ISRCTN53038326 https://doi.org/10.1186/ISRCTN53038326

IMU838 and oseltamivir in the treatment of COVID-19

Submission date
01/09/2020

Recruitment status
No longer recruiting

Registration date
23/09/2020

Overall study status
Completed

Last Edited
16/10/2024

Condition category
Infections and Infestations

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

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 April 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 aim of this study is to investigate whether the use of a new medication (IMU-838) taken alongside an already approved medication used to treat viruses (oseltamivir, commonly known as Tamiflu, which is used to treat influenza) improves the time it takes to recover from COVID-19. IMU-838 has demonstrated beneficial effects in treating autoimmune and chronic inflammatory diseases (e.g. rheumatoid arthritis). It has been shown to be safe and well-tolerated, with minimal side effects reported. It is not yet known if this new drug will be effective in treating COVID-19, but there is promising evidence to suggest that they may be, particularly when used together with oseltamivir.

Who can participate?
Adult patients with suspected or confirmed COVID-19

What does the study involve?
Following the consent and screening participants will be allocated at random (like rolling a dice) into one of the two possible treatment options: IMU-838 plus oseltamivir, or oseltamivir alone. Both treatments will be given by mouth, in tablet form, twice a day for 14 days. If participants

are discharged before 14 days they can continue treatment at home, as advised by the healthcare team. The treatments given are in addition to the standard care they will receive during the stay in hospital. In order to monitor participants throughout the study, the researchers will collect follow up information from them or their hospital records while they are taking the treatment and for 14 days after they have finished. This information will be collected by individuals who are authorised to access patient health records and may involve a doctor or research nurse contacting participants by telephone once they have been discharged to ask a few questions and to monitor their progress and health.

What are the possible benefits and risks of participating?
There may or may not be medical benefits from taking part in this study. It is hoped that the treatment may reduce the symptoms associated with COVID-19 and speed up recovery, but this cannot be guaranteed. Participation in this study may benefit future patients with COVID-19.

Where is the study run from?
University Hospitals Coventry and Warwickshire NHS Trust (UK)

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

Who is funding the study?
1. LifeArc (UK)
2. Immunic AG (Germany)

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.

Contact information

Type(s)
Scientific

Contact name
Mr Shivam Joshi

Contact details
Research & Development
4th Floor Rotunda, ADA40006
University Hospitals Coventry & Warwickshire
Clifford Bridge Road
Walsgrave
Coventry
United Kingdom
CV2 2DX

Type(s)
Scientific

Contact name
Prof Ramesh Arasaradnam

Contact details
Division of Surgery/Gastroenterology
University Hospitals Coventry & Warwickshire NHS Trust
University of Warwick/Coventry University
Clifford Bridge Road
Coventry
United Kingdom
CV2 2DX

Additional identifiers

EudraCT/CTIS number
2020-001805-21

IRAS number
282532

ClinicalTrials.gov number
NCT04516915

Secondary identifying numbers
CPMS 45777, IRAS 282532

Study information

Scientific Title
Prospective, randomized, parallel-group, open-label study to evaluate the efficacy and safety of IMU-838, in combination with oseltamivir, in adults with coronavirus disease COVID-19

Acronym
IONIC

Study objectives
HO: There will be no significant difference in time to clinical improvement in patients on IMU-838 + oseltamivir and standard hospital care, in comparison with oseltamivir + standard hospital care, in adults with COVID-19.
HA: Time to clinical improvement will be significantly better in patients on IMU-838 + oseltamivir and standard hospital care, in comparison with oseltamivir + standard hospital care, in adults with COVID-19.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 15/05/2020, Wales Research Ethics Committee 1 Cardiff (Health and Care Research Wales, Castlebridge 4 15-19, Cowbridge Road East, Cardiff, CF11 9AB, UK; +44 (0)2920 785738; Wales.REC1@wales.nhs.uk), REC ref: 20/WA/0146

Study design
Randomized; Interventional; Design type: Treatment, Drug

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 the contact details to request a patient information sheet

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

Interventions
This study comprises of a screening period, a 14-day treatment period, and up to a 14-day follow-up period evaluating the efficacy of the IONIC intervention in comparison to oseltamivir alone. All participants will receive standard care in addition to the IONIC intervention or oseltamivir, consistent with WHO recommendations.

As this is a Phase 2b trial, clinical improvement (based on the 7-point ordinal scale) is considered an acceptable outcome measurement in line with the WHO's recommendations on research and development for COVID-19.1 The WHO also recommends assessing mortality, which is a secondary endpoint in the present trial.

The lead site of the study is University Hospital Coventry and Warwickshire NHS Trust. The study will be initiated as a single-centre trial, however, depending upon recruitment rate as well as the information gathered from the interim analysis, the study may include other NHS trusts interested in participating.

Study groups:
1. Control group: oseltamivir 75 mg BID and standard care
2. Interventional group: IMU-838 (22.5 mg BID) plus oseltamivir 75 mg BID and standard care (IONIC intervention)

All patients will receive standard care as necessary (e.g. supplemental oxygen, non-invasive and invasive ventilation, antibiotic agents, vasopressor support and renal-replacement therapy) as required and determined by local practice. After Day 14, all patients will continue with appropriate standard care as decided by the clinical care team.

Patient identification/screening
Patients who have been either diagnosed or awaiting test for COVID-19 will be briefly informed about the study. They will be offered a participant information sheet (PIS) at this time detailing this study. Posters and PISs will also be available to view or collect respectively in the clinical area. Interested patients will be referred to a member of the research team who will perform initial screening as per the inclusion and exclusion criteria, explain the study in more detail and answer any questions. Patients will be given appropriate time between being introduced to the study and consenting.

Screening
Hospitalised patients meeting the eligibility criteria will be included in the trial. The following information will be recorded by the attending clinician or delegate:
1. Patient details (e.g. name, NHS number, date of birth, sex)
2. Relevant clinical history
3. COVID-19 symptom onset date
4. COVID-19 severity as assessed by the need for supplemental oxygen or ventilation /extracorporeal membrane oxygenation
5. Major comorbidity (e.g. chronic liver disease)
6. Date of hospitalisation
7. Contraindication to the study drug regimens (in the opinion of the attending clinician)
8. Pregnancy test
9. Blood test (liver function test)*
*If not conducted as part of standard care

Consent
Informed consent should be obtained from each patient before enrolment into the study. However, if the patient lacks the capacity to give consent due to the severity of their medical condition (e.g. acute respiratory failure or need for immediate ventilation), then consent may be obtained from a relative acting as the patient's legally designated representative. Further consent will then be sought with the patient if they recover sufficiently.

Due to the poor outcomes in COVID-19 patients who require ventilation (>90% mortality in one cohort), patients who lack the capacity to consent due to severe disease (e.g. needs ventilation), and for whom a relative to act as the legally designated representative is not immediately available, randomisation and consequent treatment will proceed with consent provided by a treating clinician (independent of the clinician seeking to enrol the patient) who will act as the legally designated representative. Consent will then be obtained from the patient's personal legally designated representative (or directly from the patient if they recover promptly) at the earliest opportunity.

Randomisation
Variable block randomisation will be carried out using an online validated randomisation sequence generator, as part of the Electronic Data Capture (EDC) system where the treatment allocation will be recorded (https://helpdesk.castoredc.com/article/50-the-randomization-algorithm-in-castor). The block sizes to be used in the randomisation sequence will be selected by the trial statistician.

Participants will be randomized on a 1:1 basis to the IONIC intervention (IMU-838 [22.5 mg BID] plus oseltamivir (75 mg BID) and standard care) or control group (oseltamivir (75 mg BID plus) standard care), stratified by centre, age and sex.

Written consent for entry into the trial must be obtained prior to randomization. Pre-randomization eligibility checks will be carried out to ensure that potential participants meet the eligibility criteria and are not randomized in error. Data validation will also be built into the EDC system to prevent randomization unless the participant is eligible.

Only trained staff with the assigned user rights will be able to randomize participants using their unique username and password. An email notification will be automatically generated once the participant has been randomized. This email confirmation of the participant's allocation will be sent to the CI and trial team.

Collecting follow-up assessments
The following information will be ascertained at the time of death or discharge or at 28 days after randomization (whichever is sooner):
1. Vital status (alive/dead, with date and presumed cause of death, if appropriate)
2. Hospitalisation status (inpatient/discharged, with date of discharge, if appropriate)
3. Use of ventilation (none/previous/ongoing, with days of use and type, if appropriate)
4. Use of renal dialysis or haemofiltration (none/previous/ongoing)

Clinical data aligns where possible with routine care. In order to increase efficiency and reduce the burden on research and clinical teams, clinical data will be recorded using the WHO-ISARIC (World Health Organization–International Severe Acute Respiratory and Emerging Infections Consortium) case record form (https://isaric.tghn.org). Data will be collected on ISARIC data collection forms and directly into an IONIC web-based system alongside the ISARIC platform. This information will be obtained and entered into the web-based system by a member of the hospital clinical or research staff.

Follow-up information is to be collected on all study participants, irrespective of whether or not they complete the scheduled course of allocated study treatment. Study staff will seek follow-up information through various means including medical staff, reviewing information from medical notes, routine healthcare systems, and registries.

Withdrawal criteria
A decision by a participant that they no longer wish to continue receiving study treatment should not be considered to be a withdrawal of consent for follow-up. However, participants are free to withdraw consent for some or all aspects of the study at any time if they wish to do so. In accordance with regulatory guidance, de-identified data that have already been collected and incorporated in the study database will continue to be used (and any identifiable data will be destroyed).

End of study definition
The end of the study will be defined at the date of the last participant's End of Study assessment (added 07/06/2022) or the last long term follow-up date due, whichever comes later.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
IMU838, oseltamivir

Primary outcome measure
Time-to-clinical improvement; defined as the time from randomization to a 2-point improvement on a 7-point ordinal scale, or discharge from hospital or death (whichever occurs first). A clinically significant difference is defined as a difference of at least a 2-point improvement on the WHO ordinal scale; Timepoint(s): 14 days after randomization

Secondary outcome measures
1. Adverse events (AEs) and serious adverse events (SAEs), including COVID-19 worsening and incidence of laboratory abnormalities, measured using patient notes or as reported by participant throughout the hospitalisation and every other day after discharge and during follow-up period of 14 days; laboratory abnormalities documented using patient notes at baseline, 7 days, 14 days, end of treatment or discharge
2. Proportion of patients with two-point change on WHO ordinal scale at Day 7, 14 and 28 (± 2 days)
3. Proportion of patients free of invasive ventilation, renal replacement therapy or ECMO, measured using patient notes at Day 7 and 14
4. Hospital length of stay and length of stay in Intensive care, measured using patient notes at day 7, 14 and 28 (± 2 days) or discharge
5. Mortality measured using patient notes at day 28
6. Time from treatment initiation to death (days), measured using patient notes at death

Overall study start date
23/03/2020

Completion date
21/09/2022

Eligibility

Key inclusion criteria
1. Male or non-pregnant female patients at least 18 years old
2. Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)-2 infection
2.1. Confirmed cases: prospective participants who test positive to a validated specific SARS-CoV-2 nucleic acid test or has the virus identified by electron microscopy or viral culture, as per local trust policy <= 5 days before randomization
2.2. Probable/Suspected case: prospective participants who have been in contact with a confirmed case of COVID-19, AND has mild to severe Covid-19 clinical symptoms AND radiographic evidence* of pulmonary infiltrates consistent with COVID-19 disease
3. Moderate to severe COVID-19 requiring hospitalisation defined as:
3.1. Clinical status category 3-5 (inclusive) on the 7-point clinical status category scale as proposed by the World Health Organisation (WHO) master protocol:
I. Category 3: hospitalized, no oxygen therapy
II. Category 4: hospitalized, oxygen by mask or nasal prongs
III. Category 5: hospitalized, non-invasive ventilation or high-flow oxygen
*where routinely available, no tests will be requested for research purpose

Participant type(s)

Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 120; UK Sample Size: 120

Total final enrolment
42

Key exclusion criteria
1. General exclusion criteria:
1.1. Allergic or hypersensitivity to the IMU-838, oseltamivir, or any of the ingredients
1.2. Pregnant or breastfeeding or with the intention to become pregnant during the study
1.3. Participants who cannot take trial medication orally
2. Concomitant medication or medical history:
2.1. If the attending clinician believes that there is a specific contraindication to the IONIC intervention (see Appendix 3; section 9.1.2 in protocol)
2.2. Patient has a medical or concomitant disease history preventing him to participate (for further information please see; Appendix 3 in protocol)
3. COVID-19 related exclusion criteria:
3.1. Participation in any other interventional clinical trial for an experimental treatment for COVID-19

Date of first enrolment
22/06/2020

Date of final enrolment
20/05/2022

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University Hospitals Coventry and Warwickshire NHS Trust
Walsgrave General Hospital
Clifford Bridge Road
Coventry

United Kingdom
CV2 2DX

Sponsor information

Organisation
University Hospitals Coventry and Warwickshire NHS Trust

Sponsor details
c/o Ceri Jones
4th Floor Rotunda
UHCW
Clifford Bridge Road
Coventry
England
United Kingdom
CV2 2DX
+44 (0)2476965031
ceri.jones@uhcw.nhs.uk

Sponsor type
Hospital/treatment centre

Website
http://www.uhcw.nhs.uk/

ROR
https://ror.org/025n38288

Funder(s)

Funder type
Industry

Funder Name
Immunic AG

Funder Name
LifeArc

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Planned publication of the protocol
2. All efforts will be made to ensure that the results arising from the study are published in a timely fashion, in established peer-reviewed journals. Results will be disseminated to collaborators, colleagues, health professionals and participants via internal and external conferences and seminars, newsletters, and via interested groups, including local healthcare commissioning groups. The researchers are working on a formalised publication plan targeting specific journals and will update accordingly.

Intention to publish date
31/03/2025

Individual participant data (IPD) sharing plan
Data from this study will be made available to researchers who provide a methodologically sound proposal in writing to the Sponsor, following the publication of the main study paper. Anonymised, individual participant data, data dictionary, study protocol and statistical analysis plan will be accessible upon application.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		17/11/2022	18/11/2022	Yes	No
HRA research summary			28/06/2023	No	No