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

Submission date
12/12/2023

Recruitment status
No longer recruiting

Registration date
18/12/2023

Overall study status
Completed

Last Edited
02/01/2026

Condition category
Other

[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
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 PO2 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 (≥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 (≥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

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Protocol serial number
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

Primary study design
Interventional

Study design
Single-centre physiological study

Study type(s)
Other

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(s)
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.

Key secondary outcome(s)
Venous blood erythropoietin concentrations before and after roxadustat, measured using blood samples taken at baseline and thereafter at 3 hours and 6 hours

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

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
19 Years

Upper age limit
60 Years

Sex
All

Total final enrolment
12

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
13/05/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University of Oxford
Department of Physiology, Anatomy & Genetics
Sherrington Building
Parks Road
Oxford
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OX1 3PT

Sponsor information

Organisation
University of Oxford

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, 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

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). Any data will be fully anonymised and therefore no additional consent is required.

IPD sharing plan summary

Available on request