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A study to assess several different treatments that may be useful for patients with COVID-19

Submission date	Recruitment status	[_] Prospectively registered
01/12/2020	Recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
07/12/2020	Ongoing	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
30/07/2025	Infections and Infestations	

Plain English summary of protocol

Background and study aims
COVID-19 is a condition caused by the coronavirus (called SARS-CoV-2) that was first identified in late 2019. This virus can infect the respiratory (breathing) system. Some people do not have symptoms but can carry the virus and pass it on to others. People who have developed the condition may develop a fever and/or a continuous cough among other symptoms. This can develop into pneumonia. Pneumonia is a chest infection where the small air pockets of the lungs, called alveoli, fill with liquid and make it more difficult to breathe.

In 2020, the virus had spread to many countries around the world and neither a vaccine against the virus or specific treatment for COVID-19 has yet been developed. As of March 2020, it is advised that people minimise travel and social contact, and regularly wash their hands to reduce the spread of the virus.
Groups who are at a higher risk from infection with the virus, and therefore of developing COVID-19, include people aged over 70 years, people who have long-term health conditions (such as asthma or diabetes), people who have a weakened immune system and people who are pregnant. People in these groups, and people who might come into contact with them, can reduce this risk by following the up-to-date advice to reduce the spread of the virus.

The AGILE study aims to assess several different treatments that may be useful for patients with COVID-19. These treatments have been recommended for testing by a team of experts (the AGILE Scientific Advisory Board) based on strict criteria.
The aims of this study are to determine, in people with COVID-19, the following:
• The safety of the study drug and any side effects that might be associated with it
• How much of the study drug gets into the bloodstream
• How quickly the body removes the study drug and its active ingredients once the body has processed it
• How well the study drug might be able to reduce complications of COVID-19

Although these treatments show promise, nobody knows if any of them will turn out to be more effective in helping patients recover than the standard of care at home as recommended by

their doctor (which all patients currently receive).
The treatment being assessed in Candidate Specific Trial Protocols, of which currently there is no active and recruiting trials (as of Jan 2024), and CST-9 is at the planning stage.

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

CST-3A:
A Multicentre, Adaptive, Phase I trial to Determine the optimal dose, Safety and Efficacy of Nitazoxanide for the Treatment of COVID-19

CST-3B:
A Multicentre, Adaptive, Phase I/II trial to Determine the optimal dose, Safety and Efficacy of Nitazoxanide for the Treatment of COVID-19

CST-5:
A Randomized, Multicentre, Seamless, Adaptive, Phase I/II Platform Study to Determine the Phase II dose of VIR-7832, and Evaluate the Safety and Efficacy of VIR-7831 and VIR-7832 for the Treatment of COVID-19

CST-6:
A Randomized, Multicentre, Seamless, Adaptive, Phase I/II Platform Study to Determine the Phase II dose and to Evaluate the Safety and Efficacy of intravenous Favipiravir for the Treatment of COVID-19

CST-8:
A Randomised, Multicentre, Seamless, Adaptive, Phase I Platform Study to Determine the recommended Phase II dose and Evaluate the Safety and Efficacy of an antiviral combination of Molnupiravir and Paxlovid® for the Treatment of COVID-19

CST-9:
A Multicentre, Adaptive Phase II Platform Trial to Evaluate the Safety, Efficacy and Virological response of ALG-097558 as monotherapy and in combination with Remdesivir in high-risk population for the Treatment of COVID-19 disease.

Who can participate?
To be eligible for the AGILE study, there are a variety of inclusion and exclusion criteria dictated by the Master Protocol of AGILE; however, each candidate will have their own inclusion and exclusion criteria dictated in its own separate protocol.

Inclusion Criteria: Adult patients (≥18 years) who have confirmed infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

We will also include both severe and mild-moderate patients defined according to the WHO Clinical Progression Scale as follows:
Group A (severe disease): Patients with clinical status of Grades 5 (hospitalised, oxygen by mask or nasal prongs), 6 (hospitalised, non-invasive ventilation or high flow oxygen), 7 (hospitalised, intubation and mechanical ventilation, pO2/FiO2 ≥150 or SpO2/FiO2 ≥200), 8 (hospitalised mechanical ventilation pO2/FiO2 <150 (SpO2/FiO2 <200) or vasopressors or 9 (hospitalised, mechanical ventilation pO2/FiO2 <150 and vasopressors, dialysis or ECMO).
Group B (mild-moderate disease): Ambulant or hospitalised patients with peripheral capillary

oxygen saturation (SpO2) >94% RA
N.B. If any Candidate Specific Trials (CST) are included in the community setting, the CST protocol will clarify whether patients with suspected SARS-CoV-2 infection are also eligible (e.g. ICD-10 U0.71 COVID-19).

We will also include healthy volunteers as a separate group: Group C (Healthy Volunteers)

What does the study involve?
CST-2:
Patients will take EIDD-2801 (molnupiravir) versus the standard of care to confirm an optimal dose for the study during Phase I. For Phase II, patients will be given study drug or placebo to determine the ability of study drug to improve viral clearance.

CST-3A:
Patients will be given 1500mg of nitazoxanide twice daily for 7 days to determine the safety and optimum dosing schedule in healthy volunteers.

CST-3B:
The Phase Ib drug dose was informed by the CST-3A study and is currently 1500mg BID. The phase Ib is complete and will be reviewed by the Safety Review Committee (SRC). The Safety Review Committee will determine the Phase II dosing requirement.
CST-5: Doses of VIR-7832 or placebo will be administered via IV infusion to patients in doses of 50mg, 150mg or 500mg followed by a Phase II of VIR-7832 versus VIR-7831 versus placebo.

CST-6:
Phase I: Multiple doses of IV Favipiravir will be administered by intravenous (IV) infusion over 1 hour. Dosing regimen will be every 12 hours for 7 days duration. The starting dose will be 600mg (BID), and dose escalations to 1200mg (BID), 1800mg (BID) and 2400mg (BID) are anticipated as well as a de-escalation dose of 300mg (BID) if necessary, with de-escalation and escalation guided by emerging safety data and decision by the Safety Review Committee (SRC). Duration of monitoring will be 29 days post-first dose.

CST-8:
Molnupiravir 800mg twice a day (BD) in combination with Paxlovid® (300mg nirmatrelvir + ritonavir 100mg) twice a day (BD) for 5 days as starting dose, versus standard of care, with a de-escalation protocol reducing in increments of molnupiravir to 600mg BD, then 400mg BD if required. The dose of Paxlovid® will be fixed for all cohorts.

CST-9:
Twice daily dose of ALG-097558 (monotherapy arm) versus the twice daily dose of ALG-097558 in combination with RDV (combination arm) versus standard-of-care therapy (SoC arm) with an early futility analysis.

Full details of the specific visits and the procedures are included in the current versions of the patient information sheet for each candidate study.

What are the possible benefits and risks of participating?
We do not know if the treatments being tested will be therapeutic (have a beneficial effect) or help with the symptoms of COVID-19, but this study should help inform how we treat future patients.

CST-2:
EIDD-2801 (molnupiravir) is being developed for the treatment of infections caused by highly pathogenic coronaviruses, including SARS-CoV-2. As of 20th March 2021, following completion of the Phase I study analysis with no evidence of Dose 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.

CST-3A:
The purpose of this study is to determine if taking nitazoxanide is safe at frequent and higher dosing over a longer treatment period. Therefore, there are no benefits to taking part in this study. Higher single doses of nitazoxanide (up to 4000 mg) have previously been given to people in other clinical trials. The maximum nitazoxanide dose that will be given in this study will be 3500 mg per day. It is not known whether higher doses of nitazoxanide, given for 7 days, will increase its side effects. However, you will be closely monitored for any side effects during the clinical trial.

CST-3B:
The possible benefits are improvements to the patient's condition (COVID-19). The possible risks are potential gastrointestinal issues, such as diarrhoea and nausea.

CST-5:
We do not know if the treatment being tested will be therapeutic (have a beneficial effect) or help you with your symptoms, but this study should help inform how we treat future patients. VIR-7832 works by blocking the virus from entering the body's cells so it cannot make more of itself. VIR-7832 has been extensively tested in monkeys and it was well tolerated in monkeys up to a 600-fold higher dose than the dose being tested in the first dose group (cohort). VIR-7832 has been administered to 18 participants during the first phase of the study and was well tolerated by the participants. Due to the small number of participants who have had the drug, there is still limited information about its effects and side effects and VIR-7832 may have side effects that are currently unknown.
There is a remote chance that the study drug (like any drug product) may cause an allergic reaction, which in some cases may be severe. This is known as an anaphylactic reaction. An anaphylactic reaction may require emergency treatment. Report any unusual signs or symptoms you notice to the Unit medical staff straight away.

There is a theoretical risk that antibody infusion may make the disease worse via antibody-dependent enhancement (ADE). ADE occurs if specific antibodies against a virus cause the virus to replicate faster, rather that slow or stop it. ADE has been observed most clearly in the context of Dengue fever; but it is unclear if this reaction occurs and/or is clinically significant in COVID-19. The study team will monitor you closely for any signs of side effects from the study drug. Similarly to VIR-7832, VIR-7831 is a monoclonal antibody, a type of protein designed to recognise a specific target on the SARS-CoV-2 virus, the virus that causes acute COVID-19 infection. It is approved by the NHS and used to treat symptomatic acute COVID-19 infection in adults and adolescents (from 12 years and weighing at least 40kg).

If there are any changes to the potential risks associated with the study drug during the study, patients will be informed by the study doctor. Patients may also experience other unwanted effects or discomforts with the study procedures. Full details of the risks of the study drug and procedures are included in the current version of the patient information sheet.

CST-6:
Favipiravir, the drug under investigation, is already used in tablet form as a treatment for influenza. In this study, the drug will be formulated as a liquid suitable for hospital use in an intravenous drip. By directly injecting it into the cells (intracellular), the drug may be more potent. This may potentially benefit patients already in hospital with Covid.
However, the novel liquid formulation has not been tested, and the optimum dosage is unknown. The present Phase I aims to identify this, with Phase II further investigating the safety and efficacy of this drug.

CST-8:
The possible benefits are a reduced risk of hospitalisation or death.
Each of the drugs in the combination, when used individually, are drugs are currently licensed for the treatment of mild to moderate coronavirus disease (Covid-19), however, there is limited information about the use of the drugs in combination. This Phase I study aims to establish a safe dose that can be used in further research in a larger Phase II study.

CST-9:
This Phase II study aims to determine the safety and tolerability of ALG-097558 alone and in combination with the nucleoside analogue Remdesivir (RDV). ALG-097558 of 600 mg twice daily (Q12H) for 5 days in this study may result in clinically meaningful efficacy outcomes (e.g., shorter time to symptom resolution, reduction in viral load) in high-risk subjects with acute SARS-CoV-2 infection.

Where is the study run from?
The University of Liverpool is the sponsor of AGILE. Sites will be across the UK and be experienced clinical research facilities within NHS sites.

When is the study starting and how long is it expected to run for?
CST-2: Ended
CST-3A: Ended
CST-3B: Ended
CST-5: Ended
CST-6: Ended
CST-8: Ended
CST-9: Dec 2024 - July 2026

Who is funding the study?
CST-2: Ridgeback Biotherapeutics (the US-based company that manufactures and supplies EIDD-2801) and the National Institute for Health Research (UK)
CST-3A: Unitaid
CST-3B: Unitaid
CST5: GlaxoSmithKline/Vir-Biotechnology with further support from other funding streams
CST-6: UKRI MRC and DHSE
CST-8: UKRI MRC
CST-9: UKRI MRC, Wellcome Trust and Aligos Therapeutics

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
2020-001860-27

Integrated Research Application System (IRAS)
282781

ClinicalTrials.gov (NCT)
NCT04746183

Protocol serial number
UoL001542i, CPMS 45759, IRAS 282781

Study information

Scientific Title

AGILE master platform protocol - seamless Phase I/IIa platform for the rapid evaluation of candidates for COVID-19 treatment

Acronym

AGILE

Study objectives

Current hypothesis as of 04/05/2021:
Coronaviruses are a large family of viruses that cause illness ranging from the common cold to more severe disease. In late 2019 a novel coronavirus-induced disease (COVID-19) emerged in humans in Wuhan, China. This is caused by a new strain that has not been seen in humans before, novel coronavirus (SARS-CoV-2). The symptoms of COVID-19 include a combination of a fever, cough, difficulty breathing, muscle pain and tiredness.
About 19 out of 20 patients who get coronavirus get better without coming to hospital. Of those who are admitted to hospital, most also get better, but some may need oxygen or mechanical ventilation before they do so. However, a few percent do not get better. The progression from early symptoms to severe pneumonia requiring oxygen support or mechanical ventilation often takes one to two weeks. The virus is highly contagious and is causing an enormous strain on NHS resources. There are currently no approved drugs that prove to treat and improve the outcomes of people with COVID-19. There is therefore an urgent need to rapidly evaluate potential new treatments. The AGILE platform master protocol allows the incorporation of a range of identified and yet-to-be-identified candidates as potential treatments for adults with COVID-19 into the trial. Candidates will be added into the trial via candidate-specific trial (CST) protocols of the master protocol as appendices. Inclusion of new candidates will be determined by an independent COVID-19 Therapeutics Advisory Panel based on pre-clinical data, evidence in the clinical setting and GMP capabilities. The UK-CTAP will specify an appropriate set of doses to be evaluated for a given candidate, dictated by existing knowledge of the candidate from any prior use in humans. Each candidate will be evaluated in its own trial (within this master protocol), randomising between candidate and control with 2:1 allocation in favour of the candidate. Each dose will be assessed for safety sequentially in cohorts of 6 patients. Once a phase II dose has been identified efficacy will be assessed by seamlessly expanding into a larger cohort.

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Previous hypothesis:
Coronaviruses are a large family of viruses that cause illness ranging from the common cold to more severe disease. In late 2019 a novel coronavirus-induced disease (COVID-19) emerged in humans in Wuhan, China. This is caused by a new strain that has not been seen in humans before, novel coronavirus (SARS-CoV-2). The symptoms of COVID-19 include a combination of a fever, cough, difficulty breathing, muscle pain and tiredness.
About 19 out of 20 patients who get coronavirus get better without coming to hospital. Of those who are admitted to hospital, most also get better, but some may need oxygen or mechanical ventilation before they do so. However, a few percent do not get better. The progression from early symptoms to severe pneumonia requiring oxygen support or mechanical ventilation often takes one to two weeks. The virus is highly contagious and is causing an enormous strain on NHS resources. There are currently no approved drugs that prove to treat and improve the outcomes of people with COVID-19. There is therefore an urgent need to rapidly evaluate potential new treatments. The AGILE platform master protocol allows the incorporation of a range of identified and yet-to-be-identified candidates as potential

treatments for adults with COVID-19 into the trial. Candidates will be added into the trial via candidate-specific trial (CST) protocols of the master protocol as appendices. Inclusion of new candidates will be determined by the AGILE Scientific Advisory Board (SAB) based on pre-clinical data, evidence in the clinical setting and GMP capabilities. The AGILE SAB will specify an appropriate set of doses to be evaluated for a given candidate, dictated by existing knowledge of the candidate from any prior use in humans. Each candidate will be evaluated in its own trial (within this master protocol), randomising between candidate and control with 2:1 allocation in favour of the candidate. Each dose will be assessed for safety sequentially in cohorts of 6 patients. Once a phase II dose has been identified efficacy will be assessed by seamlessly expanding into a larger cohort.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 12/05/2020, West Midlands – Edgbaston Research Ethics Committee (3rd Floor Barlow House, Minshull Street, Manchester, M1 3DZ; +44 (0)20 7104 8122; Edgbaston.rec@hra.nhs.uk), ref: 20/WM/0136

Study design
Multicentre multi-arm multi-dose multi-stage open-label adaptive seamless Phase I/II Bayesian randomized platform trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
COVID-19 (SARS-CoV-2 infection)

Interventions
Current interventions as of 20/11/2024:

CST-2:
Phase I – Patients randomised to EIDD-2801 or standard of care (SOC). EIDD-2801 administered orally, twice daily (BID) for 10 doses (5 or 6 days). The starting dose was established based on safety and pharmacokinetics from a healthy volunteer study, sample size variable depending on dose escalation decisions, and patients recruited in cohorts of 6 patients and randomised in a 2:1 ratio between EIDD-2801 and SOC using permuted block randomisation. Patients are followed up until Day 29.

CST-2:
Phase II - Patients randomised to EIDD-2801 and SOC or Placebo and SOC. EIDD-2801 or placebo administered orally, twice daily (BID) for 10 doses (5 or 6 days). The dose of EIDD-2801 will be determined by the recommended dose from Phase I. Patients randomised 1:1 between EIDD-2801 and placebo using permuted block randomisation stratified by site. Patients are followed up until Day 29. 180 patients to be recruited.

CST-3:
(A) Healthy volunteers recruited in cohorts of twelve patients per cohort (36 patients max), with patients taking 1500 mg twice daily (max dose of 3500 mg total daily dose) of nitazoxanide. This trial has now completed recruiting and will move to CST-3B (COVID-19 patients) which is taking part internationally.

CST-5:
Phase I – patients randomised to VIR-7932 or placebo in cohorts of 3 with 8 patients each (total of 24 patients). This is a randomised and blinded 3:1 with doses of up to 500mg VIR-7832 will be evaluated. The doses will be either 50 mg, 150 mg or 500 mg or placebo. Administration will be via intravenous infusion.

CST-5:
Phase II – an additional 125 patients planned to be randomised 2:2:1 to VIR-7832, VIR-7831 or placebo of dose levels of 500mg for VIR-7832 or VIR-7831 or placebo. Patients will be followed up until Day 169.

CST-6:
A Randomized, Multicentre, Seamless, Adaptive, Phase I/II Platform Study to Determine the Phase II dose and to Evaluate the Safety and Efficacy of intravenous Favipiravir for the Treatment of COVID-19. Phase I: Multiple doses of IV Favipiravir will be administered by intravenous (IV) infusion over 1 hour. The dosing regimen will be every 12 hours for 7 days duration. The starting dose will be 600mg (BID), and dose escalations to 1200mg (BID), 1800mg (BID) and 2400mg (BID) are anticipated as well as a de-escalation dose of 300mg (BID) if necessary, with de-escalation and escalation guided by emerging safety data and decision by the Safety Review Committee (SRC). The duration of monitoring will be 29 days post-first dose.

CST-8:
A Randomised, Multicentre, Seamless, Adaptive, Phase I Platform Study to Determine the recommended Phase II dose and Evaluate the Safety and Efficacy of an antiviral combination of Molnupiravir and Paxlovid® for the Treatment of COVID-19. Molnupiravir 800mg twice a day (BD) in combination with Paxlovid® (300 mg nirmatrelvir + ritonavir 100 mg) twice a day (BD) for 5 days as starting dose, versus standard of care, with a de-escalation protocol reducing in increments of molnupiravir to 600 mg BD, then 400 mg BD if required. The dose of Paxlovid® will be fixed for all cohorts.

CST-9a:
A Multicentre, Adaptive Phase II Platform Trial to Evaluate the Safety, Efficacy and Virological response of ALG-097558 as monotherapy and in combination with Remdesivir in high-risk population for the Treatment of COVID-19 disease. Twice daily dose of ALG-097558 (monotherapy arm) versus the twice daily dose of ALG-097558 in combination with RDV (combination arm) versus standard-of-care therapy (SoC arm) with an early futility analysis.

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Previous interventions as of 05/01/2024:

CST-2: Phase I – Patients randomised to EIDD-2801 or standard of care (SOC). EIDD-2801 administered orally, twice daily (BID) for 10 doses (5 or 6 days). The starting dose established based on safety and pharmacokinetics from healthy volunteer study, sample size variable

depending on dose escalation decisions, patients recruited in cohorts of 6 patients and randomised in a 2:1 ratio between EIDD-2801 and SOC using permuted block randomisation. Patients are followed up until Day 29.

CST-2: Phase II - Patients randomised to EIDD-2801 and SOC or Placebo and SOC. EIDD-2801 or placebo administered orally, twice daily (BID) for 10 doses (5 or 6 days). Dose of EIDD-2801 will be determined by the recommended dose from Phase I. Patients randomised 1:1 between EIDD-2801 and placebo using permuted block randomisation stratified by site. Patients are followed up until Day 29. 180 patients to be recruited.

CST-3: (A) Healthy volunteers recruited in cohorts of twelve patients per cohort (36 patients max), with patients taking 1500 mg twice daily (max dose of 3500 mg total daily dose) of nitazoxanide. This trial has now completed recruiting and will move to CST-3B (Covid 19 patients) which is taking part internationally.

CST-5: Phase I – patients randomised to VIR-7932 or placebo in cohorts of 3 with 8 patients each (total of 24 patients). This is a randomised and blinded 3:1 with doses of up to 500mg VIR-7832 will be evaluated. The doses will be either 50 mg, 150 mg or 500 mg or placebo. Administration will be via intravenous infusion.

CST-5: Phase II – additional 125 patients planned to be randomised 2:2:1 to VIR-7832, VIR-7831 or placebo of dose levels of 500mg for VIR-7832 or VIR-7831 or placebo. Patients will be followed up until Day 169.

CST-6:
A Randomized, Multicentre, Seamless, Adaptive, Phase I/II Platform Study to Determine the Phase II dose and to Evaluate the Safety and Efficacy of intravenous Favipiravir for the Treatment of COVID-19

CST-8:
A Randomised, Multicentre, Seamless, Adaptive, Phase I Platform Study to Determine the recommended Phase II dose and Evaluate the Safety and Efficacy of an antiviral combination of Molnupiravir and Paxlovid® for the Treatment of COVID-19

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Previous intervention as of 04/05/2021:

CST-2: Phase I – Patients randomised to EIDD-2801 or standard of care (SOC). EIDD-2801 administered orally, twice daily (BID) for 10 doses (5 or 6 days). The starting dose established based on safety and pharmacokinetics from healthy volunteer study, sample size variable depending on dose escalation decisions, patients recruited in cohorts of 6 patients and randomised in a 2:1 ratio between EIDD-2801 and SOC using permuted block randomisation. Patients are followed up until Day 29.

CST-2: Phase II - Patients randomised to EIDD-2801 and SOC or Placebo and SOC. EIDD-2801 or placebo administered orally, twice daily (BID) for 10 doses (5 or 6 days). Dose of EIDD-2801 will be determined by the recommended dose from Phase I. Patients randomised 1:1 between EIDD-2801 and placebo using permuted block randomisation stratified by site. Patients are followed up until Day 29. 180 patients to be recruited.

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CST-5: Phase I – patients randomised to VIR-7932 or placebo in cohorts of 3 with 8 patients each (total of 24 patients). This is a randomised and blinded 3:1 with doses of up to 500mg VIR-7832 will be evaluated. The doses will be either 50 mg, 150 mg or 500 mg or placebo. Administration will be via intravenous infusion.

CST-5: Phase II – additional 125 patients planned to be randomised 2:2:1 to VIR-7832, VIR-7831 or placebo of dose levels of 500mg for VIR-7832 or VIR-7831 or placebo. Patients will be followed up until Day 169.

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Previous intervention:

CST-2: Phase I – Patients randomised to EIDD-2801 or standard of care (SOC). EIDD-2801 administered orally, twice daily (BID) for 10 doses (5 or 6 days). The starting dose established based on safety and pharmacokinetics from healthy volunteer study, sample size variable depending on dose escalation decisions, patients recruited in cohorts of 6 patients and randomised in a 2:1 ratio between EIDD-2801 and SOC using permuted block randomisation. Patients are followed up until Day 29

CST-2: Phase II - Patients randomised to EIDD-2801 and SOC or Placebo and SOC. EIDD-2801 or placebo administered orally, twice daily (BID) for 10 doses (5 or 6 days). Dose of EIDD-2801 will be determined by the recommended dose from Phase I. Patients randomised 1:1 between EIDD-2801 and placebo using permuted block randomisation stratified by site. Patients are followed up until Day 29. 180 patients to be recruited

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
EIDD-2801 (molnupiravir), nitazoxanide, VIR-7832, VIR-7831, ALG-097558, remdesivir

Primary outcome(s)
CST-2: Phase I:
1. Dose-limiting toxicity (DLT) using CTCAE version 5 (grades 3 and above) over 7 days
2. CTCAE grading related to platelets and/or lymphocytes
CST-2: Phase II:
1. Time to negative PCR measured using SARS-CoV-2 nose/throat swab at screening, Days 1, 3, 5, 8, 11, 15, 22 and 29

Key secondary outcome(s))
CST-2: Phase I:
1. AEs, SAEs, physical findings, vital signs and laboratory parameters at screening, Days 1, 3, 5, 8,

11, 15, 22 and 29
2. Concentrations of EIDD-2801 and EIDD-1931 in plasma measured using validated bioanalytical methods on Days 1 and 5
3. Qualitative (and quantitative when possible) PCR for SARS-CoV-2 by nasal swab (for viral titres PCR and virus characterisation) assessed at screening, Days 1, 3, 5, 8, 11, 15, 22 and 29
4. Patient-Reported Outcomes using FLU PRO Questionnaire on days 1, 3, 5, 8, 11, 15, 22 and 29
5. Score on the WHO Progression Scale at day 15 and 29
6. NEWS2 (based on vital signs – heart rate, BP, respiratory rate, temperature, oxygen saturation) assessed during on days 15 and 29
7. Mortality at Days 15 and 29 (time from randomisation to death)

CST-2: Phase II:
Measured using case report forms unless otherwise indicated:
1. PROMs (FLU-PRO) at day 15 and 29
2. Mortality at days 15 and 29
3. Time from randomisation to death (up to Day 29)
4. Time from randomisation to hospitalisation
5. Incidence of SpO_2 <92% (based on at least 2 consecutive recordings on the same day, lasting at least one day)
6. Duration (days) of oxygen use
7. Duration (days) of mechanical ventilation
8. Incidence of new mechanical ventilation use and duration (days) of new mechanical ventilation use
9. Actual versus planned candidate treatment received
10. NEWS2 assessed during study visit on Days 15 and 29 (change from baseline and actual scores)
11. Score on the WHO Progression Scale at day 15 and 29
12. AEs, SAEs, physical findings, vital signs and laboratory parameters at screening, Days 1, 3, 5, 8, 11, 15, 22 and 29

Completion date
31/07/2026

Eligibility

Key inclusion criteria
The CST protocol inclusion criteria will take precedence over the master protocol inclusion criteria. Patients are eligible to be included in the study only if all of the following criteria apply (as well as all criteria from the appropriate CST protocol):
1. Adults (≥18 years) with laboratory-confirmed* SARS-CoV-2 infection (PCR)
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 below) and male patients who are sexually active with WOCBP must agree to use a highly effective method of contraception from the first administration of trial treatment, throughout trial treatment and for the duration outlined in the candidate-specific trial protocol after the last dose of trial treatment
*If any CSTs are included in the community setting, the CST protocol will clarify whether patients with suspected SARS-CoV-2 infection are also eligible

Standard additional criteria that may be applied per CST protocol:
Group A (severe disease)
4.1. Patients with clinical status of Grades 5 (hospitalised, oxygen by mask or nasal prongs), 5 (hospitalised, on non-invasive ventilation, or high flow oxygen), 7 (hospitalised, intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200), 8 (hospitalised mechanical ventilation pO_2/FiO_2 <150 (SpO_2/FiO_2 <200) or vasopressors) or 9 (hospitalised, mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis or ECMO), as defined by the WHO Clinical Progression Scale
Group B (mild-moderate disease)
4.2. Ambulant or hospitalised patients with the following characteristics peripheral capillary oxygen saturation (SpO_2) >94% RA

Additional criteria specific to Candidate Specific Trial (CST-2) as of 30/11/2020 are:
5. Has signs or symptoms of COVID-19 that began within 5 days of 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 4th week

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Patients are excluded from the study if any of the following criteria apply (as well as all criteria from the appropriate CST protocol):
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 breastfeeding
4. Anticipated transfer to another hospital which is not a study site within 72 hours
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
N.B. The CST protocol exclusion criteria will take precedence over the master protocol exclusion criteria.
Additional criteria specific to Candidate Specific Trial (CST-2) as of 30/11/2020 are:
* The master protocol stipulates ‘Exclusion Criteria 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.
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 50x109/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.

Date of first enrolment
08/03/2020

Date of final enrolment
31/07/2026

Locations

Countries of recruitment
United Kingdom

England

South Africa

Study participating centre
NHS University Hospitals of Liverpool Group
Royal Liverpool University Hospital
Prescot Street
Liverpool
United Kingdom
L7 8XP

Study participating centre
Southampton General Hospital Clinical Research Facility
Southampton General Hospital
Tremona Road

Southampton
United Kingdom
SO16 6YD

Study participating centre
Central Manchester University Hospitals NHS Foundation Trust
Trust Headquarters, Cobbett House
Manchester Royal Infirmary
Oxford Road
Manchester
United Kingdom
M13 9WL

Study participating centre
Royal Free London NHS Foundation Trust
Royal Free Hospital
Pond Street
London
United Kingdom
NW3 2QG

Sponsor information

Organisation
University of Liverpool

ROR
https://ror.org/04xs57h96

Funder(s)

Funder type
Government

Funder Name
NIHR Southampton Clinical Trials Unit

Funder Name

Ridgeback Biotherapeutics

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Unitaid

Funder Name
GlaxoSmithKline

Alternative Name(s)
GlaxoSmithKline plc., GSK plc., GlaxoSmithKline plc, GSK

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Funder Name
Vir Biotechnology

Alternative Name(s)
Vir Biotechnology Inc, Vir Biotechnology, Inc., Vir

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Department of Health and Social Care

Alternative Name(s)
Department of Health & Social Care, DH

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Wellcome Trust

Alternative Name(s)
Wellcome, WT

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Funder Name
Aligos Therapeutics

Results and Publications

Individual participant data (IPD) sharing plan
Current IPD sharing plan as of 20/11/2024:
Individual participant data will be made available from each AGILE Candidate Specific Trial (CST) Protocol, including data dictionaries, for approved data-sharing requests. Individual participant data will be shared that underlie the results reported in any publications, after de-identification and normalisation of information (text, tables, figures, and appendices). The study protocol and statistical analysis plan will also be available. Anonymous data will be available for request from three months after the publication of the article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate, signed a Data Sharing Agreement. Data will be shared once all parties have signed relevant data-sharing documentation, covering the University of Liverpool's conditions for sharing. Proposals should be directed to livagile@liverpool.ac.uk.

Previous IPD sharing plan:
Individual participant data will be made available from each AGILE Candidate Specific Trial (CST) Protocol, including data dictionaries, for approved data-sharing requests. Individual participant data will be shared that underlie the results reported in any publications, after de-identification and normalisation of information (text, tables, figures, and appendices). The study protocol and statistical analysis plan will also be available. Anonymous data will be available for request from 3 months after the publication of the article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate, signed a Data Sharing Agreement. Data will be shared once all parties have signed relevant data-sharing documentation, covering SCTU conditions for sharing and if required, an additional Data Sharing Agreement from Sponsor. Proposals should be directed to ctu@soton.ac.uk.
In addition, when the database from each Candidate Specific Trial Protocol is locked, analysed and published we will make the data available to the academic community via www.clinicalstudydatarequest.com

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	Molnupiravir versus placebo in unvaccinated and vaccinated patients with early SARS-CoV-2 infection in the UK (AGILE CST-2): a randomised, placebo-controlled, double-blind, phase 2 trial	19/10/2022	24/10/2022	Yes	No
Protocol article	protocol	19/06/2020	03/12/2020	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes