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A therapeutic study in pre-ICU patients admitted with coronavirus using repurposed drugs

Submission date
15/05/2020

Recruitment status
No longer recruiting

Registration date
15/05/2020

Overall study status
Completed

Last Edited
05/03/2024

Condition category
Infections and Infestations

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] 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.

Current knowledge about severe COVID-19 related disease suggests that patients develop an over activation of their immune system in response to the infection, which may lead to organ. Several medications licensed for patients with autoimmune disease can be used to prevent such over activation of the immune response.

This trial plans to recruit patients at an early stage in the disease course, around early infection and when the patient is starting to show mild lung complications. The purpose is to prevent organ damage and reduce the need to transfer patients to ICU and for ventilated breathing support.

Who can participate?
Adults over 18 years, strongly suspected to have a COVID-19 related disease (with or without a positive COVID-19 test), who are suitable candidates for the intervention.

What does the study involve?
Participants will be randomly allocated to receive Baricitinib in addition to standard of care, or Ravulizumab in addition to standard of care, or standard of care only. Participants will be monitored for up to 14 days with follow up visits at day 28 and day 90 after the first dosing visit.

What are the possible benefits and risks of participating?
There are no known benefits of participating in this trial.
The effect of the drugs will be analysed during the trial to make efficient decisions about efficacy and futility (e.g. lack of efficacy and risk of harm) of the trial treatments. This enables us to stop recruiting if any serious risks arise.

Where is the study run from?
Addenbrookes Hospital (UK)

When is the study starting and how long is it expected to run for?
May 2020 to October 2021

Who is funding the study?
1. Eli Lilly and Company UK Ltd.
2. Alexion Pharmaceuticals UK

Who is the main contact?
Unfortunately, this study is not recruiting public volunteers at this time. This is because the research isn't ready for volunteers yet or the researchers are directly identifying volunteers in certain areas or hospitals. Please do not contact the research team as they will not be able to respond. For more information about COVID-19 research, visit the Be Part of Research homepage (https://bepartofresearch.nihr.ac.uk/).

Study website
https://cctu.org.uk/portfolio/COVID-19/TACTIC/

Contact information

Type(s)
Scientific

Contact name
Dr Joseph Cheriyan

ORCID ID
http://orcid.org/0000-0001-6921-1592

Contact details
Cambridge University Hospitals NHS Trust/Univ of Cambridge
Box 110, Level 3
ACCI Building
Cambridge University Hospitals NHS FT

Hills Rd
Cambridge
United Kingdom
CB2 0QQ
+44 (0)1223 336517
eh560@medschl.cam.ac.uk

Type(s)
Public

Contact name
Miss Elena Hernan Sancho

Contact details
Cambridge Clinical Trials Unit
Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital
Cambridge
United Kingdom
CB2 0QQ
+44 (0)1223 349132
cuh.cctu@nhs.net

Additional identifiers

EudraCT/CTIS number
2020-001354-22

IRAS number
282213

ClinicalTrials.gov number
NCT04390464

Secondary identifying numbers
CCTU0303; IRAS 282213

Study information

Scientific Title
mulTi-Arm Therapeutic study in pre-ICu patients admitted with Covid-19 – Repurposed Drugs (TACTIC-R)

Acronym
TACTIC-R

Study objectives
1. Immune modulatory therapy is superior to standard of care alone
2. Reduction of exaggerated host immune response to COVID-19 in patients at late stage 1/early stage 2 disease, reduces the composite of progression of these patients to organ failure or death and also reduces late sequelae of infection

3. Clinical and biochemical markers can be used to stratify each patient to an effective therapeutic agent and can report early on efficacy of the therapeutic approach

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 04/05/2020, East of England - Cambridge Central Research Ethics Committee (Royal Standard Place, Nottingham, NG1 6FS, UK; +44 (0)207 104 8388; cambridgecentral.rec@hra.nhs.uk), ref: 20/EE/0135

Study design
Randomized parallel arm open-label multicentre Phase IV platform trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
https://cctu.org.uk/portfolio/COVID-19/TACTIC/trials-open-to-recruitment/tactic-r

Health condition(s) or problem(s) studied
Late stage 1/stage 2 COVID-19-related disease, COVID-19 (SARS-CoV-2 infection)

Interventions
Eligible patients will be randomised to receive 1:1:1 to one of the following treatment arms (each in addition to standard of care (SoC))

Arm 1: Baricitinib oral tablets (4mg OD) in addition to standard of care
Arm 2: Ravulizumab intravenous infusion (single dose, weight-based dosing) in addition to standard of care
Arm 3: Standard of care

Randomisation will be carried out using a validated central automated web-based randomisation system.

Arm 1 Participants will be given 4mg of Baricitinib PO (2 x 2mg tables, once daily) on days 1-14 PO.
Dose adjustments for age and renal function.

Arm 2 Participants will receive Ravulizumab as a single intravenous infusion, Ravulizumab weight-based dosing regimen:
Body weight range (kg) Dose (mg)

≥ 40 to < 60 2,400
≥ 60 to < 100 2,700
≥ 100 3,000

Duration of follow up:
There will be two follow up visits at day 28 and day 90 after the first dosing visit.

Assessments will include the following:
• Discharge status
• Vaccination status (for ravulizumab arm only)
• Return to normal function status (numeric rating scale 0-10)
• Mortality status
• Adverse event reporting
• ECOG and MRC scores

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Baricitinib, ravulizumab

Primary outcome measure
Time to incidence (up to Day 14) of the composite endpoint of:
1. Death
2. Mechanical ventilation
3. Extracorporeal membrane oxygenation
4. Cardiovascular organ support (balloon pump or inotropes)
5. Renal failure (estimated creatinine clearance (by Cockcroft-Gault formula) <15 ml /min/1.73 m2), haemofiltration or dialysis
All measured using patient records

Secondary outcome measures
Measured using patient records:
1. Change in clinical status as assessed on 7-point ordinal scale compared to baseline
2. Time to each of the individual endpoints of the composite primary outcome measure
3. Proportion of patients with adverse events of special interest in each treatment arm
4. Time to Sp02 >94% on room air (excluding chronically hypoxic individuals)
5. Time to first negative SARS-CoV2 PCR
6. Duration of oxygen therapy (days)
7. Duration of hospitalisation (days)
8. All cause mortality at day 28
9. Time to clinical improvement (defined as >2 point improvement from day 1 on 7-point ordinal scale)

Pulmonary 7-point scale:
1 Death
2 Mechanical Ventilation or ECMO
3 Non-invasive ventilation or high flow oxygen

4 Low flow oxygen
5 Hospitalised – no oxygen
6 Discharged; normal activities not resumed
7 Discharged; normal activities resumed

Overall study start date
01/05/2020

Completion date
01/10/2021

Eligibility

Key inclusion criteria
1. Be aged 18 years and over
2. Have clinical picture strongly suggestive of COVID-19-related disease (with/without positive COVID-19 test) AND
2.1. Risk count (as defined above) >3 OR
2.3. Risk count 3 if risk count includes “Radiographic severity score >3”
3. Be considered an appropriate subject for intervention with immunomodulatory in the opinion of the investigator
4. Be able to be maintained on venous thromboembolism prophylaxis or current maintenance therapy during inpatient dosing period, according to local guidelines

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
375

Total final enrolment
417

Key exclusion criteria
1. Inability to supply direct informed consent from patient or from Next of Kin or Independent Healthcare Provider on behalf of patient
2. Mechanical ventilation at time of prior to dosing
3. Contraindications to study drugs, including hypersensitivity to the active substances or any of the excipients
4. Currently on any of the study investigational medicinal products
5. Known unresolved Neisseria meningitidis infection

6. Unwilling to be vaccinated against Neisseria meningitidis or receive prophylactic antibiotic cover until 2 weeks after vaccination
7. Known active tuberculosis (no blood screening required)
8. Known active Hepatitis B or C (no blood screening required); active varicella zoster.
9. Concurrent participation in any interventional clinical trial including COVID-19-related disease trials (observational studies allowed)
10. Patient moribund at presentation or screening
11. Pregnancy at screening (or unwillingness to adhere to pregnancy advice in protocol)
12. Unwillingness to adhere to breastfeeding advice in protocol.
13. Either alanine transaminase or aspartate transaminase (ALT or AST) > 5 times the upper limit of normal
14. Stage 4 severe chronic kidney disease or requiring dialysis (i.e. Cockcroft Gault estimated creatinine clearance < 30 ml /min/1.73 m2)
15. Currently receiving probenecid or chronic IVIG treatment
16. Any medical history or clinically relevant abnormality that is deemed by the principal investigator and/or medical monitor to make the patient ineligible for inclusion because of a safety concern

Date of first enrolment
07/05/2020

Date of final enrolment
22/06/2021

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Addenbrookes Hospital
Cambridge University Hospitals NHS Foundation Trust
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
King’s College Hospital
Kings’ College Hospital NHS Foundation Trust
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
Guy's and St Thomas's Hospital
Guy's and St Thomas's NHS Foundation Trust
Great Maze Pond
London
United Kingdom
SE1 9RT

Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation Trust

Sponsor details
Hills Road
Cambridge
England
United Kingdom
CB2 0QQ
+44 (0)1223 254472
cuh.cctu@nhs.net

Sponsor type
Hospital/treatment centre

Website
https://www.cuh.org.uk/cctu

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Industry

Funder Name
Eli Lilly and Company

Alternative Name(s)
Lilly, Eli Lilly & Company, Eli Lilly & Co., Eli Lilly And Co

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Funder Name
Alexion Pharmaceuticals

Alternative Name(s)
Alexion

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.
The protocol (not peer reviewed) available at the study website.
Ownership of the data arising from this trial resides with the trial team and the sponsor. On completion of the trial the data will be analysed and tabulated and a Final Trial Report prepared. However, given the nature of this international pandemic, preliminary data may be reported prior to the completion the study, or if interim analyses are adequate for dissemination of critical safety or efficacy data. Any bloods done as part of the protocol or as part of observational studies will need to adhere to the pre-agreed publications policy of the TACTIC core research trial team. The sponsor will provide, if practicable, advanced notice of any publications to Alexion Pharma UK. At conclusion of the study a fully anonymised dataset will be placed in the public domain. Data sharing within a federated consortium of UK investigators across the four nations will be adopted.

Intention to publish date
01/05/2023

Individual participant data (IPD) sharing plan

Full individual participant data (deidentified) will be available to researchers who provide a methodologically sound proposal, available for 24 months after publication of the trial. Proposals should be directed to Dr Frances C Hall (fch22@medschl.cam.ac.uk). Data requestors will need to sign a data access agreement. Data will be shared via a secure data access system.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	08/07/2020	10/07/2020	Yes	No
HRA research summary			28/06/2023	No	No
Results article		14/11/2023	05/03/2024	Yes	No