ISRCTN38597726 https://doi.org/10.1186/ISRCTN38597726

Gefapixant and breathing control in long COVID

Submission date
04/08/2026

Recruitment status
Not yet recruiting

Registration date
04/08/2026

Overall study status
Ongoing

Last Edited
04/08/2026

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
Long COVID is a condition in which people continue to have health problems for many months or years after a COVID-19 infection. It is a big health and economic problem in the UK, still affecting 2 million people in 2024 and costing £8 billion each year. Many people with long COVID experience ongoing breathing difficulties. The cause remains unclear, but growing evidence points to disrupted brain and nervous system control of breathing rather than a lung-specific problem. A key part of this breathing control system is the carotid chemoreflex. This is driven by small organs in the neck called the carotid bodies, which monitor the amount of oxygen and carbon dioxide in the blood, sending signals into the brain adjusting breathing, heart rate and blood pressure. Our recent research shows that the carotid chemoreflex is overly sensitive in people with long COVID without other health problems. Dopamine has been used to study the carotid chemoreflex in disease. However, its systemic off-target effects limit interpretation of results, and the need for intravenous infusion limits its therapeutic potential in chronic conditions. Recently the P2X3 receptor in the carotid body has been identified as driving carotid chemoreflex overactivity in certain diseases, including heart failure.
Gefapixant is an oral tablet licensed for use in the UK and specifically acts on P2X3 receptors. This study aims to determine whether P2X3 blockade via a one-off dose of gefapixant reduces chemoreflex sensitivity in people with long-COVID. We will monitor whether hyperventilation at rest is reduced and breathing efficiency during exercise is improved with acute P2X3 receptor blockade compared to placebo. Our study will determine whether P2X3 receptors are involved in carotid chemoreflex hyperactivity in people with long COVID. Potentially P2X3 receptor blockade could be used as a treatment for patients with long COVID and ongoing breathing difficulties.

Who can participate?
Patients aged 18-75 years with a diagnosis of long COVID and breathlessness that affects their daily lives.

What does the study involve?
Three study visits at the Clinical Research Facility, Bristol. Visit 1 is a screening visit and will involve five questionnaires, a 12-lead ECG, lung function tests, urine dipstick and pregnancy tests, height, weight, office blood pressure measurements, and a blood sample. Participants will also be sent home with a 24-hour blood pressure monitor. Visits 2 and 3 will be identical, except participants will receive a different tablet (gefapixant or placebo) each day in a randomised

order. Resting ventilation assessments and hypoxic ventilatory response testing will be completed. A ramped exercise tolerance test will also be performed. Ventilation, blood pressure, oxygen saturation and heart rate will be continuously recorded throughout the visits.

What are the possible benefits and risks of participating?
You will get a heart tracing, full blood pressure screen, and blood tests, which may be of some benefit from a health check-up point of view; however, these tests should not be relied upon for the identification of undiagnosed medical conditions. Taking part in this study will help us understand more about the science underlying long COVID and how the carotid body is involved in it. We want to learn more about the mechanisms of long COVID to help identify a treatment to improve some of the symptoms that people with long COVID experience.
During respiratory (breathing) monitoring, a mask will be fitted that allows us to measure what you are breathing in and out. There are no risks to breathing room air at rest. We will give you a tablet called gefapixant or placebo which we expect will not give any side effects. We will monitor you closely at all times. The main side effect of a single dose is a change in taste, which is reversible and returns to normal following the elimination of gefapixant from the plasma (about 6 hours). A research nurse or doctor will always be present during the study. During the hypoxic ventilatory response testing, breathing nitrogen can cause some short-lived dizziness or light-headedness. The nitrogen can be immediately switched off and clears from the breathing circuit in seconds. Oxygen levels return to normal quickly after the nitrogen is switched off, and additional oxygen can be given if needed. For the bike exercise test, we will ask you to cycle for up to 12 minutes. A research nurse and researcher will be with you at all times, and if you feel unwell, the test can be stopped at any time. The inherent side effects of exhaustive exercise may be experienced.

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

When is the study starting and how long is it expected to run for?
November 2026 to January 2028

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Hazel Blythe, hazel.blythe@bristol.ac.uk, sn18632@bristol.ac.uk

Contact information

Type(s)
Public, Scientific, Principal investigator

Contact name
Dr Emma Hart

Contact details
University of Bristol, Biomedical Sciences Building
Bristol
United Kingdom

BS8 1TD
+44 (0)117 331 1971
emma.hart@bristol.ac.uk

Type(s)
Scientific

Contact name
Dr Hazel Blythe

Contact details
Biomedical Sciences Building, University of Bristol
Bristol
United Kingdom
BS8 1TD
+44 (0)117 331 1971
hazel.blythe@bristol.ac.uk

Additional identifiers

Study information

Scientific Title
Targeting the carotid chemoreflex via purinergic receptors in patients with long COVID and persistent breathing difficulties

Study objectives
Aim 1: To determine whether a single dose of a P2X3 receptor antagonist; oral dose of gefapixant: 45 mg) reduces carotid chemoreceptor sensitivity in long COVID patients versus a placebo.
Aim 2: To determine whether gefapixant, a single dose of a P2X3 receptor antagonist (gefapixant versus placebo), reduces hyperventilation at rest in patients with long COVID.
Aim 3: To determine whether a single dose of a P2X3 receptor antagonist (gefapixant versus placebo) improves breathing efficiency during exercise in patients with long COVID.

Ethics approval required
Ethics approval required

Ethics approval(s)
Not yet submitted

Primary study design
Interventional

Allocation
Randomized controlled trial

Masking
Blinded (masking used)

Control
Placebo

Assignment
Crossover

Purpose
Basic science

Study type(s)

Health condition(s) or problem(s) studied
People with long-COVID and breathlessness that affects daily life

Interventions
A single dose of oral gefapixant (45 mg) tablet will be used as a mechanistic tool to investigate whether P2X3 receptors contribute to carotid chemoreflex hyperactivity in patients with long-COVID

We will randomise using Sealed Envelope. The drug and placebo will be received by all patients in a randomised order, so the drug or placebo will be given in visits 2 or 3.

Intervention Type
Drug

Phase
Not Applicable

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

Primary outcome(s)
1. Hypoxic ventilatory response (HVR) at rest measured using chemoreflex sensitivity, calculated as the increase in minute ventilation divided by the SpO2% (termed the hypoxic ventilatory response or HVR and expressed as L/min/SpO2%), at 2-3 hours after taking gefapixant or placebo

Key secondary outcome(s)
1. Resting normoxic tidal volume measured with spirometry, 2-3 hours after taking gefapixant or placebo
2. Resting end-tidal pressure of carbon dioxide ($PETCO_2$) measured with spirometry, 2-3 hours after taking gefapixant or placebo
3. Resting ratio of minute ventilation to carbon dioxide production (VE/VCO_2) measured with spirometry, 2-3 hours after taking gefapixant or placebo
4. Resting dyspnoea measured using the visual analogue scale, 2-3 hours after taking gefapixant or placebo
5. Resting minute ventilation measured with spirometry, 2-3 hours after taking gefapixant or placebo
6. Resting breathing frequency measured with spirometry, 2-3 hours after taking gefapixant or placebo
7. Resting blood pressure measured continuously with Finapres finger blood pressure cuff, 2-3

hours after taking gefapixant or placebo
8. Resting heart rate measured continuously using a three-lead ECG, 2-3 hours after taking gefapixant or placebo
9. Minute ventilation measured using a face mask and gas analyser continuously (breath-by-breath) throughout exercise
10. Respiratory rate measured using a face mask and gas analyser continuously (breath-by-breath) throughout exercise
11. Oxygen consumption measured using a face mask and gas analyser continuously (breath-by-breath) throughout exercise
12. Dyspnoea score measured using the visual analogue scale every 2 minutes throughout exercise and at peak exercise

Completion date
05/01/2028

Eligibility

Key inclusion criteria
1. 18-75 years old
2. Self-reported positive PCR or antibody test before vaccination
3. Not hospitalised for any COVID-19 infection
4. Breathlessness affecting their daily lives, measured by Modified Yorkshire COVID-19 Rehabilitation Scale (used in some long-COVID clinics)

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
75 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Body mass index ≥35 kg/m²
2. Diagnosed with severe asthma or uncontrolled asthma
3. Pregnancy/breastfeeding women
4. Ongoing requirement of oxygen therapy
5. Moderate anaemia (Hb <100 g/dl)
6. Taking antihypertensive, nitrate, steroid or immunosuppressant medication or medication
7. Major illness, e.g., cancer, inflammatory disease (including vasculitis) or receiving palliative care

8. History of organ transplantation or candidate for organ transplantation
9. History of chronic fatigue syndrome prior to COVID-19 infection
10. Diagnosed cardiovascular disease (including current non-benign arrhythmia, chronic heart failure)
11. History of major psychiatric disorder including bipolar disorders, schizophrenia, schizoaffective disorder, major depression
12. Diagnosis of structural lung disease (such as COPD or pulmonary fibrosis)
13. Diagnosed liver or renal disease
14. Congenital or acquired neurological conditions (including dementia), language disorders, repeated or chronic pain conditions (excluding menstrual pain and minor sporadic headaches)
15. Diabetes mellitus
16. Symptoms of febrile illness 2 weeks before experiment
17. Lower respiratory tract symptoms at time of screening visit (visits would be rearranged)
18. Excessive alcohol consumption (>28 units/week) or use of illicit drugs
19. History of tobacco smoking within last 12 months
20. Inability to understand instructions given in English
21. Surgery under general anaesthesia within 3 months
22. History of stroke
23. Heart transplant
24. Coronary revascularisation
25. Haemodialysis or peritoneal dialysis
26. Participating in another study for an investigational medicinal product
27. Any contraindication to gefapixant or its derivatives, or severe drug allergies
28. Estimated glomerular filtration rate (eGFR) <30 ml/min

Date of first enrolment
02/11/2026

Date of final enrolment
03/01/2028

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
NIHR Bristol Clinical Research Facility
60 St Michael's Hill
Bristol
England
BS2 8DX

Sponsor information

Organisation
University of Bristol

ROR
https://ror.org/0524sp257

Funder(s)

Funder type

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not expected to be made available