☐	☐	☐	☐
Coughed up mucus or phlegm	☐	☐	☐	☐	☐

	0 times	1 time	2 times	3 times	4 or more times
How many times did you vomit?	☐	☐	☐	☐	☐
How many times did you have diarrhea?	☐	☐	☐	☐	☐

In the past 24 hours, did you have any of the following symptoms?

	No	Yes
Loss of smell	☐	☐
Loss of taste	☐	☐

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APPENDIX 3: DAILY SURVEY

To be completed on D1-10, and D28

FLU-PRO© Plus GLOBAL ADDITIONAL DAILY DIARY ITEMS:

Items to be asked in daily diary through to Day 10, and on Day 28 along with the FLU-PRO© symptom items.

1. Overall, how severe were your infection symptoms today? (Please select one response only)
   - ☐0 No flu symptoms today
   - ☐1 Mild
   - ☐2 Moderate
   - ☐3 Severe
   - ☐4 Very severe

2. Overall, how were your infection symptoms today compared to yesterday? (Please select one response only)
   - ☐1 Much better
   - ☐2 Somewhat better
   - ☐3 A little better
   - ☐4 About the same
   - ☐5 A little worse
   - ☐6 Somewhat worse
   - ☐7 Much worse

3. How much did your infection symptoms interfere with your usual activities today? (Please select one response only)
   - ☐1 Not at all
   - ☐2 A little bit
   - ☐3 Somewhat
   - ☐4 Quite a bit

4. Have you returned to your usual activities today?
   - ☐1 Yes
   - ☐0 No

5. In general, how would you rate your physical health today? (Please select one response only)

☐5 Excellent

☐4 Very Good

☐3 Good

☐2 Fair

☐1 Poor

6. Have you returned to your usual health today?

☐1 Yes

☐0 No

☐5 Very much

GENERAL DAILY DIARY ITEMS:

1. Have you taken your daily medication as prescribed today?

☐ Yes

☐ No

☐ Not applicable

2. Take your vitals: (time of day:_____:_____ hh:mm)

- Pulse _____ beats per minute
- Temperature _____ °C
- Oxygen saturation level _____ %

3. Have you taken any other medications?

☐ Yes

☐ No

If "yes", describe: _____

_____

_____

4. Have you observed any change or new complaint since you last completed the survey?

☐ Yes

☐ No

If "yes", describe: _____

_____

_____

APPENDIX 4: WHO ORDINAL SCALE FOR CLINICAL IMPROVEMENT

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalized: moderate disease	Hospitalized, no oxygen therapy*	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized: severe disease	Hospitalized; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation, pO_2/FIO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

ECMO=extracorporeal membrane oxygenation; FiO_2=fraction of inspired oxygen; NIV=non-invasive ventilation; pO_2=partial pressure of oxygen; SpO_2=oxygen saturation
*If hospitalised for isolation only, record status as for ambulatory patient.
WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis*. 2020; 20: e192-e197