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A research trial to find out if tocilizumab helps adults with Long Covid feel better

Submission date
23/11/2022

Recruitment status
No longer recruiting

Registration date
18/01/2024

Overall study status
Ongoing

Last Edited
20/08/2025

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
To date, over 1 million adults have been admitted into UK hospitals with COVID-19. Approximately only one in three people feel fully recovered 1 year after discharge. There are an estimated 2 million people living with Long Covid. Previous research has shown that proteins involved in inflammation are higher in adults who have the worst health outcomes. One of these proteins is called interleukin-6 (IL-6). Tocilizumab is a drug which lowers the levels of IL-6. The aim of this study is to test whether tocilizumab can help people with 'inflammatory' Long Covid feel better.

Who can participate?
People who do not feel fully recovered at least 3 months after COVID-19 and have ongoing whole-body inflammation measured by a commonly used blood marker

What does the study involve?
Participants will be put into two groups at random. One group will receive tocilizumab injections for 12 weeks and the other group will receive placebo injections (sterile solution without the drug). Injections will be weekly or fortnightly depending upon the participant's weight. The main outcome is a questionnaire to assess how people feel related to their health. Other outcomes involve questionnaires to assess symptoms, physical and mental health, an assessment of brain fog, tests of physical performance and activity, and a breathing test. Blood and urine samples will be collected for detailed assessment. After consent and eligibility, there are three main research visits: at the start and end of the treatment period, and 12 weeks after the end of the treatment period. Any adverse events will be reported. Two optional sub-studies involve taking images/scans of the lungs and body organs, and more detailed breathing tests.

What are the possible benefits and risks of participating?
Tocilizumab is used across the world to treat other inflammatory conditions such as rheumatoid arthritis. It is given by an injection under the skin. Side effects from the medication include lowering the immune system and liver problems. Participants at high risk of these problems will be excluded. This trial is categorised as Type B = somewhat higher than the risk of standard medical care. The study is using tocilizumab out of current clinical indications and licensing. However, tocilizumab at the dose we are proposing is currently used safely in other long-term

conditions where IL6 is raised and part of the underlying inflammatory pathway causing disease. Current standard practice for Long COVID involves no medication specifically for the Long COVID disease process and specifically no anti-interleukin (IL) 6 agents. Therefore, any side effects of the medication are above the risk of standard medical care for Long COVID. There is no indication that patients with Long COVID would have a higher risk of side effects than other patient populations.
A comprehensive compilation of clinical and nonclinical data on tocilizumab is available in the Investigators Brochure. The main side effects are:
Very common (>10%): upper respiratory tract infections, injection site reaction
Common (10%-1%): cellulitis, oral herpes simplex, Herpes zoster, abdominal pain, mouth ulceration, gastritis, rash, pruritus, urticaria, headache, dizziness, increased hepatic transaminases, increased weight, hypertension, leucopenia, neutropenia, hypercholesterolemia, peripheral oedema, hypersensitivity reaction, cough, dyspnoea, conjunctivitis
Uncommon (<1%): diverticulitis, stomatitis, gastric ulcer, increased total bilirubin, hypertriglyceridemia, nephrolithiasis, hypothyroidism
The researchers will mitigate these as far as possible by excluding participants that would be high risk of side effects and by careful monitoring of potential side effects which can be measured through serial blood tests. The main side effects are neutropenia (a low type of white cell count), thrombocytopenia (low platelet count) and hepatitis (liver inflammation), therefore blood tests of neutrophils, platelets and liver function tests will be monitored every 4 weeks. Specific and clear dose adjustments are provided in the protocol based on the tocilizumab investigator brochure (IB).
There is no data to support the safety of tocilizumab during pregnancy to date and therefore for this trial the assumption is Tocilizumab is not safe during pregnancy and therefore any participant or participant's spouse who is either pregnant or planning a pregnancy in the same timeframe would be excluded. Pregnancy tests (urine) will be performed at each visit. A serum pregnancy test will be performed at screening.

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

When is the study starting and how long is it expected to run for?
March 2023 to December 2025

Who is funding the study?
Genentech Roche (USA)

Who is the main contact?
1. Mrs Victoria Harris, phosp-i@leicester.ac.uk
2. Dr Rachael Evans, phosp-i@leicester.ac.uk

Contact information

Type(s)
Scientific

Contact name
Mrs Victoria Harris

Contact details

NIHR Leicester Biomedical Research Centre - Respiratory
Department of Infection, Immunity and Inflammation
Glenfield Hospital
Groby Road
Leicester
United Kingdom
LE3 9QP
+44 (0)116 250 2670
phosp-i@leicester.ac.uk

Type(s)
Principal investigator

Contact name
Dr Rachael Evans

Contact details
Groby Road
Leicester
United Kingdom
LE3 9QP
+44 (0)116 0300 030 1573
phosp-i@leicester.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2022-003211-29

Integrated Research Application System (IRAS)
1006298

Protocol serial number
0862, IRAS 1006298, CPMS 60222

Study information

Scientific Title
A Phase IIa double-blind, randomized placebo-controlled trial of tocilizumab to investigate the effect on health-related quality of life in adults with Long COVID and persistent inflammation

Acronym
PHOSP-I

Study objectives
Primary objective
The primary objective is to compare the effect of 12 weeks of subcutaneous (s/c) tocilizumab versus 12 weeks of s/c placebo on health-related quality of life.

Secondary objectives
1. To compare the effect of 12 weeks of s/c tocilizumab versus 12 weeks of s/c placebo on symptoms, mental health, physical performance, daily physical activity, cognitive impairment, multi-organ function and systemic inflammation.
2. To investigate the sustainability of any effect at 12 weeks after medication/placebo cessation on the primary and secondary outcome measures.

Sub-study exploratory objectives:
1. To compare the effects of 12 weeks of tocilizumab versus 12 weeks of placebo on respiratory health using pulmonary function testing and computed tomography (CT) thoracic imaging.
2. To compare the effects of 12 weeks of tocilizumab versus 12 weeks of placebo on multi-organ health using magnetic resonance imaging.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 21/12/2023, West Midlands - Edgbaston Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8155, +44 (0)207 104 8357; edgbaston.rec@hra.nhs.uk), ref: 23/WM/0234

Study design
Double-blind randomized placebo-controlled parallel-group trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Long COVID

Interventions
Tocilizumab/placebo subcutaneously for 12 weeks

Dosage: 162 mg subcutaneous injection.
Frequency of administration: body weight <100 kg 162 mg fortnightly/body weight ≥100 kg 162 mg weekly for 12 weeks.
Details of the randomisation process: Participants will be allocated to treatment groups using a mixed minimisation/randomisation procedure, designed to maintain balance with respect to:
1. Study site (1-15)
2. EQ5D-5L UI (<0.70 / ≥0.70)
3. CRP level (≤20 mg/L / >20 mg/L)
4. Participation in the MRI sub-study (Yes/No)
5. Acute admission/tocilizumab status (non-hospitalised/hospitalised, no tocilizumab /hospitalised, with tocilizumab)

All patients included in the trial be assigned a unique trial number to identify the participant throughout the trial. Randomisation using a web-based randomisation system will be provided by Glasgow CTU. The research staff at sites will provide the trial ID number and minimisation information and, if eligible, the randomisation group will be allocated.

Blinded new participant randomisation e-mail confirmations will be sent to the research nurse (s), investigator and pharmacy staff as required. In addition, the randomisation notification will be sent electronically to the Interactive Web Response System (IWRS) supplier, with details of the trial ID number and randomisation group to allow drug supply management at site. Information may be shared back to the Glasgow CTU server, from the IWRS system, to allow for cross-checking between systems.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Tocilizumab

Primary outcome(s)
Health-related quality of life measured using Euroqol five-dimension five-level questionnaire – utility index assessed at baseline, after 12 weeks (+2 weeks) of IMP/Placebo and after a further 12 weeks (+2 weeks) after the end of the intervention period

Key secondary outcome(s))
Measured at baseline, after 12 weeks (+ 2 weeks) of IMP/Placebo and after a further 12 weeks (+2 weeks) after the end of the intervention period:
1. Symptoms measured using Symptom Questionnaires – fatigue and breathlessness (FACIT-Fatigue and Dyspnoea-12)
2. General and respiratory disease-specific health-related quality of health measured using EQ5D-5L Visual Analog Scale and St George's Respiratory Questionnaire
3. Mental health measured using anxiety and depression questionnaires GAD-7 and PHQ-9
4. Physical performance measured using the Incremental Shuttle Walking Test, the Short Physical Performance Battery (SPPB) and hand grip strength
5. Daily physical activity measured using an accelerometer worn for 14 days
6. Cognitive impairment measured using Montreal Cognitive Assessment (MoCA)
7. Multi-organ function measured using blood biomarker levels (including full blood count, natriuretic peptides, kidney and liver function) spirometry, and urine and stool samples.
8. Systemic inflammation measured using a blood test for C-reactive protein
9. Frailty and activities of daily living measured using Fried's frailty criteria and Nottingham Activities of Daily Living Scale

Exploratory outcomes:
Respiratory health substudy:
Pulmonary pathophysiology assessed by CT thorax and full pulmonary function tests at baseline and after 12 weeks (+4 weeks) after IMP/Placebo:
1. Pulmonary pathology on CT thoracic imaging such as ground-glass opacities, interstitial abnormalities, established pulmonary fibrosis, or small airways disease suggestive of ongoing post-COVID pulmonary changes

2. Pulmonary function tests include spirometry, transfer factor, residual volume and total lung capacity

Multi-organ health substudy:
MRI markers of multi-organ inflammation evaluated by describing the presence or absence of multiorgan abnormality (defined as MRI abnormalities involving two or more organs including the lungs) at baseline and after 12 weeks (+4 weeks) after IMP/Placebo:
1. The composite score based on relative difference in myocardial extracellular volume, myocardial T1, liver cT1, renal T1, and lung parenchymal signal intensity heterogeneity index post-treatment will be used.

Exploratory objectives using the bioresource:
1. Inflammatory profile measured using blood (up to 100 ml) and urine (up to 100 ml) samples obtained at up to four time points: baseline, after 8 weeks (+/-2 weeks) of treatment/placebo, end of treatment/placebo at 12 weeks (+2 weeks) and 12 weeks (+2 weeks) after treatment /placebo
2. A subset of serum, plasma, whole blood, cells and urine samples will be subject to multi-omic assays to analyse the effect of treatment vs placebo on putative inflammatory biomarkers in the blood and urine, and their association with outcomes. This may include, but is not limited to, measurement of proteins, gene expression (mRNA), metabolites, cell populations and lipids related to the inflammatory response and other biological processes (for example, tissue damage and repair).
3. DNA will be analysed using either genome-wide microarray or next-generation sequencing (targeted, whole exome or whole genome) approaches to identify whether specific genetic variants, or combinations thereof, are associated with treatment response and outcomes
4. Stool samples will be collected for virus detection and other analyses at baseline, end of treatment/placebo at 12 weeks and 12 weeks after treatment/placebo.

Completion date
31/07/2026

Eligibility

Key inclusion criteria
1. Age ≥18 years old and ≤80 years old
2. Clinical diagnosis of COVID-19 at least 3 months prior to consent. Patient-reported positive test is acceptable
3. Patient does not feel fully recovered at recruitment after COVID-19 (response no or unsure to “do you feel fully recovered from your COVID-19”)
4. CRP >5 mg/L persistently raised after contracting COVID-19 and prior to randomisation
5. Euroqol EQ5D-5L utility index ≤0.90 units prior to randomisation
6. Reasonable understanding of the English language assessed by the research team (i.e. able to understand the risks of taking part in the trial and complete the measurements including the patient-reported outcome measures)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
80 years

Sex
All

Key exclusion criteria
Current exclusion criteria as of 16/01/2025:

1. Other comorbidity indicating survival at one year from consent is unlikely
2. Active malignancy or on treatment for malignancy
3. Unable or unwilling to provide written consent
4. Inability to comply with protocol-directed procedures and assessments
5. Current immunosuppression therapy including oral corticosteroids
6. Prior use of the trial drug within 3 months of consent (including intra-venous Tocilizumab for acute COVID). 3 months is five-half lives of tocilizumab
7. Involvement in other trials involving an IMP either concurrently or within four months of consent - to allow washout. This includes medications prescribed for acute COVID studies.
8. Previous adverse event to tocilizumab, either a severe allergic reaction or deranged liver function tests
9. Hepatic transaminases greater than three times the upper limit of normal
10. Low neutrophil (below 2 x 109/L) or low platelet levels (below 100 x 10e3/µL)
11. Signs of active infection
12. Receipt of live vaccine within 3 months or planning a live vaccine during the trial period. Most COVID vaccines are not live.
13. Pregnancy or breastfeeding, or planning a pregnancy during the trial period or unable or unwilling to meet the contraception criteria (see below)
14. Latent TB: to be excluded with IGRA testing and if positive exclude and refer for treatment as per national guidelines.
15. New diagnosis or on treatment for HIV
16. Past history of diverticulitis
17. Significant alcohol or substance misuse
18. History of clinically significant hypersensitivity reaction or significantly deranged liver function tests with other medication
19. Hepatitis B
20. Exclude Hepatitis C if untreated: on testing antibody positive and detectable viral load. If antibody positive, but viral load negative compatible with previous infection only participant can be included.
21. Supervised exercise rehabilitation programme including exercise training, or other rehabilitation therapy for example fatigue management or breathing retraining lasting for a minimum of 4 sessions within three months of consent or planned to occur during the trial period
22. New medication for Long Covid symptoms started within six weeks of consent

23. No new weight management medication to start within three months of consent or during the trial period, for example glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors

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Previous exclusion criteria:

1. Other comorbidity indicating survival at one year from consent is unlikely
2. Active malignancy or on treatment for malignancy
3. Unable or unwilling to provide written consent
4. Inability to comply with protocol-directed procedures and assessments
5. Current immunosuppression therapy including oral corticosteroids
6. Prior use of the trial drug within 3 months of consent (including intra-venous Tocilizumab for acute COVID). 3 months is five-half lives of tocilizumab
7. Involvement in other trials involving an IMP either concurrently or within four months of consent - to allow washout. This includes medications prescribed for acute COVID studies.
8. Previous adverse event to tocilizumab, either a severe allergic reaction or deranged liver function tests
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19. Hepatitis B
20. Exclude Hepatitis C if untreated: on testing antibody positive and detectable viral load. If antibody positive, but viral load negative compatible with previous infection only participant can be included.
21. Supervised exercise rehabilitation programme within three months of consent or planned to occur during the trial period

Date of first enrolment
01/02/2024

Date of final enrolment
31/10/2025

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
University Hospitals of Leicester NHS Trust
Glenfield Hospital
Groby Road
Leicester
United Kingdom
LE1 5WW

Study participating centre
Guy's & St Thomas Hospital
Westminster Bridge Road
London
United Kingdom
SE1 7EH

Study participating centre
Kings College Hospital
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
NIHR University College London Hospitals Clinical Research Facility
University College London Hospitals NHS Foundation Trust
4th Floor
170 Tottenham Court Road
London
United Kingdom
W1T 7HA

Study participating centre
Oxford University Hospitals NHS Foundation Trust
John Radcliffe Hospital
Headley Way
Headington
Oxford

United Kingdom
OX3 9DU

Study participating centre
Sheffield Teaching Hospitals NHS Foundation Trust
Northern General Hospital
Herries Road
Sheffield
United Kingdom
S5 7AU

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

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2GW

Study participating centre
Glasgow Royal Infirmary
84 Castle Street
Glasgow
United Kingdom
G4 0SF

Study participating centre
Manchester University Hospitals NHS Foundation Trust
Wythenshawe Hospital
Southmoor Road
Wythenshawe
Manchester

United Kingdom
M23 9LT

Study participating centre
Northern Care Alliance NHS Foundation Trust
Salford Royal Hospital
Stott Lane
Eccles
Salford
United Kingdom
M6 8HD

Sponsor information

Organisation
University of Leicester

ROR
https://ror.org/04h699437

Funder(s)

Funder type
Industry

Funder Name
Genentech Roche

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

Research data will be shared with bona fide researchers in different organisations, including those in other countries or in commercial organisations. Access to data will be managed through the Trial Management Group (TMG) and formal application requests will be submitted to the TMG by researchers requesting data. Once permission has been granted by the TMG data will be released to collaborators. Data will be labelled with a unique study number in place of any identifiable data (pseudonymised). Contractual agreements will be put in place prior to any

sharing of data. Some trial data (anonymised questionnaire data) will be suitable for sharing for research.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Study website	Study website	11/11/2025	11/11/2025	No	Yes