AGILE PLATFORM PROTOCOL

CANDIDATE SPECIFIC TRIAL PROTOCOL 2 (CST-2): EIDD-2801 (molnupiravir)

Master Protocol Title: AGILE: Seamless Phase I/IIa Platform for the Rapid Evaluation of Candidates for COVID-19 treatment

CST-2 version 9 05-MAY-22

SPONSOR: University of Liverpool
COORDINATING CENTRE: Southampton Clinical Trials Unit

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LIST OF ABBREVIATIONS SPECIFIC TO THIS CANDIDATE SPECIFIC TRIAL (CST) PROTOCOL

BID	Twice daily
EIDD-2801-1001-US/UK	First in Human trial using EIDD-2801, being conducted by Covance
HV	Healthy Volunteer
MAD	Multiple Ascending Dose
NHC	N-hydroxycytidine NHC
NOAEL	No-observed-adverse-effect-level
PCR	Polymerase Chain Reaction
PRO(M)	Patient Reported Outcome (Measures)
RP2D	Recommended phase II dose
SAD	Single Ascending Dose
SOC	Standard of Care
SRC	Safety Review Committee
VEEV	Venezuelan equine encephalitis virus

1 CANDIDATE SPECIFIC PROTOCOL SUMMARY

1.1 CANDIDATE SPECIFIC SYNOPSIS

Short title:	**AGILE: Seamless Phase I/IIa Platform for the Rapid Evaluation of Candidates for COVID-19 treatment**– CST-2 EIDD-2801 (molnupiravir)
Full title:	**CST-2:** A Randomized, Multicentre, Seamless, Adaptive, Phase I/II Platform Study to Determine the optimal dose, Safety and Efficacy of EIDD-2801 (molnupiravir) for the Treatment of COVID-19

Phase:	Seamless Phase I/II
Population:	Adult out-patients (≥18 years) with laboratory confirmed COVID-19, who are within 5 days of symptom onset.
Primary Objective:	**Safety Objective**: To determine the safety and tolerability of multiple ascending doses of EIDD-2801 (molnupiravir). **Efficacy Objective**: To determine the ability of EIDD-2801 (molnupiravir) to improve viral clearance (time to negative PCR).
Secondary Objective:	**Pharmacokinetic (PK) Objective (Phase I only)**: To define PK of EIDD-2801 (molnupiravir) and its circulating metabolites in plasma following multiple doses administered to patients with COVID-19. Samples (optional) will be taken whilst patient is in clinic (for up to 4 hours) following initial dosing and on day 5. **Clinical Objective:** To determine the ability of EIDD-2801 (molnupiravir) to reduce the duration of signs and symptoms of COVID-19 in patients based on a patient reported outcome tool.
Translational Objective:	**Pharmacokinetic (PK) Objective (Phase I only):** To define non-plasma PK of EIDD-2801 (molnupiravir) and its circulating metabolites following multiple doses administered to patients with COVID-19 through samples of saliva, tears, dried blood spots and nasal swabs. Samples (optional in phase II) will be taken whilst patient is in clinic (for up to 4 hours) following initial dosing and on day 5. **Pharmacodynamic (PD) Objective (Phase I and II):** To characterise virus and host immune response through samples of serum and nose/throat swab. Samples will be taken whilst patient is in clinic during screening (not serum) and on days 1, 5, 11, 15 and 29. Translational swabs **collected in transport media at days 1, 3 and 5 will be stored to determine the effect of EIDD-2801** (molnupiravir) **on SARS-CoV-2 viral culture.**
Rationale:	EIDD-2801 (molnupiravir) (also known as MK-4482 or Molnupiravir) is being developed for the treatment of infections caused by RNA viruses, specifically for COVID-19 and other CoV infections, influenza, and VEEV. This study is designed to define a dose that is optimal for treating COVID-19 patients. Currently, there is no approved antiviral therapeutic for the treatment of COVID-19. An antiviral drug is urgently needed. EIDD-2801 (molnupiravir) has demonstrated activity against SARS-CoV-2 in vitro, and SARS-CoV as well as MERS-CoV in vitro and in vivo. EIDD-2801 (molnupiravir) has shown efficacy against CoV in animal models.

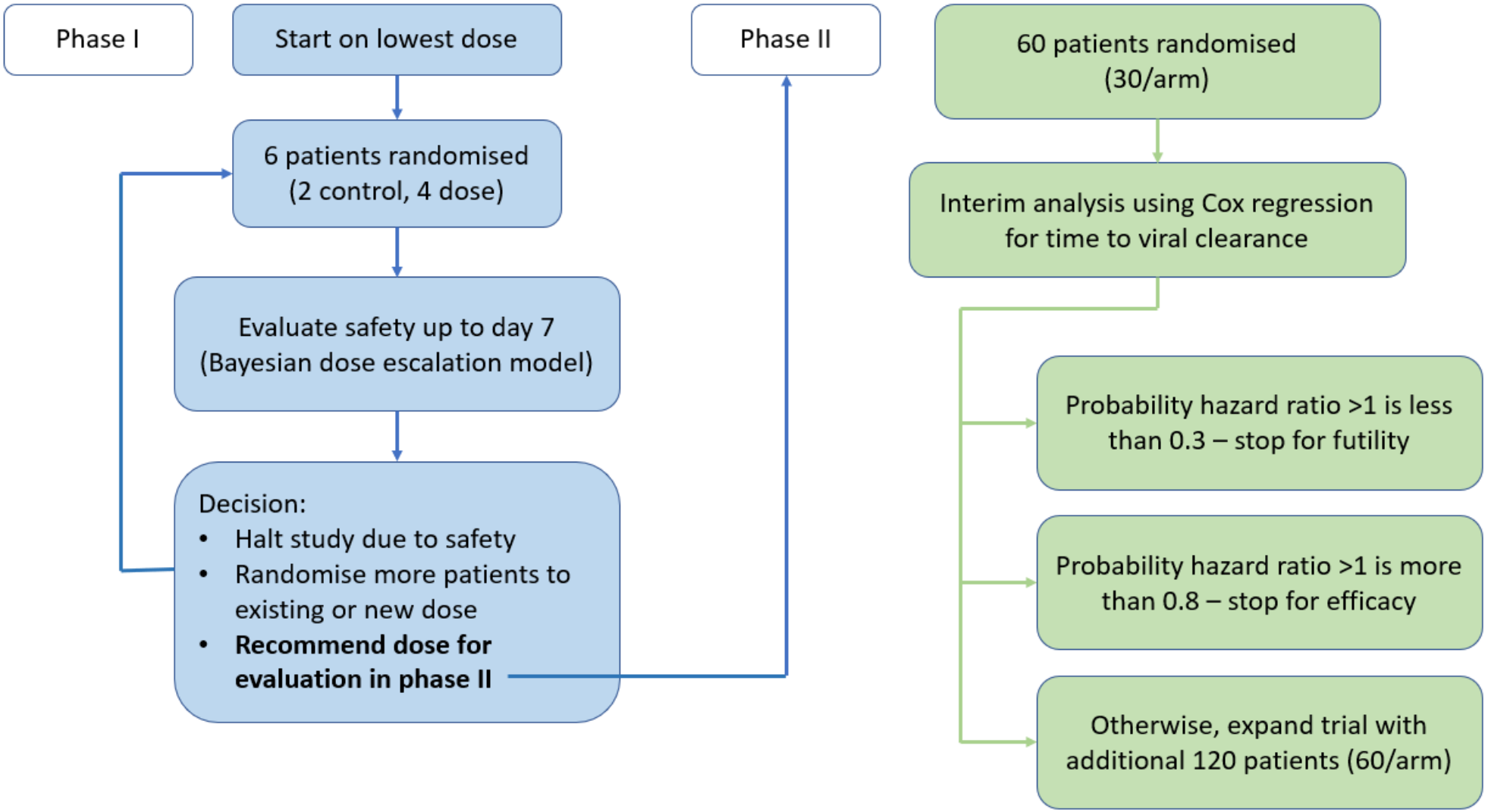
Trial Design:	Open-label 2:1 randomised controlled phase I of EIDD-2801 (molnupiravir) versus standard of care followed by a 1:1 blinded controlled parallel group Phase II trial of EIDD-2801 (molnupiravir) versus placebo. A phase I will be carried out to confirm the optimal dose in this group. Following a safety review, EIDD-2801 (molnupiravir) will be tested for efficacy in a blinded placebo controlled randomised phase II trial.
Sample size:	**Phase I:** Variable depending on dose escalation decisions, patients will be recruited in cohorts of 6 patients. **Phase II:** A maximum of 180 participants, with efficacy review after 60.
Investigational Medicinal Product/s:	EIDD-2801 (molnupiravir) will be administered in this study. EIDD-2801 (molnupiravir) (also known as MK-4482) is the 5'-isopropyl ester prodrug of the broadly active, direct-acting antiviral ribonucleoside analog EIDD-1931.
Dosage Regimen / Duration of Treatment:	**Phase I:** EIDD-2801 (molnupiravir) will be administered orally, twice daily (BID) for 10 doses (5 or 6 days). The starting dose will be established based on safety and pharmacokinetics from the EIDD-2801 (molnupiravir)-1001-US/UK study, and dose escalations may occur as described in this CST. **Phase II:** As per Phase I, with the recommended Phase II dose of 800mg twice daily (BID).)

URL for Databases and Phase I Randomisation:	www.imedidata.com

Primary Trial Endpoints:	**Phase I**: Dose limiting toxicity (DLT) using CTCAE version 5 (grades 3 and above) over 7 days CTCAE grading related to platelets and/or lymphocytes (see section 6.9) **Phase II**: Time to negative PCR
Secondary Trial Endpoints:	**Phase I:** • AEs, SAEs, physical findings, vital signs and laboratory parameters • Concentrations of EIDD-2801 (molnupiravir) and its circulating metabolites in plasma • Qualitative (and quantitative when possible) PCR for SARS-CoV-2 by nasal swab. • Patient Reported Outcomes (FLU PRO) • Score on the WHO Progression Scale[11] at day 15 and 29 • NEWS2 assessed during on days 15 and 29.

	• Mortality at Days 15 and 29 (time from randomisation to death). **Phase II:** • PROMs (FLU-PRO) at day 15 and 29. • Mortality at Days 15 and 29 • Time from randomisation to death (up to Day 29) • Time from randomisation to hospitalisation • Incidence of SpO_2 <92% (based on at least 2 consecutive recordings on the same day, lasting at least one day) • Duration (days) of oxygen use • Duration (days) of mechanical ventilation • Incidence of new mechanical ventilation use and duration (days) of new mechanical ventilation use. • Actual versus planned candidate treatment received • NEWS2 assessed during study visit on Days 15 and 29 (change from baseline and actual scores) • Score on the WHO Progression Scale[11] at day 15 and 29. • AEs, SAEs, physical findings, vital signs and laboratory parameters
Translational endpoints:	• Concentrations of EIDD-2801 (molnupiravir) and its circulating metabolites in saliva, tears, blood spots, and nasal mucosal secretions. (Phase I only) • Future Cultural Endpoints (Translational swabs collected in transport Media)
Total Number of Sites:	One site (Phase I) with additional sites to be added as required to support expansion in phase II

1.2 CANDIDATE SPECIFIC TRIAL SCHEMA



1.3 SCHEDULE OF OBSERVATIONS AND PROCEDURES (Phase I and II)

	Screening (up to 5 days prior to randomisation)	**Treatment** (to commence on day of randomisation)	**Baseline (Day of randomisation) Day 1**	**Day 3**	**Day 5**	**Day 8 (±1 days)**	**Day 11 (±1 days)**	**Day 15 (±1 days)**	**Day 22 (±1 days)**	**Day 29 (±2 days)**	**Daily if in hospital**
Informed consent	X	Initial dose to be given in clinic. Treatment for dose 2 onwards to be provided for patient to take home. Dose on day 5 to be given in clinic.									
Check Eligibility	X[g]		X[g]								
Contact: AEs, con-meds, PROM IMP Compliance				telephone contact except on clinic days- Phase I only							X[a]
SARS-CoV-2 Local diagnostic nose/throat swab	X[hi]										
SARS-CoV-2 PCR nose/throat swab for viral titres PCR and virus characterisation	X[gi]		X[g]	X	X	X	X	X	X	X	
Optional SARS-CoV-2 nose/throat swab for storage for future translational research			X	X	X						
WHO Progression Scale[11]	X[g]		X[g]	X	X	X	X	X	X	X	
NEWS 2 Score – based on vital signs (heart rate, BP, respiratory rate, temp, oxygen saturation)	X[g]		X[g]	X	X	X	X	X	X	X	
12 lead ECG	X[e]										
Full Blood Count	X[g]		X[fg]		X		X	X	X	X	As per SoC
U&Es	X[g]		X[fg]		X		X	X	X	X	
Estimated GFR	X[g]		X[fg]		X		X	X	X	X	
LFTs	X[g]		X[fg]		X		X	X	X	X	
Urinary analysis			X								
Pregnancy test WOCBP (urine or serum)	X									X	

	Screening (up to 5 days prior to randomisation)	**Treatment** (to commence on day of randomisation)	**Baseline (Day of randomisation) Day 1**	**Day 3**	**Day 5**	**Day 8 (±1 days)**	**Day 11 (±1 days)**	**Day 15 (±1 days)**	**Day 22 (±1 days)**	**Day 29 (±2 days)**	**Daily if in hospital**
Medical history (including COVID-19 history)	X	Initial dose to be given in clinic. Treatment for dose 2 onwards to be provided for patient to take home. Dose on day 5 to be given in clinic.									
Patient Reported Outcome Assessment (FLU-PRO)			X	X	X	X	X	X	X	X	
Con-med/SoC review	X[g]		X[g]	X	X	X	X	X	X	X	X
Height	X										
Weight	X										
Assessment of oxygen use	X[g]		X[g]	X	X	X	X	X	X	X	X
Assessment of mechanical ventilation use											X
Targeted physical exam	X[g]		X[g]	X	X	X	X	X	X	X	
Demographics	X										
Randomisation			X								
AE assessment	X (from consent)[g]		X[g]	X	X	X	X	X	X	X	X
Chest X-ray/other imaging			If clinically indicated								
PK assessment[b, c] (saliva, tears, nasal swabs), plasma (Phase I only)			X		X						
PD assessment[d]assessment[d] (Serum Sample)			X		X		X	X		X	
Dispense Medication[c]Medication[c]			X								
Drug reconciliation[c]reconciliation[c]				X	X	X					

a) If hospitalised, a daily contact wherever possible to the hospital to obtain data.
b) Phase I only: PK sampling timepoints Phase I for Day 1 and 5: Predose (0), 0.5 h, 1 h, 2 h, 4 h post dose if patient remains in clinic for 4 h observation;
c) Phase I only: not applicable to patients allocated Standard Care arm in phase I trial.

d) for all patients.
e) 12-lead ECG and 10 second ECG rhythm strip (≥5 min supine), to be performed during screening, or on baseline day 1 prior to first dose.
f) if clinically indicated (physician discretion).
g) if Screening and Baseline/Day 1 take place on the same day, this assessment/procedure only needs to be undertaken once.
h) if patient has not yet had a positive SARS Cov-2 test, one will need to be performed locally.
i) Swabs can be performed up to 5 days prior to randomisation.

NB: The Patient/legal representative is free to withdraw consent at any time without providing a reason. When withdrawn, the patient will continue to receive standard clinical care. Follow up data will continue to be collected (unless the patient/legal representative has specifically stated that they do not want this to happen).

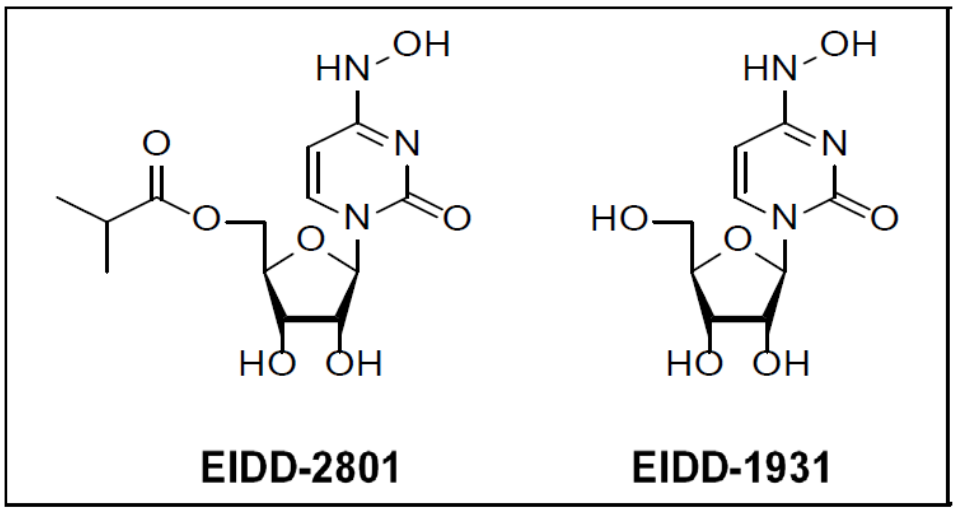
2 INTRODUCTION

2.1 BACKGROUND AND RATIONALE

EIDD-2801 (molnupiravir) (also known as MK-4482 or Molnupiravior) is the 5'-isopropyl ester prodrug of the broadly active, direct-acting antiviral ribonucleoside analog EIDD-1931 (also known as N-hydroxycytidine (NHC)).

Figure 1

Structure of EIDD-2801 and EIDD-1931



After oral delivery, the prodrug (EIDD-2801 (molnupiravir)) is rapidly hydrolyzed by circulating esterases to produce high circulating (plasma) levels of EIDD-1931. In cell culture systems, EIDD-1931 has been shown to inhibit replication of multiple viral pathogens from multiple RNA virus families including pathogenic CoV (e.g., Middle East respiratory syndrome [MERS], severe acute respiratory syndrome [SARS]-CoV and SARS-CoV-2), influenza viruses (seasonal, pandemic, and avian subtypes), respiratory syncytial virus (RSV), alphaviruses (e.g., Eastern equine encephalitis virus [EEEV], Venezuelan equine encephalitis virus [VEEV], and Chikungunya virus [CHKV]), Filoviruses (e.g., Ebola virus [EBOV]), and Zika virus (ZIKV). In addition, EIDD-2801 (molnupiravir) is active against orthopoxviruses (tested against vaccinia virus) probably because orthopoxviruses encode their own unique RNA polymerase. Antiviral activity has been verified in animal models of CoV (MERS- and SARS-CoV), influenza, RSV, VEEV, CHKV and EBOV. The primary mechanism of action of EIDD-2801 (molnupiravir) is inhibition of viral RNA replication by incorporation of the EIDD-1931 monophosphate metabolite into the viral RNA genome resulting in induction of viral error catastrophe.

The mechanism of antiviral activity of EIDD-2801 (molnupiravir) is "lethal mutagenesis"; a concept that is predicated on increasing the viral mutation rate beyond a biologically-tolerable threshold, resulting in impairment of viral fitness and leading to viral extinction.

The specifics of the mechanism are as follows. EIDD-2801 (molnupiravir) is rapidly taken up by cells and the 5'-isopropylester cleaved to liberate EIDD-1931, which is in turn phosphorylated to EIDD-2061 by host kinases[3,5]. The 5'-triphosphate, EIDD-2061, acts as a competitive alternative substrate for virally encoded RNA-directed RNA polymerases and EIDD-2061 is incorporated into nascent viral RNA. Owing to the ability of the N4-hydroxycytosine base of EIDD-1931 to tautomerize, EIDD-2061 can pair with either guanosine or adenosine, and consequently can substitute for either CTP or UTP,

respectively[2]. This results in an accumulation of mutations that increases with each cycle of viral replication. The process whereby the mutation rate is increased by exposure to a drug is referred to as Viral Decay Acceleration[4] and results in viral ablation.

Significant work has gone into validating this mechanism of action for EIDD-2801 (molnupiravir)/1931, and it has been shown for MERS-CoV, VEEV, and IAV that viruses grown in the presence of EIDD-1931 have significantly increased levels of transition mutations[1,7,9]. Multi-log decreases in virus yields were observed after treatment with EIDD-1931. Additionally, it was demonstrated for VEEV that the infectivity of virions formed in the presence of EIDD-1931 decreases from ~20% to <0.2%, and that the infectious virions are significantly Impaired in their replication ability[9]. As a consequence of this mechanism of action, the generation of drug-resistant escape mutants is practically impossible. This same effect was demonstrated for CoV[1] and influenza virus[8]. Furthermore, given the unique mechanism of action, EIDD-2801 (molnupiravir) is expected to be active against viruses resistant to other antiviral agents which have a different mechanism of action. The only data generated to date regarding the activity of EIDD-1931 against viruses resistant to other nucleoside analogs found that EIDD-1931 was active against CoV resistant to remdesivir in cell culture assays (T. Sheahan et al, preprint available at https://www.biorxiv.org/content/10.1101/2020.03.19.997890v1).

As an alternative or additional mechanism of action, it has been theorized that incorporation of EIDD-2061 into viral genomic RNA can change the thermodynamics of RNA secondary structure and thus decrease the efficiency of the promoter regions involved in RNA genome replication[6].

Rationale for using EIDD-2801 (molnupiravir) to treat covid-19 infection

EIDD-2801 (molnupiravir) has a unique dual mechanism of action against RNA viruses, including COVID-19 and other CoV infections. The compound acts as a competitive, alternative substrate for the virally encoded RNA-dependent RNA-polymerase that upon incorporation into nascent chain RNA induces increased mutational frequency in the viral genome. Incorporation quickly results in the production of non-viable virus. Additionally, the active metabolite, EIDD-1931-5'-triphosphate (EIDD-2061), may act directly as a chain terminator and arrest replication by exerting a next nucleoside effect. It is anticipated that the high barrier to resistance observed during in vitro passaging studies will translate to slow, if any, emergence of viral resistance. Resilience to viral escape is a distinguishing feature of EIDD-2801 (molnupiravir).
Currently, there is no approved antiviral therapeutic for the treatment of COVID-19. An antiviral drug is urgently needed. EIDD-2801 (molnupiravir) has demonstrated activity against SARS-CoV-2 in vitro, and SARS-CoV as well as MERS-CoV in vitro and in vivo. EIDD-2801 (molnupiravir) has shown efficacy against CoV in animal models. In mice, EIDD-2801 (molnupiravir) was active in both a prophylactic and therapeutic setting. When EIDD-2801 (molnupiravir) was administered up to 24 hours after infection with SARS-CoV or up to 12 hours after infection with MERS-CoV, a reduction in lung viral titers, protection from both lung hemorrhage and weight loss, and improvements in pulmonary function were seen, compared to vehicle-treated (control) animals.

2.2 RISK BENEFITS FOR TREATMENT ARM / IMP

EIDD-2801 (molnupiravir) is being developed for the treatment of infections caused by highly pathogenic coronaviruses, including SARS-CoV-2.

Pharmacology: The primary mechanism of action of EIDD-2801 (molnupiravir) is inhibition of viral RNA replication by incorporation of the EIDD-1931 5'-monophosphate metabolite into the viral RNA genome resulting in induction of viral error catastrophe. Primary pharmacology studies supporting the antiviral activity of EIDD-2801 (molnupiravir) were conducted *in vitro* and in mouse, guinea pig and ferret models of influenza, and in mouse models of coronavirus and Venezuelan Equine Encephalitis Virus (VEEV) infection. Primary safety pharmacology studies of EIDD-2801 (molnupiravir) revealed no

adverse effect on the CNS, cardiovascular, or respiratory systems at potential clinically relevant exposures. Incubation with panel of cardiac ion channels, including hERG, demonstrated no inhibition at concentrations of EIDD-1931 of up to 10 mM. In a GLP-compliant hERG assay, the IC50 was estimated to be > 30 µM, the highest concentration of EIDD-2801 (molnupiravir) tested. Interaction studies on CYP450 enzymes indicated that neither EIDD-2801 (molnupiravir) nor EIDD-1931 inhibited or induced CYP enzymes.

Pharmacokinetics: The pharmacokinetics (PK) of EIDD-2801 (molnupiravir) were characterized in *in vitro* and *in vivo* studies. Single and repeat dose absorption studies were conducted in mice (IP, PO), rats (IV, PO), ferrets (PO), dogs (IV, PO) and monkeys (IV, PO). EIDD-2801 (molnupiravir) was readily absorbed into animal plasmas in all species tested where it was rapidly converted to EIDD-1931, the active metabolite. Following oral administration of EIDD-2801 (molnupiravir), exposure to EIDD-1931 was generally dose proportional in all species. The bioavailability of EIDD-2801 (molnupiravir) was > 40% in mice, rats, dogs, and ferrets, while in Cynomolgus macaques the bioavailability was about 34%. EIDD-2801 (molnupiravir) is not stable in plasma or liver microsomes, where it is converted to EIDD-1931. EIDD-1931, in contrast, is more stable in plasma (t ½ > 6.5h) and liver/ intestinal microsomes (t ½ > 24h). Once EIDD-1931 is absorbed into animal plasma, EIDD-1931 is widely distributed in animal tissues where it is rapidly and efficiently converted to EIDD-1931-5'-triphosphate. The highest levels of both EIDD-1931 and EIDD-1931-5'-triphosphate are typically observed in the spleen and in the lungs of different species. EIDD-2801 (molnupiravir) and EIDD-1931 do not cause inhibition or induction of CYP450 enzymes. EIDD-1931 does not bind to the proteins in mouse, rat, dog, monkey, or human plasma.

Toxicology: The toxicity and toxicokinetics of EIDD-2801 (molnupiravir) were evaluated in preliminary 7-day maximum tolerated dose (MTD)/ dose range finding (DRF) non-GLP studies and in GLP 28-day repeat-dose studies in rats and dogs. In rats, single doses of up to 2000 mg/kg were well tolerated. In dogs, doses of 300 and 1000 mg/kg/day were not tolerated in the 7-day DRF study. Similarly, doses of 17 and 50 mg/kg/day were not tolerated in the 28-day dog study requiring early termination of these groups. In the 28-day toxicology studies, the NOAEL in rats was determined to be 500 mg/kg/day (highest dose tested) and the NOAEL in dogs was determined to be 6 mg/kg/day. In dogs, the dose-limiting toxicity was identified to be bone marrow toxicity manifested primarily as thrombocytopenia. At necropsy, adverse bone marrow changes affecting all hematopoietic cell lines and causing subsequent hematological abnormalities occurred at doses ≥17 mg/kg/day in dogs. The bone marrow changes were reversible as evidenced by essentially normal hematology after the recovery period.
Potential mutagenic effects were evaluated *in vitro* in a bacterial reverse mutation (Ames) assay and *in vivo* in a micronucleus study in rats. Two of the six bacterial strains tested in the Ames assay reverted to the wild type phenotype, thus were considered positive. The *in vitro* micronucleus assay was negative for induction of micronuclei. Two studies in rats, an *in vivo* micronucleus assay and Pig-A assay, designed to investigate mutagenic potential in mammalian systems have been completed. The in vivo micronucleus assay in rats was completed and results indicated that EIDD-2801 (molnupiravir) was negative for clastogenic activity and/or disruption of the mitotic apparatus. The results of the Pig-a mutation assay were considered equivocal since not all criteria for negative or positive response to mutagenicity were fulfilled. The preliminary results from the Big Blue® rat mutagenicity assay, in summary, MK-4482 was negative in the Big Blue® rat mutagenicity assay, a whole animal model relevant to assessment of human risk for mutagenicity. Based on the totality of the genotoxicity data, MK-4482 is not mutagenic or genotoxic in the in-vivo mammalian systems utilised by the manufacturers. One recent presentation at the Conference on Retroviruses and Opportunistic Infections March 6-10, 2021[12] used a novel mammalian haploid expression system to test for the mutagenic potential of NHC. The assay is based on CHO-K1 cells, which are functionally haploid for hypoxanthine phosphoribosyltransferase (HPRT) and utilised a modified gene mutation assay method where cells were cultured with NHC, ribavirin or favipiravir for 32 days. 6 thoiguanine was used to

select out resistant colonies which were characterised by sequencing of HPRT mRNA. The data presented supported antiviral activity of NHC, but also observed evidence of mutagenicity. This is not a standard industry method and the data are yet to be published in a peer-reviewed journal.

As of 20th March 2021, following completion of the Phase I study analysis with no evidence of Dose Limiting Toxicities and DMEC review of data relating to the first 60 patients in Phase II, no significant safety concerns have been demonstrated for EIDD-2801 and, consequently, there is no requirement for updates to the risk assessment or monitoring plan.

Ridgeback Biotherapeutics is also the sponsor of a Phase 1 First-in-Human (FIH) study in the UK which is now completed. Study EIDD-2801 (molnupiravir)-1001-US/UK was a 3-part study conducted in healthy volunteers:

Part 1 - Single Ascending Dose (SAD)
Part 2 - Food Effect (Single doses, Fed/Fasted with 14-day washout)
Part 3 - Multiple Ascending Dose (MAD)

The safety and tolerability data from this completed study have also demonstrated no significant safety or toxicity concerns.

Please refer to the latest version of the IB for more detailed findings of this study and any other trials.

3 CANDIDATE SPECIFIC OBJECTIVES AND ENDPOINTS

3.1 PHASE I OBJECTIVES & ENDPOINTS

Note that this CST has additional objectives to the Master Protocol.

Objectives	Endpoints
Primary	
To determine the safety and tolerability of multiple ascending doses of EIDD-2801 (molnupiravir) to recommend dose for phase II	• Dose limiting toxicity (DLT) using CTCAE version 5 (grades 3 and above) over 7 days • CTCAE grading related to platelets and/or lymphocytes (see section 6.9)
Secondary	
Safety objective:	AEs, SAEs, physical findings, vital signs and laboratory parameters
Pharmacokinetic Objective: To define PK of EIDD-2801 (molnupiravir) and its circulating metabolites in plasma following multiple doses administered to patients with COVID-19.	Concentrations of EIDD-2801 (molnupiravir) and its circulating metabolites in plasma
Virologic Objective: To assess the difference in viral clearance (time to negative PCR) between EIDD-2801 (molnupiravir) and control.	Qualitative (and quantitative when possible) PCR for SARS-CoV-2 by nasal swab.
Clinical Objective: To determine the ability of EIDD-2801 (molnupiravir) to reduce the duration of signs and symptoms of COVID-19 in patients.	• Patient Reported Outcome Measures (FLU-PRO) • WHO Progression Scale[11] at day 15 and 29: 0. Uninfected, no viral RNA detected 1. Ambulatory mild disease, asymptomatic; viral RNA detected 2. Ambulatory mild disease, symptomatic; independent

	3. Ambulatory mild disease, symptomatic; assistance needed 4. Hospitalised moderate disease, no oxygen therapy (If hospitalised for isolation only, record status as for ambulatory patient) 5. Hospitalised moderate disease, oxygen by mask or nasal prongs 6. Hospitalised severe disease, oxygen by NIV or high flow 7. Hospitalised severe disease, intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$ 8. Hospitalised severe disease, mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors 9. Hospitalised severe disease, mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO 10. Dead • NEWS2 assessed during study clinic visit on days 15 and 29. • Mortality at Days 15 and 29 • Time from randomisation to death (up to day 29)
Translational	
Pharmacokinetic Objective: To define non-plasma PK of EIDD-2801 (molnupiravir) and its circulating metabolites following multiple doses administered to patients with COVID-19.	Concentrations of EIDD-2801 (molnupiravir) and its circulating metabolites in saliva, tears, and nasal mucosal secretions.
Pharmacodynamics: To characterise virus and host immune response	• Change in host immune response and SARS-CoV-2 culture and sequencing (samples will be stored pending the availability of GCP-compliant assays which are currently in development)

3.2 PHASE II OBJECTIVES & ENDPOINTS

Objectives	Endpoints
Primary	
To determine the ability of EIDD-2801 (molnupiravir) to improve viral clearance.	• Time to negative PCR
Secondary	
To evaluate time to, and proportion of, clinical improvement	• PROMs (FLU-PRO) at day 15 and 29. • WHO Progression Scale[11] at day 15 and 29.
To evaluate overall mortality.	• Mortality at Days 15 and 29 (time from date of randomisation to death).
To evaluate oxygen saturation and use.	• Duration (days) of oxygen use and oxygen-free days. • Incidence of $SpO_2 < 92\%$ (based on at least 2 consecutive recordings on the same day, lasting at least one day) by day 29
To evaluate mechanical ventilation use.	• Duration (days) of mechanical ventilation Incidence of new mechanical ventilation use and duration (days) of new mechanical ventilation use.
Treatment compliance	• Actual versus planned candidate treatment received

To evaluate National Early Warning Score (NEWS2).	• NEWS2 assessed on days 15 and 29.
To further evaluate safety	• AEs, SAEs, physical findings, vital signs and laboratory parameters
Translational	
Pharmacodynamics: To characterise virus and host immune response	• Change in host immune response and SARS-CoV-2 culture and sequencing (samples will be stored pending the availability of GCP-compliant assays which are currently in development)

4 TRIAL DESIGN

This study is a parallel group, randomised controlled phase I/II Bayesian adaptive trial to assess the effect of EIDD-2801 (molnupiravir) versus control on time to viral clearance. Patients in phase I will be recruited in cohorts of minimum size six (randomised to treatment or control in 2:1 allocation ratio), with the phase I dose cohorts of six each assessed for safety. Dose-finding will be carried out as per the master protocol (section 4.2.1) with the following exceptions:

- Safety will be reviewed 7 days after the first dose.
- No borrowing of control patients is anticipated due to the eligibility criteria for this treatment.

Once a suitable dose has been identified, a 2-stage phase II study starts. The identified dose from Phase I has been established as 800mg BID. In the first stage of Phase II 60 patients are equally randomised between EIDD-2801 (molnupiravir) and placebo. If the probability of the hazard ratio between arms being greater than 1 (i.e., in favour of EIDD-2801 (molnupiravir)) is more than 0.8, the study will stop for efficacy; if this probability is less than 0.3, then the study will stop for futility. Within this range, the trial will be expanded to stage 2 of Phase II where an additional 120 patients are equally randomised between EIDD-2801 (molnupiravir) and placebo.

4.1 DATA MONITORING ETHICS COMMITTEE (DMEC)

The DMEC has reviewed results following 60 patients accrual into the phase II stage evaluating safety and efficacy. Their review was to provide a decision to either:

- Stop evaluation due to high risk of harm
- Stop evaluation due to a low probability of EIDD-2801 (molnupiravir) having a meaningful effect
- Recommend EIDD-2801 (molnupiravir) for further evaluation in a definitive trial

The DMEC decision based on review of the data for 60 patients in the first stage of Phase II, was to recommend the continuation of the trial to accrue an additional 120 patients in second stage of Phase II.
There are no further planned DMEC meetings, however the DMEC will continue to provide oversight if required for triggered reasons.

Stopping criteria for harm (Phase I only) or futility (Phase II only)
As per the master protocol, recruitment into phase I will cease if there is a >=25% probability that treatment toxicity exceeds those in controls by 30% or more.
Harm is defined by unacceptable toxicity as given by the Common Terminology Criteria for Adverse Events (CTCAE) criteria (see master protocol). Futility will be determined during phase II if after the initial 60 patients there is a less than 0.3 probability that the hazard ratio for time to viral clearance is not greater than 1.

Stopping criteria for efficacy (Phase I only)
Efficacy will be established during phase II if after the initial 60 patients there is a greater than 0.8 probability that the hazard ratio for time to viral clearance is greater than 1.

4.2 SAFETY REVIEW COMMITTEE (SRC) AND DOSE ESCALATION PROCESS (PHASE I ONLY)

The SRC will review each dose cohort of 6 patients.

Membership of the SRC will include the Chief Investigator (Saye Khoo) Chair of SRC, a principal investigator (PI) or delegate from the investigational site, one independent clinical member, representation from Ridgeback Biotherapeutics, trial statistician and trial manager. At the chair's discretion, members who are unable to attend may be asked to provide comment to the chair to enable information to be shared.

This study will be informed by the EIDD-2801 (molnupiravir)-1001-US/UK trial, which will have SAD and MAD safety data ahead of the doses used in this trial.

A clinical member of the SRC will attend the SAD and MAD dose escalation calls in the EIDD-2801 (molnupiravir)-1001-US/UK healthy volunteer study at the Covance Clinical Research Unit(s). Emerging safety data from the healthy volunteer and patient studies will be shared in this meeting. Any urgent safety data (e.g. SAE, SUSAR, severe AEs) emerging from the healthy volunteer or patient study will be communicated to all sites conducting CST-2 EIDD-2801 (molnupiravir) trial as soon as reasonably practicable. More detail is in treatments section below. Dosing with or without food may be updated depending on emerging data from the FIH trial (EIDD-2801 (molnupiravir)-1001-US/UK).

For each cohort, the SRC will review all available safety data up to a minimum of day 7. This is inclusive of AE data, vital signs data, ECG data and clinical laboratory evaluations.

4.3 JUSTIFICATION FOR DOSE

The dose of EIDD-2801 (molnupiravir) administered in this protocol will be a dose that has been studied in a single ascending dose study and found to produce plasma exposures in human that are expected to be within the efficacious dose range based on scaling from animal models of disease. Dose escalation will be guided by pharmacokinetic data and efficacy data from the previous cohorts as well as data from the FIH study. The magnitude of the dose escalation will be no more than a doubling from the previously tested dose.

The no observed adverse event limit (NOAEL) in the most sensitive species (dog) was 6 mg/kg/day over a 28 day treatment period. Treatment in this study is limited to up to 6 days. The starting dose in the FIH SAD study was 50 mg and dose escalations through 1600mg as a single dose and 800 mg BID for 5.5 days were completed.

This trial will run at a dose where there is sufficient safety data from the Phase I study of EIDD-2801 (molnupiravir)-1001-US/UK as deemed by the SRC.

The SRC and DMEC have recommended a dose of 800mg BID for Phase II of this study on the basis of the safety and tolerability data from the Phase I component of this study.

5 SELECTION AND ENROLMENT OF PATIENTS

5.1 PATIENT RECRUITMENT PROCESS

As stated in section 5.3 (in addition to all the other eligibility criteria), patients will have signs or symptoms of COVID-19 that began within 5 days prior to the planned first dose of study drug. These patients will be identified in a number of ways:

- Through the GP surgery texting patients who fit the eligibility criteria (i.e. male or female ≥ 18 years) based on a local GP search. These text messages may be sent more than once to remind patients that the study is ongoing if symptoms of COVID-19 develop
- Via a letter sent incrementally to eligible patients from their GP surgery
- Via a poster campaign (placed in community based areas)
- Via an ethically approved research database held by the site. A database search may be completed of patients who have consented to be contacted about trials.
- Social media platforms (e.g. Facebook and Twitter)
- Opportunistically, through them calling their GP or the site directly.
- Opportunistically, patients are signposted to the AGILE CST-2 clinical trial sites and contact details provided when they contact NHS 111/119 with a COVID-19 like syndrome.
- We will collaborate with local and supra-regional testing laboratories (Pillar 1 and 2), Local Clinical Commissioning Groups (CCGs) and Local Public Health and local authority testing facilities (or the equivalent in the devolved nation) to aid recruitment and provide research opportunities to the general public when they are arranging access to a COVID-19 test via the CCG/local Public Health or local authority route. The potential participant will be made aware of the AGILE CST-2 trial by the relevant testing team. This may include the potential participant providing verbal consent to the CCG, Local Public Health and local authority testing facility teams allowing them to pass contact their information to the research study team.
- Through liaison with local Public Health Authorities and Primary Care sites, patients testing positive through the national testing mechanism will be contacted and provided with information (e.g. poster/PIS) for the AGILE clinical trial
- In the event of COVID-19 outbreaks in workplaces or educational settings (e.g. university halls of residences) AGILE CST-2 posters and PISs will be provided to exposed personnel.

All potential patients will be invited for a screening visit (see section 8.1) to determine if they are eligible. Informed consent will take place prior to trial specific procedures.

5.2 INFORMED CONSENT

Refer to AGILE Master Protocol.

5.3 INCLUSION CRITERIA

The main trial inclusion criteria are outlined in the master protocol and listed below.

1. **For the purpose of the EIDD-2801 (molnupiravir) candidate-specific trial inclusion criteria 1 has been amended from the Master protocol to**:

   Adults (≥18 years) with laboratory-confirmed SARS-CoV-2 infection (PCR) who are within 5 days of symptom onset.

2. Ability to provide informed consent signed by study patient or legally acceptable representative.
3. Women of childbearing potential (WOCBP, as defined in section 5.5 of the master protocol) and male patients who are sexually active with WOCBP must agree to use two effective methods of contraception, one of which should be highly effective (as outlined in section 5.5 of the Master Protocol). For women, from the first administration of trial treatment, throughout trial and up to 50 days after the last follow up visit (50 days after day 29) and for men with female partners of child bearing potential, from the first administration until 100 days after last follow up visit (100 days after day 29).
4. Group B (mild-moderate disease): Ambulant with the following characteristics peripheral capillary oxygen saturation (SpO_2) >94% RA *(NB this differs to the Master Protocol which also includes hospitalised patients in this group).*

Additional criteria specific to this candidate are:

5. Has signs or symptoms of COVID-19 that began within 5 days prior to the planned first dose of study drug.
6. Is in generally good health (except for current respiratory infection) and is free of uncontrolled chronic conditions.
7. Is willing and able to comply with all study procedures and attending clinic visits through the 4^{th} week.

5.4 EXCLUSION CRITERIA

The main trial exclusion criteria are outlined in the master protocol as:

1. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >5 times the upper limit of normal (ULN)
2. Stage 4 severe chronic kidney disease or requiring dialysis (i.e., estimated glomerular filtration rate <30 mL/min/1.73 m^2)
3. Pregnant or breast feeding
4. *
5. Allergy to any study medication
6. Patients taking other prohibited drugs (as outline in CST protocol) within 30 days or 5 times the half-life (whichever is longer) of enrolment
7. Patients participating in another CTIMP trial

** The master protocol stipulates '4' as 'anticipated transfer to another hospital which is not a study site within 72 hours'. This is not applicable to this protocol as patients are expected to be out-patients.*

For the purpose of the EIDD-2801 (molnupiravir) candidate-specific trial the following exclusion criteria also apply:

8. Has a febrile respiratory illness that includes pneumonia that result in hospitalisation, or requires hospitalisation, oxygenation, mechanical ventilation, or other supportive modalities.
9. Has a platelet count less than $50x10^9$/L.
10. Is experiencing adverse events or laboratory abnormalities that are Grade 3 or above based on the CTCAE v5 grading.
11. Has clinically significant liver dysfunction or renal impairment.
12. Has history of Hepatitis C infection or concurrent bacterial pneumonia.

13. Has received an experimental agent (vaccine, drug, biologic, device, blood product, or medication) within 30 days prior to the first dose of study drug.
14. In the opinion of the investigator, has significant end-organ disease as a result of relevant comorbidities: chronic kidney disease, congestive heart failure, peripheral vascular disease including diabetic ulcers.
15. Has a SaO_2 <95% by oximetry or has lung disease that requires supplemental oxygen.
16. Has any condition that would, in the opinion of the investigator, put the patient at increased risk for participation in a clinical study.

5.5 SCREEN FAILURES

Refer to AGILE Master Protocol

5.6 REGISTRATION / RANDOMISATION PROCEDURES

Refer to AGILE CST-2 Randomisation Procedure Guidance document.

5.7 CONTRACEPTION

Refer to AGILE Master protocol.
N.B. For this CST – male and female patients of child-bearing potential must agree to use **TWO** forms of effective contraception, one of which should be highly effective (as defined in section 5.5 of the Master Protocol).

Acceptable, additional birth control methods which <u>may not</u> be considered as highly effective include:
Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
Male or female condom with or without spermicide
Cap, diaphragm or sponge with spermicide

A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

For female patients, contraception should be used from day of first study drug through to 50 days after the last follow up visit (50 days after Day 29).

For male patients, contraception should be used from day of first study drug through to 100 days after the last follow up visit (100 days after Day 29).

For participants who practice true abstinence, when this is in line with the preferred and usual lifestyle of the participant, contraceptive requirements do not apply.
For participants who are exclusively in same-sex relationships, contraceptive requirements do not apply.
Male participants with pregnant partners should use condoms from the time of dosing until 100 days after receiving the last dose of the study drug.

6 TREATMENTS

EIDD-2801 (molnupiravir) is considered an investigational medicinal product for the purpose of this protocol.
EIDD-2801 (molnupiravir) and the matching placebo (for phase II) will be provided free of charge by Ridgeback Biotherapeutics for patients recruited to the trial and will be study specific investigational stock.

During Phase I, the capsules will be supplied at 0 (placebo), 25, 100 and 200 mg strengths. For capsules, a wet granulated blend formulation will be filled into hydroxypropyl methylcellulose (HMPC) capsules. The capsule formulation consists of standard pharmaceutical excipients and includes hydroxy-propyl cellulose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

For Phase II, the capsules will be supplied at 0 (placebo) and 200mg strengths only.

6.1 TREATMENT SCHEDULE

Both EIDD-2801 (molnupiravir) and the placebo are provided as a capsule. Patients will receive the oral study drug treatment or placebo (phase II only) for dosing on days 1-5 or 6 depending on timing of first dose. Patients will take the capsule(s) twice daily for a maximum of 10 doses. (Dose 1 & 2 and 9 & 10 could be split over 2 days if patient receives initial dose in the afternoon). Patients will be administered the first dose of study drug/placebo (phase II) in the clinic and dispensed study drug for BID dosing at home.
Patients will return to the clinic on Days 3, 5 and 8, bringing their study medication with them for drug accountability. They will receive a dose of study drug in the clinic on Day 5 and the remaining doses of study drug will be sent home with the patient for self-administration.

N.B. Patients in the control arm of the Phase I will receive SOC, patients in the control arm of the phase II will receive Placebo + SOC.

6.2 IMP SUPPLY & PREPARATION

The IMP is provided by Ridgeback Biotherapeutics (US). The bulk IMP will be shipped to Covance (Leeds) for further manufacturing. Covance will prepare the unit dose presentation and labels for the investigational product and matched placebo. The resulting IMP will be quality assured (QA) and qualified person (QP) released by Covance before being shipped to Sites for use in this study. Please refer to the pharmacy manual for details on supply, storage and preparation.

6.3 PRODUCT STORAGE AND STABILITY

IMP/placebo should be stored at controlled room temperature defined as 15- 25°C (59 -77°F). Excursions permitted between 15- 30°C (59 - 86°F) for up to 24 hours. If excursions occur which are outside of this range, the pharmacy staff should contact SCTU to determine the course of action. Additional stability data may be available which would allow continued use of the study drug, or study drug may need to be replaced.

6.4 ADMINISTRATION

EIDD-2801 (molnupiravir) will be administered BID (morning and evening) orally for a total of 10 doses. Study drug will be administered in the fasting state (fasted for 2 hours prior to administration) with water* unless interval data indicates that the fed state is preferable from a pharmacokinetic standpoint. Patient must also fast for one hour after administration.

**240ml of water when drug is given in clinic. When taken at home, take with water; no specific volume required.*

If patients miss a dose; record as missed dose if delayed by longer than four hours, and take when next due. If able to take within four hours, take as soon as able within that time. If longer than 4 hrs the dose is omitted.

6.5 ACCOUNTABILITY

Drug accountability logs will be provided to sites who will be responsible for maintaining records during the study as follows:

- Amount of study medication received
- Amount distributed to each patient
- Amount of unused drug returned or destroyed at the Sponsors request

In the event of necessary disposal of opened but wasted medication, the disposal should be documented appropriately (i.e. witnessed), in accordance with applicable local regulations, and GCP procedures.

Drug accountability logs will be returned to SCTU for compliance checks.

Patients will be asked about study medication use at their visits on days 3, 5 and 8 and will be asked to bring any unused medication back at those visits to enable pill counts to take place for accountability. Patients will also be provided with a diary to record drug administration at home that they will return to clinic to be reviewed by the research team.

6.6 CONCOMITANT MEDICATIONS

Information on any treatment received by the patient, along with dose, frequency and therapeutic indication, from 30 days prior to starting trial up to End-of-Study-Visit will be recorded in the electronic case report form (eCRF).

No drug:drug interaction studies have been conducted with EIDD-2801 (molnupiravir). Therefore, the investigator should use discretion regarding the use of concomitant medications.

Cytochrome P450 inhibition and inductions assays were conducted (see Investigator Brochure). No restrictions to concomitant medications are required based on the results of the CYP P450 enzyme metabolism studies.

6.7 PROHIBITED AND RESTRICTED THERAPIES DURING THE TRIAL

There are no prohibited or restricted clinical treatments.

6.8 DOSE COHORTS (PHASE I ONLY)

The first cohort (6 patients) will receive dose recommended from Covance (EIDD-2801 (molnupiravir)-1001-US/UK) healthy volunteer study; subsequent cohorts will be determined by tolerability within this trial (modelled as per the Master protocol) and the Covance parallel trial, EIDD-2901-1001-US/UK trial, with escalations determined by the SRC. Dose levels considered will range from 300 to 800mg BID. It will not exceed the highest dose tested in the SAD in healthy volunteers. A dose that has been determined as not suitable or safe for dose escalation in the FIH trial will not be evaluated in CST-2 EIDD-2801 (molnupiravir) without an amendment.

Phase I

First active dose, every dose level; only one active (one patient) will be dosed; at 24hours if no safety concerns, the rest of the cohort will all be able to be dosed. This will be documented and reviewed by the local site PI(s) with oversight from the CI.

6.9 DEFINITION OF AN EVALUABLE PATIENT FOR PHASE I

An evaluable patient for the phase I part will be all control patients and all patients randomised to EIDD-2801 (molnupiravir) who have had at least one dose.

6.10 STOPPING CRITERIA (PHASE I ONLY)

Please refer to AGILE master protocol. In addition, this study includes pre-defined halting criteria for reduction in platelets and/or lymphocytes from baseline deemed attributable to EIDD-2801 (molnupiravir) (and not due to the worsening of underlying disease).

If two (2) patients in a dosing cohort meet the pre-defined criteria as below, and the events are attributable to EIDD-2801 (molnupiravir), dosing is halted until the SRC have had the opportunity to review all available safety and PK data and determine whether to stop or proceed.

The SRC may recommend:

1) halt the study;
2) reduce the dose tested; or
3) recommence the study.

In all instances, the SRC decision will be documented, and Trial Steering Committee (TSC) informed.

Specifically, for haematological assessments of platelets and lymphocytes:

For patients with baseline values within the normal range [1]	**OR**	For patients with baseline values that qualify as a Grade 2 or 3 event [2]
A decrease in platelets and/or lymphocytes sufficient to qualify as a Grade 3 event per the CTCAE Version 5 criteria affecting 2 patients in a dosing cohort;		If ≥ 2 patients in a dosing cohort experience a ≥ 2 CTCAE Version 5 grade change of worsening severity in either platelets or lymphocytes;
AND		
The decrease(s) in platelets and/or lymphocytes reported is considered of likely relationship to EIDD-2801 (molnupiravir) administration and not a worsening of underlying disease		

[1] as determined by local laboratory reference ranges

[2] per the CTCAE Version 5 criteria

6.11 CRITERIA TO CONDUCT DOSE ESCALATION (PHASE I ONLY)

Doses are deemed to be safe if the risk of toxicity being 30% larger in EIDD-2801 than SoC is less than 25%. The dose with the highest probability that the additional risk of toxicity being between 15% and 25% will be chosen for the next cohort.

6.12 BLINDING AND PROCEDURES FOR EMERGENCY UNBLINDING (PHASE II ONLY)

This section is applicable to the Phase II randomised part of the study only.

6.12.1 Methods for ensuring blinding

Study drug will be labelled using a unique number. EIDD-2801 (molnupiravir) and matching placebo solid oral formulation (capsule) will be identical and presented in the same packaging to ensure blinding of the study drug.

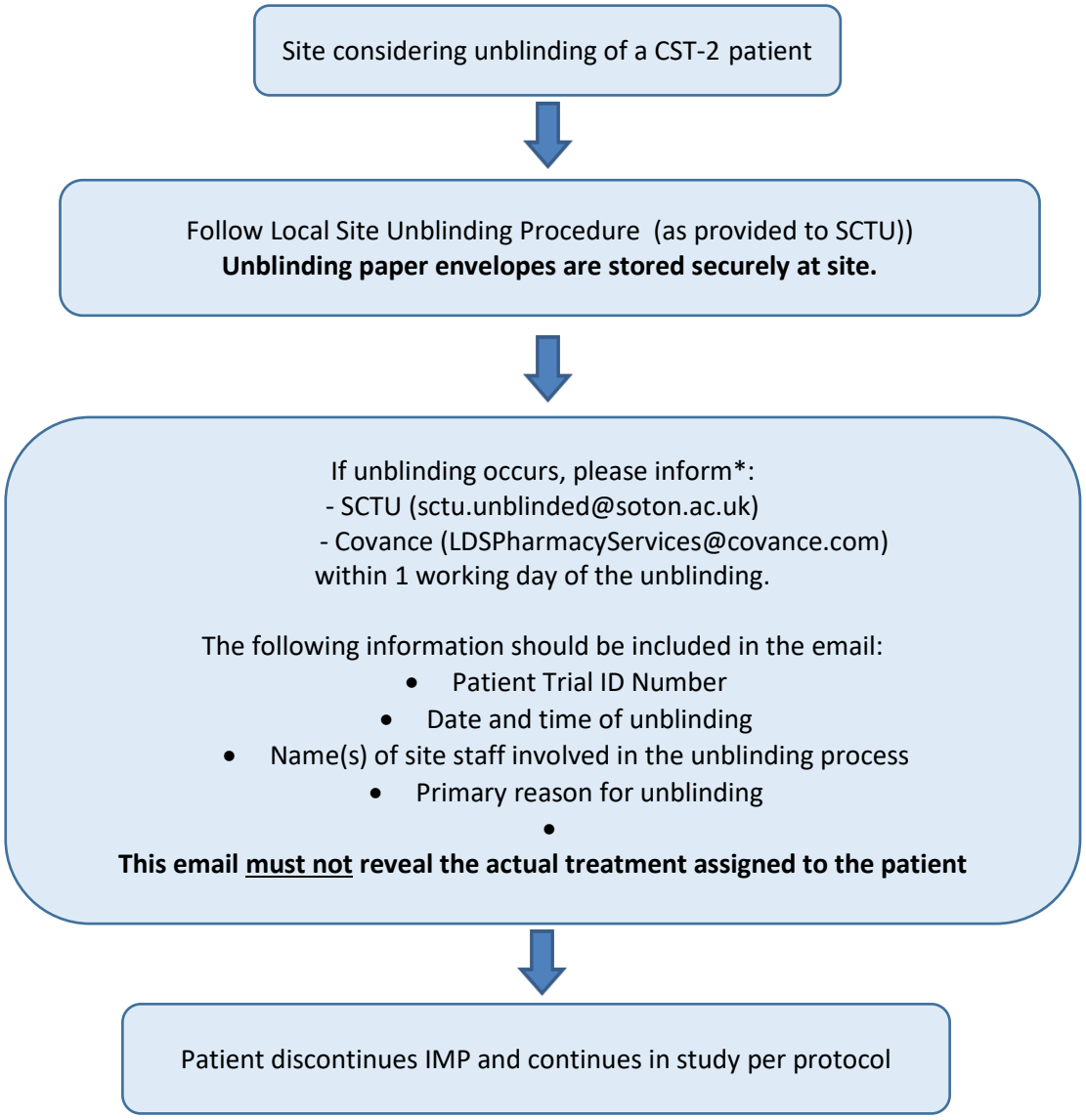
6.12.2 Methods for unblinding

Individual treatment codes, indicating the treatment allocation for each randomised patient, will be provided to site staff. The treatment code should not be broken except in medical emergencies when the safe management of the patient requires immediate knowledge of the treatment allocation.

Where unblinding is being considered the decision should first be discussed whenever practical with the Chief Investigator. However, where this is not possible in an emergency situation, the

Investigator should determine that the information is necessary (it will alter the patient's immediate management) prior to breaking the blind.

If unblinding is being considered, please follow the actions below:



* If unblinding request was due to an adverse event (AE), AE documentation must be completed.

It is the site's responsibility to ensure 24 hour access to unblinding is available to all staff that may have to perform this function.

Patients must cease IMP in the event of unblinding but will remain in follow up.

SCTU/Covance retain the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IMP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data

until all decisions on the evaluability of the data from each individual patient have been made and documented.

At the end of the study after data lock, patients can be contacted by sites to inform them of their treatment allocation.

7 DISCONTINUATION OF STUDY TREATMENT AND PATIENT DISCONTINUATION/WITHDRAWAL

Please see section 7 in the Master AGILE protocol.

8 STUDY ASSESSMENT AND PROCEDURES

8.1 SCREENING PROCEDURES

As per the AGILE Master Protocol, screening procedures to be carried out up to 5 days prior to randomisation and include:

- Informed Consent
- Assessment using the WHO Progression Scale[11]:
    0. Uninfected, no viral RNA detected
    1. Ambulatory mild disease, asymptomatic; viral RNA detected
    2. Ambulatory mild disease, symptomatic; independent
    3. Ambulatory mild disease, symptomatic; assistance needed
    4. Hospitalised moderate disease, no oxygen therapy (If hospitalised for isolation only, record stats as for ambulatory patient)
    5. Hospitalised moderate disease, oxygen by mask or nasal prongs
    6. Hospitalised severe disease, oxygen by NIV or high flow
    7. Hospitalised severe disease, intubation and mechanical ventilation pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200
    8. Hospitalised severe disease, mechanical ventilation pO_2/FiO_2 <150 (SpO_2/FiO_2 <200) or vasopressors
    9. Hospitalised severe disease, mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO
    10. Dead

- Full blood count
- Urea and electrolytes
- Estimated GFR
- Liver Function Tests
- Women of childbearing potential: Pregnancy test (serum or urine) - to be performed during screening, or on baseline day 1 prior to first dose
- Medical history (including COVID-19 history e.g. symptom onset)
- Concomitant medication and standard of care review
- Height and weight
- Assessment of oxygen use
- Demographics review
- Adverse Event Assessment (from consent)

The following assessment, listed in the master protocol, is not required at screening in this candidate specific trial protocol:

- Assessment of mechanical ventilation use

In addition, for EIDD-2801 (molnupiravir) candidate specific trial protocol the following are required:

- SARS-CoV-2 nose/throat swabs for viral titres PCR and virus characterisation (if not already performed within the 4 days prior to screening)
- NEWS2 Score - vital signs (5 minutes supine heart rate and blood pressure, respiratory rate, body temperature, oxygen saturations)
- 12-lead ECG and 10 second ECG rhythm strip (≥5 min supine), to be performed during screening, or on baseline day 1 prior to first dose.
- Targeted physical exam

8.2 TRIAL PROCEDURES

It is anticipated that all patients will receive treatment in the community. Any patients who require hospitalisation for COVID-19 will have met the efficacy endpoint, however, study drug should be continued if possible, and an effort will be made to collect interim virology information, drug-related serious adverse events, and End-of-Study assessments if possible. In lieu of a study visit, study staff will work to obtain equivalent data from study admission records. Pertinent information from the hospitalisation will be collected including need for supplemental oxygenation, mechanical ventilation, days of hospitalization, and death.

Note that this CST visit schedule differs from the Master Protocol and is the schedule to be used for all patients enrolled onto this candidate specific trial.

8.2.1 EIDD-2801 (molnupiravir) Dosing Schedule

Capsule(s) to be taken twice daily for a maximum of 10 doses. (Dose 1 & 2 and 9 & 10 could be split over 2 days if patient receives initial dose in the afternoon).

Dose 1	Day of randomisation (in clinic)
Dose 2	12 hours +/- 6hrs after dose 1 – before food (at home)
Dose 3	Fasted for min of 2 hours (administered at home)
Dose 4	Fasted for min of 2 hours (administered at home)
Dose 5	Fasted for min of 2 hours (administered at home)
Dose 6	Fasted for min of 2 hours (administered at home)
Dose 7	Fasted for min of 2 hours (administered at home)
Dose 8	Fasted for min 2 hours (administered at home or in clinic)
Dose 9	Fasted for min 2 hours (administered at home or in clinic)
Dose 10	Fasted for min of 2 hours (administered at home)

Doses should ideally be taken at the same time each day, aiming for 12 hours apart.

Before food; patients must have fasted for 2 hours before taking medication, and one hour after. The rationale for this allows time for the stomach to empty prior to dosing, and the one hour after allows drug to be absorbed without any food interference.

Patients must be observed in clinic by research team for 4 hours, after the first dosing with IMP. This applies to the first 4 patients on IMP in each dosing tier in phase I. Unless the recommendation is made by the SRC to amend this to further patients, all other patients do not need to be observed after dosing. (Phase I only)

Assessments during and After Treatment Period

Patients will come to clinic to confirm eligibility and complete screening and baseline procedures. Patients will receive the first dose of study drug following completion of baseline procedures. Exact time of administration will be recorded.

Patients who have PK sampling in the phase I cohort will remain in clinic for 4 hours after the first dose. (Phase I only)

8.2.2 Baseline Visit (Day 1, day of randomisation):

The following assessments are to be carried out on the day of randomisation. Patients should commence treatment on the day of randomisation (i.e. Day 1).

- SARS CoV-2 nose/throat swab for viral titres PCR and virus characterisation[a]
- Assessment using the WHO Progression Scale[11 a]:
  0. Uninfected, no viral RNA detected
  1. Ambulatory mild disease, asymptomatic; viral RNA detected
  2. Ambulatory mild disease, symptomatic; independent
  3. Ambulatory mild disease, symptomatic; assistance needed
  4. Hospitalised moderate disease, no oxygen therapy (If hospitalised for isolation only, record status as for ambulatory patient)
  5. Hospitalised moderate disease, oxygen by mask or nasal prongs
  6. Hospitalised severe disease, oxygen by NIV or high flow
  7. Hospitalised severe disease, intubation and mechanical ventilation $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$
  8. Hospitalised severe disease, mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors
  9. Hospitalised severe disease, mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO
  10. Dead

- Non-Ventilated Patients: National Early Warning Score 2 (NEWS2) Assessment[a]:
  - Respiration rate
  - Oxygen saturation (if falls below 92% the test is to be repeated).
  - Systolic blood pressure
  - Pulse rate
  - Level of consciousness or new confusion*
  - Temperature

*The patient has new-onset confusion, disorientation and/or agitation, where previously their mental state was normal – this may be subtle. The patient may respond to questions coherently, but there is some confusion, disorientation and/or agitation. This would score 3 or 4 on the GCS (rather than the normal 5 for verbal response), and scores 3 on the NEWS system.

- Concomitant medication and standard of care review[a]
- Assessment of oxygen use[a]
- Targeted physical exam[a]
- Adverse event assessment[a] including any that appear from FLU-PRO questionnaire

In addition for EIDD-2801 (molnupiravir) candidate specific trial protocol the following procedures will also take place on Day 1:

- Review inclusion and exclusion criteria and confirm eligibility
- Urinary analysis
- Safety Laboratory Evaluations (inclusive of FBC, U+Es, eGFR, LFT) if clinically indicated (physician discretion)[a].
- Patient Reported Outcome Measures (FLU-PRO)
- Randomisation

- Dispense study medication (initial dose to be taken in clinic)- patient will be provided with a diary to record drug administration at home.
- PK samples - for patients in phase I SOC arm (Refer to laboratory manual for timings of sample collection)
- Pharmacodynamic sample (serum)
- Optional SARS-CoV-2 nose/throat swab for storage for future translational research (collected in transport Media)transport media)

[a]If Screening and Baseline/Day 1 take place on the same day, this Baseline/Day 1 assessment/procedure does not need to be undertaken/repeated (as undertaken at Screening).

The following schedule differs from the AGILE master protocol:

8.2.3 Days 2, 4, 6: Telephone contact to document: drug compliance, adverse events, concomitant medication use (Phase I only).

8.2.4 Days 3 & 8 Visit:

(Day 8 +/- 1 day permitted)

As per AGILE Master Protocol

- SARS-CoV-2 nose/throat swab for viral titres PCR and virus characterisation
- AE Assessment (from consent) including any that appear from FLU-PRO questionnaire
- Concomitant medication use

In addtion for EIDD-2801 (molnupiravir) candidate specific trial protocol:

- NEWS 2 Score- vital signs (5 minutes supine heart rate and blood pressure, respiratory rate, body temperature, oxygen saturations on room air (if falls below 92% the test is to be repeated).
- Assessment using the WHO Progression Scale[11]:
    0. Uninfected, no viral RNA detected
    1. Ambulatory mild disease, asymptomatic; viral RNA detected
    2. Ambulatory mild disease, symptomatic; independent
    3. Ambulatory mild disease, symptomatic; assistance needed
    4. Hospitalised moderate disease, no oxygen therapy (If hospitalised for isolation only, record status as for ambulatory patient)
    5. Hospitalised moderate disease, oxygen by mask or nasal prongs
    6. Hospitalised severe disease, oxygen by NIV or high flow
    7. Hospitalised severe disease, intubation and mechanical ventilation pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200
    8. Hospitalised severe disease, mechanical ventilation pO_2/FiO_2 <150 (SpO_2/FiO_2 <200) or vasopressors
    9. Hospitalised severe disease, mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO
    10. Dead
- Patient Reported Outcome Measures (FLU-PRO)
- Evaluation of concomitant medication
- Assessment of oxygen use
- Targeted physical exam
- Drug reconciliation

- Day 3 - Optional SARS-CoV-2 nose/throat swab for storage for future translational research (Transport Media)

8.2.5 Specific Assessments on Day 5, 11, 22:

(Day 11 & 22 visits +/- 1 day permitted)

As per the AGILE- Master Protocol:

- SARS-CoV-2 nose/throat swab for viral titres PCR and virus characterisation
- Full blood count
- Urea and electrolytes
- Estimated GFR
- Liver Function Tests
- Concomitant medication and standard of care review
- AE assessment including any that appear from FLU-PRO questionnaire
- Pharmacodynamic sample (serum) (day 5, 11 only)

In addition for EIDD-2801 (molnupiravir) candidate specific trial protocol:

- NEWS 2 Score- vital signs (5 minutes supine heart rate and blood pressure, respiratory rate, body temperature, oxygen saturations on room air (if falls below 92% the test is to be repeated))
- Assessment using the WHO Progression Scale[11]:
  0. Uninfected, no viral RNA detected
  1. Ambulatory mild disease, asymptomatic; viral RNA detected
  2. Ambulatory mild disease, symptomatic; independent
  3. Ambulatory mild disease, symptomatic; assistance needed
  4. Hospitalised moderate disease, no oxygen therapy (If hospitalised for isolation only, record status as for ambulatory patients)
  5. Hospitalised moderate disease, oxygen by mask or nasal prongs
  6. Hospitalised severe disease, oxygen by NIV or high flow
  7. Hospitalised severe disease, intubation and mechanical ventilation $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$
  8. Hospitalised severe disease, mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors
  9. Hospitalised severe disease, mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO
  10. Dead

- Patient Reported Outcome Measures (FLU-PRO)
- Assessment of oxygen use
- Targeted physical exam
- Dispense study medication (initial dose to be taken in clinic) – Day 5 only
- PK samples (Phase I only) – Day 5 only - not for patients in phase I SOC arm (Refer to laboratory manual for timings of sample collection)
- Drug reconcilation (day 5 only)
- Day 5 - Optional SARS-CoV-2 nose/throat swab for storage for future translational research (Transport Media)

8.2.6 Days 7, 9, 10, 12, 13, 14: contact to document: adverse events, concomitant medication use and PROM (Phase I only)

8.2.7 Day 15 (+/- 1 Day) Visit:

As per the AGILE Master Protocol, the following assessments are to be carried out on Day 15 (±1 days) (N.B. day of randomisation and start date of treatment is Day 1):

- SARS-CoV-2 nose/throat swab for viral titres PCR and virus characterisation
- Assessment using the WHO Progression Scale[11]:
  0. Uninfected, no viral RNA detected
  1. Ambulatory mild disease, asymptomatic; viral RNA detected
  2. Ambulatory mild disease, symptomatic; independent
  3. Ambulatory mild disease, symptomatic; assistance needed
  4. Hospitalised moderate disease, no oxygen therapy
  5. Hospitalised moderate disease, oxygen by mask or nasal prongs
  6. Hospitalised severe disease, oxygen by NIV or high flow
  7. Hospitalised severe disease, intubation and mechanical ventilation $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$
  8. Hospitalised severe disease, mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors
  9. Hospitalised severe disease, mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO
  10. Dead

- NEWS 2 Score - vital signs (5 minutes supine heart rate and blood pressure, respiratory rate, body temperature, oxygen saturations on room air (if falls below 92% the test is to be repeated))
- Full blood count
- Urea and electrolytes
- Estimated GFR
- Liver Function Tests
- Concomitant medication and standard of care review
- AE assessment including any that appear from FLU-PRO questionnaire
- Pharmacodynamic sample (serum)

In addition for EIDD–2801 candidate specific trial protocol the following procedures are also required:

- Patient Reported Outcome Measures (FLU-PRO)
- Evaluation of concomitant medication
- Assessment of oxygen use
- Targeted physical exam

8.2.8 Day 29 (+/- 2days) End-of-Study Visit:

As per the AGILE Master Protocol the following assessments are to be carried out on Day 29 (±2 days) (NB day of randomisation and start date of treatment is Day 1).

- Assessment using the WHO Progression Scale[11]:
  0. Uninfected, no viral RNA detected

1. Ambulatory mild disease, asymptomatic; viral RNA detected
2. Ambulatory mild disease, symptomatic; independent
3. Ambulatory mild disease, symptomatic; assistance needed
4. Hospitalised moderate disease, no oxygen therapy
5. Hospitalised moderate disease, oxygen by mask or nasal prongs
6. Hospitalised severe disease, oxygen by NIV or high flow
7. Hospitalised severe disease, intubation and mechanical ventilation $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$
8. Hospitalised severe disease, mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors
9. Hospitalised severe disease, mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO
10. Dead

- NEWS 2 Score - vital signs (5 minutes supine heart rate and blood pressure, respiratory rate, body temperature, oxygen saturations on room air (if falls below 92% the test is to be repeated))
- Full blood count
- Urea and electrolytes
- Estimated GFR
- Liver Function Tests
- Concomitant medication and standard of care review
- AE assessment including any that appear from FLU-PRO questionnaire
- Pharmacodynamic sample (serum)

In addition for EIDD–2801 candidate specific trial protocol the following procedures are also required:

- SARS-CoV-2 nose/throat swab for viral titres PCR and virus characterisation
- Pregnancy test (urine) for women of child bearing potential
- Patient reported outcome measures (FLU-PRO)
- Assessment of oxygen use
- Targeted physical exam

If patient is hospitalised every effort will be made to follow up the patient and collect all data as detailed in the Schedule of Assessments.

8.2.9 SoC review/SoC Assessments

If imaging (CXR, chest CT, chest MRI) is done as standard care, the investigation and outcome should be recorded on the clinical trial database. All imaging done at any timepoints until the final follow-up (day 29) should be recorded.

8.3 SAMPLE REQUIREMENTS

PK study (Phase I only)

Samples are only required for the patients being observed for 4 hours after dosing in Phase I (i.e. not required for patients randomised to SoC). For these patients the sample collection is required as part of the consent.

Phase I samples

Samples will be required at day 1 and day 5, collected pre-dose, 0.5hours, 1hour, 2hours, and 4 hours post dose.

Matrix	Sample/collection tube	Day of sampling (Day 1 and Day 5)				
		Pre-dose	0.5hour post dose	1hour post dose	2hours post dose	4hours post dose
Plasma	K2 EDTA tube	2.0mL	2.0mL	2.0mL	2.0mL	2.0mL
Tears	Schirmer Tear Test Strips	2 swabs	2 swabs	2 swabs	2 swabs	2 swabs
Saliva	Salivette™ tubes	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL
Nasal swab	Synthetic absorptive matrices strips (SAM)	2 swabs	2 swabs	2 swabs	2 swabs	2 swabs
Dried blood spot	100 µL whole blood from K2 EDTA tube per spot onto dried blood spot card (hemsep cards)	2 spots (100 µL each) on 1 card	2 spots (100 µL each) on 1 card	2 spots (100 µL each) on 1 card	2 spots (100 µL each) on 1 card	2 spots (100 µL each) on 1 card

All samples will need to be processed and frozen for batch shipment to Covance, Harrogate (plasma), or Bioanalytical Facility, University of Liverpool (tears, saliva, nasal swab, dried blood spot).

Further details are provided in the lab manual.

8.3.1 Pharmacokinetic Sample Analysis (Phase I only)

Concentrations of EIDD-2801 (molnupiravir) and its circulating metabolites will be determined from plasma, saliva, nasal swabs, dried blood spots and tears samples using validated bioanalytical methods.

8.3.2 Pharmacokinetic Parameter Determination (Phase I only)

Concentrations of EIDD-2801 (molnupiravir) and its circulating metabolites in plasma, saliva, nasal swabs, dried blood spots and tears will be listed and summarised.

Pharmacokinetic parameters will be calculated using standard non-compartmental techniques.

Where possible the following parameters will be determined: C_{max}, T_{max}, $AUC_{0-4.}$ Additional parameters, such as $t_{1/2}$ and AUC_{inf} may be calculated where appropriate.

Modelling approaches may also be used, where appropriate. Population PK modelling and simulation may be performed with the PK samples (i.e. sparse PK samples) to derive the PK parameters: C_{max}, T_{max}, $AUC_{0-4,}$ AUC_{inf} and $t_{1/2}$.

8.4 PHARMACODYNAMICS

Patients will be asked to give consent for use of their PCR nasal swabs collected at every clinic visit including screening, baseline, and all treatment and follow-up visits. This is mandatory for phase I and II.

The same samples used for SARS-CoV2-PCR will be used, so collection and labs will be as standard clinical practice.

The samples will be used for virus characterisation at University of Liverpool (standard lab).

An additional serum sample will be collected for the pharmacodynamic assessment on days 1, 5, 11, 15 and 29.

Serum Sample Collection

Sample	Sample/collection tube	Day 1	Day 5	Day 11	Day 15	Day 29
Serum	Serum gel tube	5ml	5ml	5ml	5ml	5ml

Further details of transfer and analysis are provided in the lab manual.

8.5 FUTURE TRANSLATIONAL RESEARCH

Optional SARS-CoV-2 nose/throat swabs for storage for future translational research to be collected at Baseline/Day 1, Day 3 and Day 5 (collected in transport media).

8.6 FOLLOW UP

Patients will be followed up to day 29.

9 SAFETY

Refer to the AGILE master protocol for full safety information. EIDD-2801 (molnupiravir) specific safety reporting information are detailed below.

9.1 ADDITIONAL SAFETY CONSIDERATIONS FOR THIS TREATMENT ARM

No adverse events are considered expected for EIDD-2801 (molnupiravir). The dose limiting toxicity in nonclinical studies involved bone marrow therefore hematologic parameters including platelet counts and counts of red and white blood cell elements will be closely monitored.

9.2 REPORTING WINDOWS

AEs/SAEs should be reported from consent until day 29.

Each time there is a change in grade of an adverse event this should be recorded on a separate log line on the adverse event form on the eCRF. Refer to the eCRF Guidance on how to report this on Rave.

The investigator should notify the trial sponsor of any death or adverse event occurring at any time after a patient has discontinued or terminated trial participation that may reasonably be related to this trial.

9.3 SAE EXPECTEDNESS

Because of the limited prior human experience with EIDD-2801 (molnupiravir), no adverse events will be considered expected.

9.4 EXCEPTIONS

For the purposes of this trial, the following SAEs do not require reporting to SCTU using the Serious Adverse Event Report Form:

- Death due to COVID-19 (Death due to COVID-19 is an efficacy endpoint)
- Disease progression due to COVID-19 (Hospitalization for COVID-19 is an efficacy endpoint)- Signs and symptoms that are considered to be related to COVID-19 will not be reported in an expedited manner for purposes of this study.
- Hospitalisations for elective treatment of a pre-existing condition (the pre-existing condition needs to have been captured within the medical history CRF)

Expectedness assessments are made against the approved Reference Safety Information (RSI). EIDD-2801 (molnupiravir) is the subject of several open, active regulatory filings presently, including:

- IND 147122 for treatment of uncomplicated influenza caused by all subtypes of circulating and emerging (drifted and shifted) IAV and IBV, including seasonal, epidemic and pandemic strains. IND 147122 was issued a Study May Proceed letter on April 7, 2020.
- IND 147734 for the treatment of infections caused by highly pathogenic coronaviruses, including COVID-19. IND 147734 is within the initial review period with FDA as of 4/15/2020.
- EudraCT 2020-001407-17 was established for Study EIDD-2801 (molnupiravir)-1001-US/UK in healthy volunteers.

In the event that new information concerning the risks and/or benefits associated with EIDD-2801 (molnupiravir) administration becomes known during the course of conduct of Study EIDD-2801 (molnupiravir)-1001-US/UK, the manufacturer commits to: 1) inform investigator's participating in the AGILE study in a timely fashion; 2) update the ICF documents as appropriate; and 3) update the Investigators Brochure accordingly.
The RSI for this candidate is specified within the document version listed in the table below:

Name of Product	IB	Section /Table No.	IB Author	Date of text revision DD-MMM-YYYY
EIDD- 2801 (MK-4482)	v3.0	7.2	Merck Sharp & Dohme Corp.,	31-Jul-2020

The nature and/or severity of the event should be considered when making the assessment of expectedness. If these factors are not consistent with the current information available then the AE should be recorded as 'unexpected'.

9.4.1 Follow Up and Post-trial SAEs

The reporting requirement for all AEs and SAEs affecting patients applies for all events occurring up to the End-of-Study visit. Ongoing SAEs following completion of study participation will be followed until resolution or return to baseline, to day 29 or until one of the end of trial criteria is met (i.e. lost to follow up, withdrawal etc.). At the Day 29 visit, the investigator should instruct each patient to report any subsequent event(s) that the patient, or the patient's general practitioner, believes might reasonably be related to participation in this trial.

9.4.2 Non-serious AEs

All adverse events should be recorded in the relevant eCRF and submitted to SCTU.

9.4.3 Pregnancy

Patients in this study should use appropriate contraception from consent through to 50 days for WOCBP and 100 days for male patients with WOCBP partners after the Day 29 follow up visit.

A preliminary fetal developmental toxicity study evaluating MK-4482 is being conducted in rats. In this study, at a dose of 1000 mg/kg/day, MK-4482-related fetal developmental findings were observed. The findings included small or absent eye, absent kidney, rib and vertebral abnormalities, presence of cervical ribs, and evidence of growth/developmental delays. The exposure in rats at 1000 mg/kg/day is 8.9-fold relative to the AUC at the clinical dose of 800 mg PO Q12H. Additional findings considered of uncertain relationship to MK-4482 (due to low incidence/magnitude) were observed at doses 200 mg/kg/day to 1000 mg/kg/day (the highest dose studied), and included post-implantation loss, a cardiovascular malformation, decreased fetal body weight, cervical ribs, and a rib malformation. There are no data in humans to understand the impact of MK-4482 on pregnancy or fetal development, as no participants receiving MK-4482 in clinical trials have become pregnant.

Until reproductive and developmental toxicity studies have been completed, administration of EIDD 2801 to pregnant females or to males or females of child fathering or childbearing potential not using the required methods of highly effective contraception is not advised. As such, pregnancy and breast-feeding are trial exclusion criteria and the use of highly effective methods of contraception (for WOCBP and males with WOCBP partners) is an inclusion criterion.

If a female patient is discovered to be pregnant during the course of treatment with EIDD 2801, the treatment will discontinue immediately. Any pregnancy up to 100 days after the Day 29 follow up visit should be reported to SCTU.

If a patient or his partner becomes pregnant between the first dose of EIDD 2801 and up to 100 days after the day 29 follow up visit, the investigator must ensure that the patient/patient's partner and the patient's/patient's partner's healthcare professional are aware that follow up information is required on the outcome of the pregnancy. Follow-up is, of course, dependent on obtaining informed consent for this from the patient (or their partner in the case of male trial patients). If the patient leaves the area, their new healthcare professional should also be informed. If the patient or partner of the patient, in the case of a male patient, becomes pregnant the Investigator must complete the Pregnancy Notification Form in the patient's eCRFs.

The investigators must notify the SCTU of this event via the Pregnancy Report Form in iMedidata Rave within 24 hours of site becoming aware. A call should also be made to the Trial Manager to notify SCTU of the pregnancy.

Should the outcome of the pregnancy result in stillbirth, neonatal death, spontaneous abortion, or birth defects, a SAE will need to be reported to the SCTU within 24 hours of site becoming aware.

9.5 SCTU RESPONSIBILITIES FOR SAFETY REPORTING

SCTU, acting on behalf of the Sponsor, will receive and process the SAR/SAE/SUSAR reports received from sites. SCTU will notify Covance PSS (who manage safety reporting on behalf of Ridgeback Therapeutics) and Ridgeback Therapeutics of all initial and subsequent updates to SAE/SAR/SUSAR reports.

Events which meet the criteria for reporting to the competent authority will be submitted by Covance to the MHRA and Merck Sharp & Dohme. The SCTU will inform the relevant Research Ethics Committee and sponsor.

Covance PSS will write the Study Specific DSUR and supply it to the SCTU. Covance PSS are responsible for reporting the DSUR to the MHRA. The SCTU will forward the DSUR to the relevant Research Ethics Committee and sponsor.

All trial relevant pharmacovigilance responsibilities and timelines are detailed in the safety management plan (SMP), which has been reviewed and approved by Sponsor, SCTU, Covance PSS and Ridgeback Biotherapeutics.

10 STATISTICS AND DATA ANALYSES

10.1 METHOD OF RANDOMISATION

During phase I, patients will be randomised in cohorts of 6 in a 2:1 ratio between EIDD-2801 (molnupiravir) and SOC using permuted block randomisation. Once the recommended phase II dose has been established patients will be randomised 1:1 between EIDD-2801 (molnupiravir) and placebo using permuted block randomisation.
Note that this CST randomisation plan differs from the Master Protocol.

10.2 SAMPLE SIZE

The sample size for phase I will be variable depending on dose escalation decisions. Patients will be recruited in cohorts of 6 patients until a decision to cease recruitment for safety or recommend a dose for further evaluation. A maximum of 180 patients are required in phase II.

The sample size for phase II is based on a survival analysis comparing EIDD-2801 (molnupiravir) to placebo, with one formal interim analysis that may stop the study for futility or efficacy. If the probability that the hazard ratio comparing groups on time to viral clearance is greater than 0.8, then EIDD-2801 (molnupiravir) will be recommended for further testing in a definitive study. This threshold applies to both the interim and final analysis. If the probability is less than 0.3 at interim, the study will stop for futility. The maximum sample size of 180 has been found to ensure that the probability of concluding that EIDD-2801 (molnupiravir) is better than placebo is 0.1 when the hazard ratio is 1 (one-sided type I error) while the power to recommend

EIDD-2801 (molnupiravir) for further testing is approximately 0.77 if the hazard ratio is 1.5 (median time to viral clearance from 14 days to 9.3 days). These figures are equivalent to increasing viral clearance from 0.75 after 28 days to 0.875.

Note that this CST sample size plan differs from the Master Protocol.

10.3 INTERIM ANALYSIS

A pre-planned interim analysis was carried out following recruitment and day 15 follow-up of 60 patients in Phase II. Following review of the interim analysis and other trial data, the DMEC recommended the trial continue as planned.

After recruitment had reached 67 of the planned 180 subjects in Phase II, both the DMEC on 19th May 2021 and the TSC on the 21st May 2021 supported the decision to proceed to a multi-site trial and to include a further pre-planned interim analysis and evaluation by the DMEC once 120 patients have been enrolled and completed 15 days of follow-up. There will be no pause in recruitment for this analysis.

The impact of the extra interim analysis is that the probability of concluding that EIDD-2801 (molnupiravir) is better than placebo when the hazard ratio is 1 (no difference) has increased from 0.1 to 0.12 (one-sided type I error). This minor increase is deemed acceptable in the phase II setting and the thresholds above will be maintained for both the extra interim analysis and the final analysis.

Note that these CST interim analyses differ from the Master Protocol.

10.4 STATISTICAL ANALYSIS PLAN (SAP)

Phase I was analysed as per the Phase I Statistical Analysis Plan v1.

The phase II primary analysis will involve the comparison of groups on time to viral clearance using a Bayesian Cox proportional hazards model. Stratification factors will be controlled for. The primary interpretation will be on the probability the hazard ratio is greater than 1.

Baseline characteristics and other endpoints will be analysed as per the principles of the master protocol (section 10.3.2).

Subgroup analyses may be undertaken based on variants of COVID and will be detailed in the SAP.

11 ETHICAL CONSIDERATIONS

11.1 SPECIFIC ETHICAL CONSIDERATIONS

Refer to AGILE Master Protocol.
In addition the phase II aspect of this trial is placebo controlled. It will be explained to the patient in the patient information sheet that they may be randomised to placebo + standard care instead of the IMP.

12 SPONSOR

The trial sponsor is University of Liverpool. Southampton Clinical Trials Unit and other organisations are delegated tasks and functions to manage the trial, under the oversight of the trial sponsor. The sponsor delegated tasks have been and will be agreed contractually and are formally documented in the Trial Task Allocation Matrix.

12.1 INDEMNITY

Refer to AGILE master protocol.
Additional liability insurance for EIDD-2801 (molnupiravir) is provided by Ridgeback Biotherapeutics LP.

12.2 FUNDING

Ridgeback Biotherapeutics, the manufacturer for the investigational medicinal product (IMP), is funding the development of EIDD-2801 (molnupiravir). This will be further supported by other funding streams.

12.3 PATIENT PAYMENTS

Patients will be paid £30 for each trial visit. Reasonable travel expenses may be provided to patients by site.

13 DATA MANAGEMENT

Refer to AGILE master protocol.

13.1 AUDITS AND INSPECTIONS

Sponsor or delegated parties may inspect investigator sites

Ridgeback Biotherapeutics may inspect the investigative sites and laboratories.

Southampton Clinical Trials Unit will notify Ridgeback of any MHRA inspection at Sponsor, site or CTU.

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15 SUMMARY OF SIGNIFICANT CHANGES TO THE CANDIDATE SPECIFIC TRIAL PROTOCOL

Protocol date and version	Summary of significant changes

v1 07 May 2020	• Initial Protocol
v2 15 May 2020	• MHRA requested change to contraception timeline
v3 10 June 2020	• Change to sponsor, trial name, contraception advice and timeline. Dosing amended to start at 300mg BD and go up to 400mg BD. Clarification of patient recruitment process. Addition of patient diaries. Clarification of SUSAR reporting arrangements
v4 19 June 2020	• Amendment to contraception section to require 2 forms of contraception, one of which is highly effective. Clarification that all patients receiving IMP in phase I will be observed in clinic for 4 hours after dosing.
v5 08 Sep 2020	• WHO clinical severity score 9-point ordinal scale assessment replaced with WHO Clinical Progression Scale[11]. • Inclusion criteria amended from ≥60 (or ≥50 with a comorbidity) to aged ≥18 with CST-specific definitions of severity added. • Exclusion criteria amended to only exclude pneumonia that results in hospitalisation (#8) and amended #9 to only exclude platelets $<50x10^9$/L. • Reference added to EIDD-2801 (molnupiravir) now also known as MK-4482 and EIDD-1931 as NHC following transfer to Merck. • Phase II Primary endpoint amended from progressive disease, hospitalisation or death up to day 29 to time to negative PCR. Progressive disease added as secondary endpoint. • Oxygen saturation added as secondary endpoint. • SARS-CoV-2 culture added as translational endpoint. • Phase II PK assessments amended from 2-3 hours post dose to 1-2 hours post dose. • Results of genotoxicity/mutagenicity assessments added. • Addition of recruitment methods via local and supra-regional testing laboratories (Pillar 1 and 2), Local Clinical Commissioning Groups (CCGs) and Local Public Health and local authority testing facilities. • Clarified acceptable, additional birth control methods which may not be considered as highly effective. • Missed dose window reduced from 6 hours to 4 hours. • Maximum dose level to considered increased from 400mg BID to 800mg BID. • Reference safety information updated to v3 of IB. • Addition of Merck to safety reporting process. • Update that Covance will write Study Specific DSUR not Covance. • Sample size calculations and interim analysis sections updated to reflect the change in Phase II primary endpoint to time to viral clearance. • Corrections/clarifications throughout

v6 13 Nov 2020	• Removal of inclusion criteria 8, 'Has someone, aged ≥ 16 living in the same household during the dosing period'. • Addition that if Screening and Baseline/Day 1 take place on the same day, assessments that are the same on both visits only need to be undertaken once. • Addition of animal study pregnancy information. • Corrections/clarifications throughout.
v7 30 MAR 2021	• Added abbreviations (BID,EID-2801 also known as molnupiravir,) • Section 1.1: Clarification that PK objectives pertain to Phase I only, addition of circulating metabolites on top of EIDD-2801 (molnupiravir),, PD endpoints clarified as Phase I and II, Addition of translational swabs in transport media), addition of IMP name molnupiravir, addition of Phase II determined dosing of 800mg twice daily, clarification of sites for each phase, removal of Phase Ib reference, clarification of expansion support in Phase II • Section 1.3: Removal of Telephone Contact for all visits and changed to generic contact whilst in hospital, addition of optional SARS-CoV-2 Nose/throat swab for future translational research, PK assessment clarified for Phase I only, removal of optional future translational PK assessments in Phase II, update to reference table to remove point (a) and update letters of reference on the table • Section 2.1: addition of IMP name molnupiravir (and throughout whole of document) • Section 2.2: Addition of preliminary results from Big Blue® rat mutagenicity assay, addition of DMEC review • Section 3.1: Clarification of PK objectives in Phase I to include metabolites • Section 3.2: Removal of PK translational objective for Phase II, addition of transport media future culture swabs) • Section 4: identified dose from Phase I added for Phase II • Section 4.1: DMEC review wording added, stopping criterias clarified as for Phase I only, futility for Phase II • Section 4.2: SRC and dose escalation process clarified as for Phase I only • Section 4.3: Dose for Phase II inserted with justification of what basis • Section 5.1: Removal of Liverpool references to make it site generic, addition of wording devolved nations to include other parts of UK, addition of primary care sites for recruitment process • Section 5.2: Updated to reflect Master Protocol • Section 6: Clarification of Phase I and Phase II IMP formulations • Section 6.2: Removal of Liverpool references to make site generic • Section 6.3: Clarification that temperature excursion to be reported to SCTU • Section 6.8: Dose cohorts clarified as for Phase I only • Section 6.10: Stopping criteria clarified for Phase I only • Section 6.11: Criteria for dose escalation clarified for Phase I only • Section 6.12: Blinding and unblinding procedures added for Phase II, removal of Liverpool procedure for unblinding to make site generic and end of trial data lock process for unblinding

	• Section 8.1: addition of EIDD-2801 (molnupiravir) specific screening of SARS-CoV-2 nose/throat swabs, removal of PD sample (serum) • Section 8.2.1: Clarification that 4 hour post dose observation only for Phase I • Section 8.2.2: brought into previous section so re-numbered rest of document onwards (assessments during and after treatment period) • Section 8.2.3: Removal of swabs for future translational research at baseline visit, removal of Urinalysis, clarification that PK samples are for Phase I patients, addition of Transport Media • Section 8.2.4: Telephone contact for Phase I only • Section 8.2.5: AE assessment clarified to include any from FLU-PRO questionnaire, addition of Day 3 optional swab for future translational research (Transport Media) • Section 8.2.6: AE assessment clarified to include any from FLU-PRO questionnaire, clarification of PK samples for Phase I only, addition at Day 5 of optional swab for future translational research (Transport Media) • Section 8.2.7: Clarified as Phase I only and removal of PROM • Section 8.3: Removal of Phase II reference in PK study • Section 8.3.1, 8.3.2: Clarification of Phase I only and addition of circulating metabolites • Section 8.4: Additional serum PD sample removed at screening • Section 8.5: Added Future Translational Research Section • Section 10.1: Stratified by site removed • Section 10.3: Interim analysis outcome added • Section 10.4: SAP referenced correctly • Section 12: delegated organisation added • Section 13.1: Sponsor delegate parties added as inspection points
v8 20 JUL 2021	• Section 10.3: Addition of an extra interim analysis at 120 patients • Section 1.3: Row added in schedule of events for diagnostic swab • Section 1.3: Diagnostic and screening swab window extended to 5 days
V9 05-MAY-2022	• Section 1.3: Screening window typo corrected to 5 days prior to randomisation • Section 5.1 Screening window clarified • Section 5.3 Screening window clarified