

DEFINE - Evaluating therapies for COVID-19

Submission date 26/05/2020	Recruitment status No longer recruiting	<input type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 22/07/2020	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
Last Edited 07/11/2022	Condition category Respiratory	<input type="checkbox"/> 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?

Dr Anya Bruce, Anya.Bruce@ed.ac.uk

Contact information

Type(s)

Public

Contact name

Dr Anya Bruce

Contact details

Queen's Medical Research Institute
Little France Crescent
Edinburgh
United Kingdom
EH16 4TJ

+44 (0)131 2429180
Annya.Bruce@ed.ac.uk

Additional identifiers

EudraCT/CTIS number
2020-002230-32

IRAS number
282934

ClinicalTrials.gov number
NCT04473053

Secondary identifying numbers
20/SS/0060, IRAS 282934

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

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).

Previous study design:

Phase IB/Phase IIa interventional randomized controlled platform trial

Primary study design

Interventional

Secondary study design

Randomised controlled trial

Study setting(s)

Hospital

Study type(s)

Treatment

Participant information sheet

Not available in web format, please use contact details to request a participant information sheet.

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 = 1.5×10^6 cells), next 3 participants will receive the middle dose (Total target cell dose = 15×10^6 cells) and the last five participants will receive the highest dose (Total target cell dose = 150×10^6 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.

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.

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.

Intervention Type

Drug

Phase

Phase II

Drug/device/biological/vaccine name(s)

Nafamostat, TD139, SARS-CoV-2 VSTs

Primary outcome measure

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, Thrombomodulin, 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

Secondary outcome measures

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-1 β , 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 deterioration 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.

Overall study start date

01/03/2020

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 $\geq 92\%$ 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

Age group

Adult

Sex

Both

Target number of participants

20 per arm. This will be driven by the particular asset. As this is a platform study, more assets will be added over time. The study will not recruit more than 200 patients. Appendices 1 and 2 (and SoC arm): 20 per arm.

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 m²), severe liver dysfunction (ALT/AST > 5x ULN) or bone marrow failure (Hb < 8g/dL AND ANC < 0.5 mm³ 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 concomitant 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**

Scotland

United Kingdom

Study participating centre

Western General Hospital

NHS Lothian

Edinburgh

United Kingdom

EH4 2XU

Study participating centre
Royal Infirmary Edinburgh
NHS Lothian
Edinburgh
United Kingdom
EH16 4SA

Study participating centre
St John's Hospital
NHS Lothian
Howden W Rd
Howden
Livingston
United Kingdom
EH54 6PP

Study participating centre
Queen Elizabeth University Hospital
1345 Govan Rd
Glasgow
United Kingdom
G51 4TF

Sponsor information

Organisation
University of Edinburgh

Sponsor details
Queen's Medical Research Institute
Little France Crescent
Edinburgh
Scotland
United Kingdom
EH16 4TJ
+44 (0)131 242 3330
ACCORD@nhsllothian.scot.nhs.uk

Sponsor type
University/education

Website
<http://www.accord.ed.ac.uk>

ROR

<https://ror.org/01nrxf90>

Organisation

NHS Lothian

Sponsor details

Queen's Medical Research Institute

Little France Crescent

Edinburgh

Scotland

United Kingdom

EH16 4TJ

+44 (0)131 242 3330

ACCORD@nhslothian.scot.nhs.uk

Sponsor type

Hospital/treatment centre

Website

<http://www.nhslothian.scot.nhs.uk/Pages/default.aspx>

ROR

<https://ror.org/03q82t418>

Funder(s)**Funder type**

Charity

Funder Name

Life Arc

Results and Publications**Publication and dissemination plan**

Scientific publications and the sharing of clinical data generated as part of this trial is crucial to better understanding COVID-19 and developing new treatments. As such, the results of each nested study detailed in the relevant appendices will be published as soon as the treatment arm has finished recruitment, data has been cleaned and any outstanding patient safety follow-ups completed.

Intention to publish date

01/05/2022

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?
Protocol article		15/12/2021	17/12/2021	Yes	No
Preprint results		10/01/2022	07/11/2022	No	No
Results article		11/02/2022	07/11/2022	Yes	No
HRA research summary			28/06/2023	No	No