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DEFINE - Evaluating therapies for COVID-19

Submission date 26/05/2020	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol
Registration date 22/07/2020	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 11/06/2026	**Condition category** Respiratory	[_] Individual participant data

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 has 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 minimize 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 key clinical feature is rapid respiratory failure requiring mechanical ventilation (MV). There are no known treatments for COVID-19. The most vulnerable in society may not survive or be suitable for MV. The pandemic is overwhelming health systems across the globe and has the potential to devastate regions of the world with poor public health and underdeveloped critical care. The anticipated scale of the epidemic is such that hospitals, and particularly intensive care facilities, may be massively overstretched and overwhelmed.

This study aims to support the re-purposing of promising pharmaceutical assets with prior use in humans through performing rapid experimental medicine feasibility studies in small groups of COVID-19 patients. The results of these studies will support further evaluation in existing national and international trial networks. The key interception is to prevent the lung damage in patients with COVID-19 that leads to respiratory failure.

Who can participate?
Patients aged 16 years or above who are COVID-19 positive.

What does the study involve?
Two treatments will be compared to standard care. Nafamostat (anti-viral and anti-coagulant) given for 7 days and TD139 (galectin 3 inhibitor) given for 14 days. Participants will be placed into groups randomly.

What are the possible benefits and risks of participating?
Benefits - There is no direct benefit. However, we believe the results of this research may bring potential benefits for similar patients in the future.
Risks - Blood sampling carries a small risk of bruising and discomfort, our doctors and nurses are very experienced in taking blood and will attempt to minimise this. If possible, the research team will use an existing line to minimise any discomfort.
Collecting samples from the throat and nasal passages can be a bit uncomfortable, this will be done as smoothly as possible and by doctors and nurses experienced in obtaining these samples.
All participants randomised to a treatment will be observed carefully for any side effects; however, there may be potential side-effects that have not previously been seen. These side effects may be mild or serious. Although the team do not anticipate this, in some cases, these side effects might be long lasting or permanent and may even be life threatening. If any negative change in the health of the patient is seen which may have an association with the treatment, the team will stop the treatment.
This trial will also involve up to two chest x-rays and CT scans. The scan of your heart and lungs are additional to those that would normally be taken. The scan uses ionising radiation to form images of the body. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. In patients with COVID-19, the chance of this happening is extremely small.

Where is the study run from?
University of Edinburgh (UK)

When is the study starting and how long is it expected to run for?
March 2020 to December 2022

Who is funding the study?
Life Arc (UK)

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT04473053

Clinical Trials Information System (CTIS)
2020-002230-32

Integrated Research Application System (IRAS)
282934

Protocol serial number
20/SS/0060

Study information

Scientific Title
DEFINE - Evaluating therapies for COVID-19

Acronym
DEFINE

Study objectives
This trial aims to support the repurposing of promising therapeutic assets with prior use in humans but without prior information on use in COVID-19, to determine the PK-PD profile of the agent, compared to standard of care supportive therapy, in small cohorts of COVID-19 patients. The results are intended to provide initial safety, pharmacokinetic and pharmacodynamic data and experimental medicine data to support further evaluation in existing national and international trial networks for candidates demonstrating appropriate impact on the dynamic marker of interest. The key interception is to mitigate the lung damage in patients with COVID-19 that leads to respiratory failure. As such, the assets in this programme will focus on abrogating putative mechanisms implicated in COVID-19 respiratory disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 03/07/2020, Scotland A REC (2nd Floor Waverley Gate, 2-4 Waterloo Place, Edinburgh, EH1 3EG, UK; +44 (0)131 4655678; manx.neill@nhslothian.scot.nhs.uk), ref: 20/SS/0066

Primary study design
Interventional

Study design
Current study design as of 22/09/2022:

The DEFINE Trial is a platform trial with new assets (treatments) being added via appendices.
Appendices 1 & 2 are Phase IB/Phase IIa interventional randomized controlled trial.
Appendix 3 is an early dose escalation safety trial phase ib/IIa interventional clinical trial (of and ATIMP).

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Previous study design:

Phase IB/Phase IIa interventional randomized controlled platform trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Prevention of lung injury in patients with COVID-19 (SARS-CoV-2 infection)

Interventions
Current interventions as of 09/09/2021, updated 22/09/2022:

Appendix 1 and 2 Interventions:
Patients will be divided into cohorts, a) community b) hospitalised requiring supplemental oxygen and c) hospitalised requiring assisted ventilation.

Two treatments will be compared to standard care. Nafamostat (anti-viral and anti-coagulant) and TD139 (galectin 3 inhibitor). For Nafamostat, it is intended that the licensed dose (0.2 mg/kg /h) in Japan will be used. Patients randomised to Nafamostat will receive a continuous intravenous infusion at 0.2 mg/kg/h for 7 days. If a participant is discharged from hospital or can no longer receive this treatment, the treatment will be stopped. For TD139, patients will inhale 5 mg x 2 (10 mg) twice daily for the first 48 h and then subsequently 5 mg x 2 (10 mg) once daily for the remaining 12 days. Unless a participant is discharged from hospital or can no longer use an inhaler – in which case treatment will be stopped at such time.

Randomisation will be performed using a web-based randomisation system (built in REDCap) hosted at the Edinburgh Clinical Trials Unit (ECTU) at the University of Edinburgh (a fully registered UKCRC CTU (registration #15)). Since these studies are designed to be small, this study will balance underlying risk across the allocations using the method of minimisation.

Follow up will be at 30, 60 and 90 days post treatment.

Appendix 3 Interventions:
Opened to recruitment Sep2022.

Appendix 3 will recruit participants satisfying cohort 2C (of the platform) - Confirmed COVID-19 positive patients with an oxygen saturation of 92% or above.

Appendix 3 of the DEFINE platform trial is not randomised, all recruited participants will receive the intervention (ATIMP).

11 participants (to a maximum of 20 participants) who have tested positive for SARS-CoV-2 within the last 2 weeks (within last 10 days at the point of screening) will receive an infusion of HLA matched SARS-CoV-2 Virus Specific T-cells (VST). The infusion will be administered in increasing doses, with the first 3 participants receiving the lowest dose (Total target cell dose = 1.5x10^6 cells), next 3 participants will receive the middle dose (Total target cell dose = 15x10^6 cells) and the last five participants will receive the highest dose (Total target cell dose = 150x10^6 cells) of VSTs. Participants will remain in hospital for a minimum of 48 hours following completion of the infusion. Follow up visits will be carried out up to and including day 7 post infusion for the period of time the participant remains in hospital. If discharged before day 7 the participant will attend the research clinic, or be offered a home visit, to carry out a day 7 follow up visit. Subsequent follow up visits will be carried out on day 14 (a telephone call), day 21 (a clinic or home visit) and 6 weeks (a telephone call) post infusion.

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Previous interventions:

Patients will be divided into cohorts, a) community b) hospitalised requiring supplemental oxygen and c) hospitalised requiring assisted ventilation.

Two treatments will be compared to standard care. Nafamostat (anti-viral and anti-coagulant) and TD139 (galectin 3 inhibitor). For Nafamostat, it is intended that the licensed dose (0.2 mg/kg /h) in Japan will be used. Patients randomised to Nafamostat will receive a continuous intravenous infusion at 0.2 mg/kg/h for 7 days. If a participant is discharged from hospital or can no longer receive this treatment, the treatment will be stopped. For TD139, patients will inhale 5 mg x 2 (10 mg) twice daily for the first 48 h and then subsequently 5 mg x 2 (10 mg) once daily for the remaining 12 days. Unless a participant is discharged from hospital or can no longer use an inhaler – in which case treatment will be stopped at such time.

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Follow up will be at 30, 60 and 90 days post treatment.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Nafamostat, TD139, SARS-CoV-2 VSTs

Primary outcome(s)
Appendices 1 & 2:
Safety of candidate agents as add-on therapy to SoC in patients with COVID-19 measured at 30,

60 and 90 days post-treatment using:
1. Haematological and biochemical safety laboratory investigations:
1.1. Haematology: Full blood count and differential white cell count
1.2. Coagulation: D-dimer, fibrinogen, activated partial thromboplastin time (aPTT), prothrombin time (PT), international normalised ratio (INR), Cd39, ecto-ADPase, nitrous oxide, PGI2, antithrombin, Thrombomodlin, protein c, EPCR, kallikrein.
1.3. Biochemistry: Random glucose, Urea and electrolytes (urea, sodium, potassium, chloride, magnesium, bicarbonate, creatinine); liver function tests (Total protein, albumin, globulin, total bilirubin, SGOT(AST), SGPT(ALT), GGT, LDH, alkaline phosphatase); C-reactive protein (CRP); ferritin; triglycerides; troponin; creatine kinase (MB fraction)
2. Physical examination performed at screening, including assessment of presenting symptoms. At subsequent assessments, a symptom-directed (targeted) physical examination will be performed as required by the condition of the patient and the presenting complaint
3. Vital signs (blood pressure/heart rate/temperature and respiratory rate)
4. Daily electrocardiogram (ECG) readings
5. Adverse events that are not related to the patient's underlying condition or clinical interventions will be recorded following consent. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment

(added 22/09/2022) Appendix 3:
To evaluate the safety of SARS-CoV-2 VSTs as add-on therapy to SoC in patients with COVID-19. Safety will be assessed using:
1. Haematological and biochemical safety laboratory investigations
2. Directed cardio-respiratory physical examination
3. Vital signs (blood pressure / heart rate / respiratory rate, temperature)
4. Adverse events

Key secondary outcome(s)

Appendices 1 & 2:
1. Pharmacokinetic (PK)/ pharmacodynamic (PD) information measured using daily blood samples
2. Response of key exploratory biomarkers during treatment period, namely IL-1β, IL-6, IL-8 and TNF-α, CXCL-10 and IL-1ra. Due to the nature of this research additional analytical tests may be developed or required in order to profile COVID-19 and develop therapies
3. Improvement or deteroriation of patients measured using WHO ordinal scale and NEWS2 score at 30, 60 and 90 days post treatment
4. Number of oxygen-free days measured at 30, 60 and 90 days post treatment.
5. Ventilator-free days and incidence and duration of any form of new ventilation use measured at 30, 60 and 90 days post treatment
6. SpO2/FiO2, measured daily from randomisation to Day 15, hospital discharge, or death
7. SARS-CoV-2 viral load measured using qualitative and quantitative polymerase chain reaction (PCR) determination of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in oropharyngeal/nasal/saliva swab while hospitalised on Days 1, 3, 5, 8, 11, 15
8. Time to discharge (days)
9. The use of renal dialysis or haemofiltration (not used/used and duration of use) at 30, 60 and 90 days post treatment

(added 22/09/2022) Appendix 3:
1. To evaluate the improvement or deterioration of patients. Assessed by changes to WHO ordinal scale and NEWS2 score
2. To evaluate the number of oxygen free days (duration (days) of oxygen use and oxygen free days)
3. Where oxygen is required, change in the ratio of the oxygen saturation to fraction of inspired

oxygen concentration (SpO2/FiO2), from baseline to 48 hours post infusion.
4. To evaluate time to discharge using duration of hospital stay due to COVID 19, and duration (days) to discharge following infusion.
Within this appendix we will also have the following non-essential secondary endpoint (data will be collected where available but are not essential to the core analysis):
To evaluate SARS-CoV-2 viral status by qualitative and quantitative polymerase chain reaction (PCR) determination of SARS-CoV-2 in oropharyngeal/nasal swab and/or saliva samples and/or blood samples.

Completion date
01/12/2023

Eligibility

Key inclusion criteria
Main inclusion criteria (all appendices)
1. Provision of informed consent
2. Aged at least 16 years
3. COVID-19 positive test (lateral flow followed by confirmatory PCR or PCR only) result within last 14 days
4. If the patient is of child bearing potential*, or is a male with a female partner with child bearing potential the patient, and their partner(s), agree to use medically-accepted contraception.

(added 22/09/2022) Appendix 3 Specific inclusion criteria:
For this Appendix all above inclusion criteria must be met. In addition, the following criteria must also be met:
1. Patient deemed capacitated to provide informed consent for themselves.
2. Maintaining oxygen saturations of ≥92% at time of screening and for 24 hours prior to commencement of infusion.
3. If the patient is of child bearing potential, or is a male with a female partner with child bearing potential, the patient, and their partner(s), agree to use a highly effective method of contraception for 4 weeks following the date of the infusion. Methods considered highly effective are those that achieve a failure rate of less than 1% per year when used consistently. This includes:
3.1. Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation
Oral
Intravaginal
Transdermal
3.2. Progesterone-only hormonal contraception associated with inhibition of ovulation:
Oral
Injectable
Implantable
3.3. Intrauterine device (IUD)
3.4. Intrauterine hormone-releasing system (IUS)
3.5. Bilateral tubal occlusion
3.6. Vasectomised partner
3.7. Sexual abstinence

Participant type(s)

Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
63

Key exclusion criteria
1. Current or recent history, as determined by the Investigator, of severe, progressive, and/or uncontrolled cardiac disease (NYHA class IV), uncontrolled renal disease (eGFR < 30 mL/min/1.73 m^2), severe liver dysfunction (ALT/AST > 5x ULN) or bone marrow failure (Hb < 8g/dL AND ANC < 0.5 mm^3 AND platelet count <50,000 µL)
2. Women who are pregnant or breastfeeding.
3. Participation in another clinical trial of an investigational medicinal product (CTIMP)
4. Known hypersensitivity to the IMP or excipients.
5. Pre-existing or concomittant use of off-label treatments for COVID-19

Date of first enrolment
03/07/2020

Date of final enrolment
22/12/2022

Locations

Countries of recruitment
United Kingdom

Scotland

Study participating centre
Western General Hospital
NHS Lothian
Edinburgh
Scotland
EH4 2XU

Study participating centre
Royal Infirmary Edinburgh
NHS Lothian

Edinburgh
Scotland
EH16 4SA

Study participating centre
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Study participating centre
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Sponsor information

Organisation
University of Edinburgh

ROR
https://ror.org/01nrxwf90

Organisation
NHS Lothian

ROR
https://ror.org/03q82t418

Funder(s)

Funder type
Charity

Funder Name
Life Arc

Results and Publications

Individual participant data (IPD) sharing plan
Data sharing is actively encouraged and the research team will provide data on request after a data sharing agreement is agreed

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		11/02/2022	07/11/2022	Yes	No
Protocol article		15/12/2021	17/12/2021	Yes	No
Basic results			11/06/2026	No	No
Funder report results			11/06/2026	No	No
HRA research summary			28/06/2023	No	No
Other publications	Narrative review	30/08/2022	01/08/2025	Yes	No
Preprint results		10/01/2022	07/11/2022	No	No
Protocol file	version 4	20/01/2021	11/06/2026	No	No