

# Investigating the effect of a medication on the blood pressure within the lungs

<b>Submission date</b> 12/12/2023	<b>Recruitment status</b> Recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 18/12/2023	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 20/02/2025	<b>Condition category</b> Other	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

The blood vessels within the lungs are unique. In other parts of the body, when there is not enough oxygen present, the blood vessels increase in size (dilate) to deliver more blood to the organs. However, in the lungs, they narrow (constrict; causing an increase in blood pressure) and we can see this using ultrasound of the heart.

These blood vessels can constrict more effectively under certain circumstances. For example, we know that when a lack of oxygen (termed hypoxia) continues for several hours, the blood vessels are able to react more strongly. This means the blood pressure in the lungs increases to a higher level. This happens because a 'signalling pathway' is activated – a cascade of steps that results in genes being switched on from our DNA.

A drug called roxadustat deliberately switches on this pathway. It is licensed in many countries, including the UK, to treat the anaemia (low haemoglobin and red blood count) that accompanies long-term kidney disease. This is a good thing, and the drug has been shown to be safe.

However, we don't yet know what this drug does to the blood vessels in the lungs in hypoxia. Based on what we know already, we would expect that it would make them react more strongly. This is important as many people around the world will be taking this drug for a long time. Therefore, the aim of this study is to give a single one-off dose of roxadustat to healthy volunteers and measure the blood pressure in the lungs (using ultrasound) when they are breathing normal air, and when they are breathing in less oxygen. This will tell us what effect the drug is having on the blood vessels in the lungs, and help guide scientists and doctors in the future.

### Who can participate?

Healthy volunteers aged 19–60 years

### What does the study involve?

At the preliminary visit participants undergo a heart ultrasound check and blood test to make sure they are able to take part. On the first study day they are randomly allocated to take either roxadustat or a placebo (sugar) tablet, and also undergo heart ultrasounds and breathe low oxygen for 30 minutes (with a mouthpiece and nose clip) for 2 hours in a comfortable, purpose-built 'chamber' – a small room with windows. On the second study day (at least 2 weeks later) participants undergo exactly the same steps as the first experiment day, but they take the

opposite tablet to the one taken on the first study date (i.e. if they took roxadustat on Day 1 they take the placebo on Day 2, and vice versa).

What are the possible benefits and risks of participating?

While there are no immediate benefits for those people participating in the project, it is hoped that this study will lead to a better understanding of the science of hypoxia and the blood pressure in the lungs, as well as important safety information for patients taking roxadustat.

**Risk 1 - Hypoxia:**

Participants will be exposed to hypoxia as per the study protocol and under identical conditions to multiple studies conducted in the same laboratory. The lowest end-tidal PO<sub>2</sub> will be 50 mmHg (equivalent to ascent to an altitude of about 3000 – 5000 m) and this is a well-established experimental technique that produces robust physiological changes without risk to the individual. The participant may notice increased work of breathing, which is a normal physiological response. Safety mechanisms are built into the experimental equipment and these have been rigorously tested over many years of approved research studies.

**Risk 2 - Roxadustat:**

This is a well-established and fully licensed drug that has gone through all the required clinical trials. It is now recommended by NICE as a treatment option for symptomatic anaemia associated with chronic kidney disease. Roxadustat treatment is known to produce a dose-dependent increase in heart rate in healthy subjects at doses over 2 mg/kg (applicable for this study) but with no adverse events reported (EMA report). Participants will be informed that a small increase in heart is to be expected, and reassured that it is normal and safe. The safety of roxadustat was evaluated in 3542 non-dialysis-dependent (NDD) and 3353 dialysis-dependent (DD) patients with anaemia and chronic kidney disease who have received at least one dose of roxadustat. The most frequent ( $\geq 10\%$ ) adverse reactions associated with roxadustat are hypertension (13.9%), vascular access thrombosis (12.8%), diarrhoea (11.8%), peripheral oedema (11.7%), hyperkalaemia (10.9%) and nausea (10.2%). The most frequent ( $\geq 1\%$ ) serious adverse reactions associated with roxadustat were sepsis (3.4%), hyperkalaemia (2.5%), hypertension (1.4%) and deep vein thrombosis (1.2%).

It should be noted, however, that these adverse events were reported from patients with chronic kidney disease on sustained dosing, and are therefore less applicable to individual healthy participants receiving a single one-off dose. A large number of healthy volunteers underwent Phase I trials and there are no reported adverse events in the literature by the reviewing authorities.

Where is the study run from?

University of Oxford (UK)

When is the study starting and how long is it expected to run for?

January 2023 to December 2025

Who is funding the study?

Medical Research Council (MRC) (UK)

Who is the main contact?

Dr Mary Slingo, [mary.slingo@dpag.ox.ac.uk](mailto:mary.slingo@dpag.ox.ac.uk)

## Contact information

**Type(s)**

Public, Scientific, Principal Investigator

**Contact name**

Dr Mary Slingo

**Contact details**

Department of Physiology, Anatomy & Genetics  
University of Oxford  
Parks Road  
Oxford  
United Kingdom  
OX1 3PT  
+44 (0)1865 272500  
mary.slingo@dpag.ox.ac.uk

**Additional identifiers****EudraCT/CTIS number**

Nil known

**IRAS number****ClinicalTrials.gov number**

Nil known

**Secondary identifying numbers**

R78515/RE001

**Study information****Scientific Title**

Modulators of the hypoxia-inducible factor (HIF) pathway (roxadustat) and their impact on the pulmonary vasculature in humans

**Study objectives**

To determine whether pharmacological upregulation of the hypoxia-inducible factor (HIF) pathway, via roxadustat, increases resting pulmonary vascular tone and/or sensitivity of the pulmonary vasculature to acute and sustained hypoxia (low inspired oxygen).

**Ethics approval required**

Ethics approval required

**Ethics approval(s)**

Approved 15/06/2023, Medical sciences interdivisional research ethics committee, CUREC 3 (Research Services, Boundary Brook House, Churchill Drive, Oxford, OX3 7GB, United Kingdom; +44 (0)1865 616575; ethics@medsci.ox.ac.uk), ref: R78515/RE001

**Study design**

Single-centre physiological study

**Primary study design**

Interventional

**Secondary study design**

Physiological study

**Study setting(s)**

University/medical school/dental school

**Study type(s)**

Other

**Participant information sheet**

Not available in web format, please use contact details to request a participant information sheet

**Health condition(s) or problem(s) studied**

Pulmonary vascular tone and sensitivity to hypoxia and the influence of activation of the hypoxia-inducible factor (HIF) pathway

**Interventions**

Participants will undergo acute and sustained hypoxia, with simultaneous transthoracic echocardiography to measure pulmonary artery systolic pressure. This will be conducted on two separate days - on one day they will have taken a placebo tablet; on the other a single dose of roxadustat, which is a drug that activates the hypoxia-inducible factor (HIF) pathway. These interventions will cross over such that each participant forms their own control. Randomization (block randomization using Sealed Envelope) will be performed by an independent researcher to determine whether placebo or roxadustat is given first. Both participants and the researcher(s) conducting the study will be blinded to the intervention. This is a study of integrative physiology to better understand the effects of hypoxia and the HIF pathway on pulmonary vascular tone.

**Intervention Type**

Mixed

**Primary outcome measure**

1. Resting pulmonary vascular tone, measured as estimated pulmonary artery systolic pressure (PASP) in mmHg, using non-invasive echocardiography via tricuspid valve regurgitation. This measurement is performed when breathing normal oxygen levels. This is measured at baseline, before roxadustat/placebo, then repeated every 30 minutes for the first 2 hours, then every hour thereafter to a total time of 6 hours.
2. PASP, measured as before using echocardiography, in response to acute (20 minutes) and sustained (2 hours) hypoxia. During the 20 minutes of acute hypoxia echocardiography is continually recorded and PASP is measured every minute. 2 hours of hypoxia is then undertaken, during which measurements are not made. Then the 20-minute study is repeated.

**Secondary outcome measures**

Venous blood erythropoietin concentrations before and after roxadustat, measured using blood samples taken at baseline and thereafter at 3 hours and 6 hours

**Overall study start date**

01/01/2023

**Completion date**

31/12/2025

## **Eligibility**

**Key inclusion criteria**

1. Male and female, aged 19–60 years old
2. Willing and able to provide informed consent for participation in the study
3. Not currently taking any significant medications (to be reviewed and confirmed on a case-by-case assessment by a clinically qualified researcher)
4. Not taking the combined oral contraceptive pill. The progesterone-only pill ('mini pill') is acceptable.
5. No pre-existing significant medical conditions – this will be decided after a case-by-case assessment by a clinically qualified researcher

**Participant type(s)**

Healthy volunteer

**Age group**

Adult

**Lower age limit**

19 Years

**Upper age limit**

60 Years

**Sex**

Both

**Target number of participants**

20

**Key exclusion criteria**

1. Inability to tolerate face mask/mouthpiece/nose clip (for experimental procedure)
2. Pregnant or breastfeeding
3. Significant regular medication that could affect the result of the study (interaction with hypoxia or a possible effect on the pulmonary vasculature) and/or has a known interaction with roxadustat.
4. Previous or current significant medical problems may be an exclusion – this will be decided after a case-by-case assessment by a clinical-qualified researcher:
  - 4.1. Pre-existing cardiorespiratory disease
  - 4.2. Pre-existing renal or hepatic impairment
  - 4.3. History of or current significant psychiatric illness
  - 4.4. History of or current significant neurological condition (e.g. epilepsy)
  - 4.5. History of or current venous thromboembolism, pulmonary embolism, or thrombophilia
  - 4.6. Current participation in other research studies
  - 4.7. Recent (within one month) excursions to altitude above 2500 m (with case-by-case

assessment for long sojourns); recent (within 1 week) air travel over 4 hours duration

4.8. Known pre-existing anaemia and/or iron deficiency

4.9. Hypersensitivity to peanut or soya (roxadustat tablets contain traces of soya lecithin and a hypersensitivity to peanut or soya is listed as a contraindication to prescription)

**Date of first enrolment**

09/01/2024

**Date of final enrolment**

31/12/2025

## **Locations**

**Countries of recruitment**

England

United Kingdom

**Study participating centre**

**University of Oxford**

Department of Physiology, Anatomy & Genetics

Sherrington Building

Parks Road

Oxford

United Kingdom

OX1 3PT

## **Sponsor information**

**Organisation**

University of Oxford

**Sponsor details**

University Offices

Wellington Square

Oxford

England

United Kingdom

OX1 2JD

+44 (0)1865 270000

RGEA.Sponsor@admin.ox.ac.uk

**Sponsor type**

University/education

**Website**

<http://www.ox.ac.uk/>

**ROR**

<https://ror.org/052gg0110>

## **Funder(s)**

### **Funder type**

Research council

### **Funder Name**

Medical Research Council

### **Alternative Name(s)**

Medical Research Council (United Kingdom), UK Medical Research Council, MRC

### **Funding Body Type**

Government organisation

### **Funding Body Subtype**

National government

### **Location**

United Kingdom

## **Results and Publications**

### **Publication and dissemination plan**

The Investigators will be involved in the writing of manuscripts, abstracts, press releases, conference presentations, and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. Participants who wish to be informed of the study result will be asked to provide an email address, to which a summary of the results would be sent once the study is complete. Open access to publications will be pursued.

### **Intention to publish date**

31/12/2026

### **Individual participant data (IPD) sharing plan**

The datasets generated during and/or analysed during the current study will be available upon request from Dr Mary Slingo ([mary.slingo@dpag.ox.ac.uk](mailto:mary.slingo@dpag.ox.ac.uk)). Any data will be fully anonymised and therefore no additional consent is required.

### **IPD sharing plan summary**

Available on request

