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# A platform to investigate the safety and effectiveness of several new medicines for the treatment of COVID-19 in hospitalised patients

**Submission date**
11/09/2020

**Recruitment status**
No longer recruiting

**Registration date**
24/09/2020

**Overall study status**
Completed

**Last Edited**
06/11/2023

**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
At hospitals across the UK, universities, companies making medicines, and the UK Government are working together to see if existing treatments for other conditions or diseases or new drugs may be used to treat people with COVID-19.
To do this, several treatments will be tested, one at a time, in people with COVID-19. Some treatments act directly against the virus when it gets into the body. Other treatments help the body's immune system (the natural defence against viral infections) to work better.
As each treatment is tested in people with COVID-19, a group of doctors and researchers will look at the results to see whether it works and how safe it is.
The medicines used will be tested in 2 stages: Stage 1 and Stage 2
Stage 1 will test how safe the medicines are when given with standard-of-care. Stage 1 will also look at whether the medicines work to improve symptoms of COVID-19. The information gathered from Stage 1 will be used to see if the medicines should continue to be tested in Stage 2 of the study.
Stage 2 will continue to look at whether the medicines work when given with standard-of-care and how safe it is. Stage 2 will further look at the effects of the medicines on the disease, such as collecting information on whether symptoms have improved, if care in the intensive care unit is needed, and survival and health status after recovery. In Stage 2, the study doctor and researchers are investigating if the medicines work to lessen the symptoms of COVID-19 or shorten the time people with COVID-19 are ill.

Who can participate?
Patients are being invited to take part in the research study because they have been feeling unwell with symptoms caused by a virus, and their health needs to be looked after in hospital. The virus is called SARS-CoV-2 (severe acute respiratory syndrome-coronavirus 2). The disease that the virus causes in infected people is called COVID-19.

What does the study involve?
Patients participating in the trial will be asked to take part in either Stage 1 or Stage 2 of the study. The patient will have some tests and assessments conducted to check that the study is

right for them. If the study is right for the patient, the treatment phase of the study will begin and will last for about 15 days.
The patient will be randomly assigned (by chance) to receive either the study drug with standard-of-care or standard-of-care only.
The patient will have some tests and assessments performed daily while they are in the hospital. These include a check of their health and whether they need oxygen, and taking blood and throat /nose swab samples to check their health. Some of the tests and assessments being done in this study would also be done as part of the standard-of-care for COVID-19, even if they did not participate in this study.
During the treatment period, blood, saliva (spit), or throat/nose swab samples will also be taken for exploratory research.

Once the patient has been discharged from the hospital, they will be asked to come back to the hospital on Day 15 and Day 29, if possible. At these visits, some of the previous tests and assessments will be repeated. If the patient is unable to return to the hospital due to being quarantined or for other safety reasons, some of the tests and assessments may be done by telephone or the hospital may arrange for a home visit by a member of the study team.

After the treatment period, the patient may be asked to return to the hospital on Day 60 (after 2 months) and Day 90 (after 3 months). This is to check how they are doing and if they have had any side effects from the study drug. Additional blood samples may also be taken for exploratory research.
Alternatively, the patient may be contacted by a member of the study team by telephone or they may visit them at home on these days.

What are the possible benefits and risks of participating?
Benefits: Participation in the research will help research efforts to understand COVID-19 and for the development of drugs and tests that could help many other people in the future.
Risks: All medicines may cause some side effects in some people. It is possible that the symptoms will not improve during the study or may even worsen. The study drugs may also involve risks to future health that we currently don’t know about. These will be discussed with participants by the treating doctor.
There are other risks associated with the COVID-19 infection and the use of supplemental oxygen, but they are not specific to this study.

Where is the study run from?
The University Hospital Southampton NHS Foundation Trust is the Sponsor for this study.

When is the study starting and how long is it expected to run for?
April 2020 to September 2021.

Who is funding the study?
UK Research and Innovation (UKRI)

Who is the main contact?
Professor Tom Wilkinson, t.wilkinson@soton.ac.uk

# Contact information

**Type(s)**
Scientific

### Contact name
Prof Tom Wilkinson

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## Additional identifiers

### Clinical Trials Information System (CTIS)
2020-001736-95

### Integrated Research Application System (IRAS)
282769

### ClinicalTrials.gov (NCT)
Nil known

### Protocol serial number
CPMS 45616, IRAS 282769

## Study information

### Scientific Title
ACCORD 2: a multicentre, seamless, Phase 2 adaptive randomisation platform study to assess the efficacy and safety of multiple candidate agents for the treatment of COVID-19 in hospitalised patients

### Acronym
COVID-19 - ACCORD-2

### Study objectives
The primary hypothesis at Stage 1 is time to response (2-point improvement in the 9-point ordinal scale, live discharge from hospital, or considered fit for discharge, as analysed at Day 29) of the candidate arm is shorter than the SoC.

The primary hypothesis at Stage 2 is time to response (as analysed at Day 29) of the candidate arm is shorter than the SoC.

### Ethics approval required
Old ethics approval format

### Ethics approval(s)

Approved 24/04/2020 South Central – Oxford C Research Ethics Committee (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)207 972 2496; oxfordc.rec@hra.nhs.uk), ref: 20/SC/0201

## Study design
Interventional randomized controlled trial

## Primary study design
Interventional

## Study type(s)
Treatment

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

## Interventions
The study consists of 2 stages:
• Stage 1 of the study (evaluation/pilot) will evaluate the candidate agents as an add-on to the SoC to assess preliminary safety and efficacy. A patient will be considered to be a responder if they show an improvement of at least 2 points (from randomisation) on a 9-point category ordinal scale, are discharged from hospital, or are considered fit for discharge (a score of 0, 1, or 2 on the ordinal scale), whichever comes first, by Day 29. The time to response will be analysed on Day 29 and used to evaluate if an agent should proceed to Stage 2 of the study. Stage 1 data will additionally be used to determine optimal study endpoints, and the number of patients to enrol into Stage 2 of the study.

• Stage 2 of the study (confirmation) is intended to provide confirmatory data of the identified candidate agents from Stage 1, to fully evaluate disease outcomes, including severe AEs, overall AEs, AESIs, disease-related co-infection complications (eg, pneumonia, septic shock), and overall mortality in an expansion stage. Patients and outcomes from Stage 1 will not form part of Stage 2.

Some candidate agents will still be in Stage 1 of the study at the point where other candidate agents have progressed to Stage 2.

First dose of candidate agent must take place within 72 hours of investigator receipt of laboratory or validated point of care test confirmation of SARS-CoV-2 infection. This may include results from a test that was performed prior to hospital admission if, in the opinion of the Investigator, it is relevant to ongoing COVID-19 infection. Any exceptions to this must be authorised by the Chief Investigator or delegate.

Patients will be randomised to receive one of the candidate agents that is being evaluated at the time of randomisation and whose inclusion/exclusion criteria they meet (as an add-on to SoC) or to a control arm where only SoC is administered.

In each stage of the study, patients will be screened on Day -1 or Day 1, and will remain in the hospital from Day 1 until fit for discharge. Dosing with the candidate agent (as an add-on to SoC) will commence on Day 1. The last day of assessments, while hospitalised, will be on Day 29. An outpatient visit will be conducted on Day 60 (±4 days), with an end-of-study visit conducted on Day 90 (±6 days).

Enrolment of patients will be continuous throughout the study for each candidate agent until the total randomisation number of planned patients for Stage 1 and Stage 2 is achieved. Enrolment under a sub-protocol for a specific candidate agent may also be stopped in the event of success or failure of the candidate agent. The Master Protocol will continue enrolling patients as long as there are candidate agents that are enrolling. It is estimated that up to 1800 patients will participate in the overall study.

Dosage of candidate agents:
Bemcentinib
Bemcentinib will be administered as a 400-mg oral loading dose on Days 1,2,and 3 followed by 200 mg once-daily oral maintenance dose for a total of 15 days. Bemcentinib should be taken once per day.

MEDI3506
MEDI3506 will be administered to participants as a single 300-mg IV dose.

Acalabrutinib
100 mg per day starting on Day 1 and continuing until Day 10.

Zilucoplan
Once-daily subcutaneous injection of 32.4 mg zilucoplan for maximum 15 days.

## Intervention Type
Drug

## Phase
Phase II

## Drug/device/biological/vaccine name(s)
Bemcentinib, tozorakimab (MEDI3506), acalabrutinib, zilucoplan

## Primary outcome(s)
Time to clinical improvement of at least 2 points (from randomisation) on a 9 point category ordinal scale, live discharge from the hospital, or considered fit for discharge (a score of 0, 1, or 2 on the ordinal scale), whichever comes first, by Day 29 (this will also define the “responder” for the response rate analyses)

## Key secondary outcome(s))
Measured from patient records unless otherwise noted:
1. The proportion of patients not deteriorating according to the ordinal scale by 1, 2, or 3 points on Days 2, 8, 15, 22, and 29
2. Duration (days) of oxygen use and oxygen-free days
3. Duration (days) of ventilation and ventilation-free days
4. Incidence of any form of new ventilation use and duration (days) of new ventilation use
5. Qualitative and quantitative polymerase chain reaction (PCR) determination of severe acute respiratory syndrome coronavirus 2 (SARS CoV 2) in oropharyngeal/nasal swab while hospitalised on Days 1, 3, 5, 8, 11, 15, and (optional) Day 29
6. Response rate (number and %) by treatment arm at Days 2, 8, 15, 22, and 29
7. Time to live discharge from the hospital
8. Mortality at Days 15, 29, and 60
9. Time from treatment start date to death

10. Change in the ratio of the oxygen saturation to fraction of inspired oxygen concentration (SpO2/FiO2), measured daily from randomisation to Day 15, hospital discharge, or death
11. Safety of candidate agents measured using:
11.1. Physical examination
11.2. Clinical laboratory examinations
11.3. Vital signs (blood pressure/heart rate/temperature/respiratory rate)
11.4. Adverse events
12. Duration (days) of ICU and hospitalisation
13. NEWS2 assessed daily while hospitalised and on Days 15 and 29
14. Time to a NEWS2 of ≤2, maintained for at least 24 hours

Exploratory:
1. Qualitative and quantitative PCR determination of SARS CoV 2 in blood and saliva (while hospitalised) on Days 1, 3, 5, 8, 11, 15, and (optional) Day 29 (may become a secondary endpoint once the assays are available). Analysis of samples collected at baseline prior to treatment and at specific time points

Bemcentinib sub-protocol specific key endpoints:
1. The proportion of patients not deteriorating according to the ordinal scale by 1, 2, or 3 points on Days 2, 8, 15, 22, and 29
2. Duration (days) of oxygen use and oxygen-free days
3. Duration (days) of ventilation and ventilation-free days
4. Incidence of any form of new ventilation use and duration (days) of new ventilation use
5. Qualitative and quantitative polymerase chain reaction (PCR) determination of severe acute respiratory syndrome coronavirus 2 (SARS CoV 2) in oropharyngeal/nasal swab while hospitalised on Days 1, 3, 5, 8, 11, 15, and (optional) Day 29
6. Qualitative and quantitative PCR determination of SARS CoV 2 in blood and saliva (while hospitalised) on Days 1, 3,5, 8, 11, 15, and (optional) Day 29 (may become a secondary endpoint once the assays are available)

### Completion date
04/09/2021

## Eligibility

### Key inclusion criteria
1. Adults (≥18 years) with SARS-CoV-2 infection confirmed by laboratory tests and/or point of care tests
2. A score of Grade 3 to 5 on the 9-point ordinal scale.
3. Is a woman who is not of childbearing potential or The patient, and their partner(s), agree to use medically-accepted double-barrier methods of contraception (e.g., barrier methods, including male condom, female condom or diaphragm with spermicidal gel) during the study and for at least 6 weeks after termination of study therapy
4. Ability to provide informed consent signed by the study patient or legally authorised representative.

### Participant type(s)
Patient

### Healthy volunteers allowed
No

## Age group
Adult

## Lower age limit
18 years

## Sex
All

## Total final enrolment
97

## Key exclusion criteria
1. Patients who have previously had a score of 6 or 7 on the 9-point ordinal scale
2. Any patient whose interests are not best served by study participation, as determined by a senior attending clinician
3. Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >5 × the upper limit of normal (ULN)
4. Known active infection with HIV or hepatitis B or C
5. Stage 4 severe chronic kidney disease or requiring dialysis (ie, estimated glomerular filtration rate <30 ml/min/1.73 m²)
6. History of the following cardiac conditions:
6.1. Myocardial infarction within 3 months prior to the first dose
6.2. Unstable angina
6.3. History of clinically significant dysrhythmias (long QT features on electrocardiogram [ECG], sustained bradycardia [≤55 bpm]), left bundle branch block, cardiac pacemaker or ventricular arrhythmia) or history of familial long QT
7. Screening 12-lead ECG with a measurable QTc interval according to Fridericia correction (QTcF) > 500 ms
8. Anticipated transfer to another hospital that is not a study centre within 72 hours
9. Allergy to any study medication
10. Experimental off-label usage of medicinal products as treatments for COVID-19
11. Patients participating in another clinical study of an investigational medicinal product

Sub-protocol for candidate agent Bemcentinib:
Additional exclusion criteria that are specific to the subprotocol are as follows:
12. Inability to swallow capsules (administration via nasogastric tube is permitted)
13. Current treatment with any agent known to cause QT prolongation. The treatment can be discontinued, with sufficient time (5 half lives) for washout, to allow inclusion of the patient
14. Screening 12-lead ECG with a measurable QTc interval according to Fridericia correction (QTcF) >450 ms
15. Clinically significant hypokalaemia. Individuals who do not meet this criterion may be rescreened once
16. Therapeutic anticoagulation with vitamin K antagonists. Note: Patients receiving low doses prescribed to maintain the patency of venous access devices may be included.
17. Previous bowel resection that would interfere with drug absorption

## Date of first enrolment
08/05/2020

**Date of final enrolment**
08/05/2021

# Locations

**Countries of recruitment**
United Kingdom

England

**Study participating centre**
**MEU Solution Ltd**
The Langley Building
Southmoor Road
Wythenshawe
United Kingdom
ME23 9QZ

# Sponsor information

**Organisation**
University Hospital Southampton NHS Foundation Trust

**ROR**
https://ror.org/0485axj58

# Funder(s)

**Funder type**
Industry

**Funder Name**
BerGenBio AS

# Results and Publications

**Individual participant data (IPD) sharing plan**
All data generated or analysed during this study will be included in the subsequent results publication

## IPD sharing plan summary

Other

## Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Results article | | 02/10/2023 | 06/11/2023 | Yes | No |
| Protocol article | | 31/07/2020 | 13/08/2021 | Yes | No |
| HRA research summary | | | 28/06/2023 | No | No |
| Participant information sheet | Participant information sheet version v2 | 11/11/2025 | 11/11/2025 | No | Yes |
| Protocol file | | 25/06/2020 | 24/09/2020 | No | No |