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Investigating the use of oral imatinib as a treatment for pulmonary arterial hypertension

Submission date
17/10/2024

Recruitment status
Recruiting

Registration date
13/01/2025

Overall study status
Ongoing

Last Edited
30/09/2025

Condition category
Circulatory System

[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
Imatinib is a potential treatment for pulmonary arterial hypertension (PAH), a rare condition in which a narrowing of the vessels carrying blood through the lungs increases resistance to blood flow, putting an increased workload on the heart. A phase III clinical trial in PAH suggested that 400 mg daily reduces the resistance and the pressure but is poorly tolerated. A dose-finding study in PAH that was recently completed found that imatinib 200 mg daily is better tolerated by patients, reduces pulmonary artery pressure and improves exercise capacity. Furthermore, the effects appeared to persist for days after the drug had been cleared from the body, suggesting that imatinib may have disease-modifying properties and be suitable for intermittent weekly dosing. This new study will investigate in more detail the time course of the response to imatinib and, to improve tolerability, examine the effect of dosing less frequently than once daily.

Who can participate?
Patients with PAH attending NHS national pulmonary hypertension referral centres living with implanted devices as part of their clinical management that provides daily reports of pulmonary artery pressure and physical activity

What does the study involve?
Patients will continue with their prescribed licensed therapies and imatinib will be added to their background treatment for up to 24 weeks, starting with 200 mg daily. In patients who respond, the dose of imatinib will be reduced to 200 mg once weekly and they will be closely observed using remote monitoring. Thereafter, the frequency of dosing may be increased, as necessary, to a maximum of 200 mg once daily, to maintain a beneficial response. The study will thus identify the optimal dosing regimen for patients with PAH.

What are the possible benefits and risks of participating?
All potential risks and burdens will be discussed with the patient prior to their consent and are described in the patient information sheet.
Side effects from the imatinib
These are dose-related and reversible on discontinuing the drug or reducing the dose. The most common at 200mg are fatigue, nausea and swelling around the eyes. A reduction in blood white

cell count may occur but this is not clinically significant at the 200mg daily dose. Less frequent side effects included diarrhoea, vomiting, skin rash, and bloating. A list of recognised side effects reported for patients with cancer who are treated with imatinib is included in the Summary of Product Characteristics document (provided with the tablets).

Blood tests

Routine blood sampling may cause pain or bruising at the site where the needle/cannula (small plastic
tube) enters one's body. It is also possible that some patients may feel lightheaded or faint during/soon after venepuncture.

ECG

The ECG is a test used to check the heart's rhythm and electrical activity. During an ECG, subjects will need to lie still for a few minutes. In particular, small sticky sensors called electrodes will be attached to the chest with adhesive pads. This may cause slight discomfort when they are being put on or taken off. Male participants may need to have small patches of hair on the chest shaved to properly connect the electrodes. Some participants may be sensitive to the adhesive pads resulting in itchy red areas where the patches were placed. This reaction should settle within a few hours.

Cardiac MRI scan

The MRI scanner contains a strong magnet. Patients with implanted devices (CardioMEMS and LINQ systems) are compatible with MR scanning. Patients will be screened to ensure safety, should they have other medical devices/contraindications. Some people may feel uncomfortable in confined spaces. Foam pads are provided during scanning to minimise any discomfort.

Pregnancy

The effect of imatinib on a human foetus (unborn baby) is unknown. Women participating in the study must not become pregnant while receiving study medication and for 28 days after the last dose of the study drug is administered. To ensure that female patients who are exposed to imatinib will not become pregnant, the following measures will be employed:

- Women participating in the study must use acceptable contraception to prevent exposure to imatinib during pregnancy. The use of acceptable contraception will be ascertained and documented by the study doctor/clinical study team closely. Each female participant who is a woman of childbearing potential (can become pregnant), must practice acceptable methods of contraception for 28 days before the baseline visit and must have a negative pregnancy test at screening.
- During study treatment, female participants of childbearing potential must continue to use two methods of acceptable contraception for 28 days after the last dose of treatment (because there may still be some drug in the body).
- In cases, where there is no history of surgical sterilisation, participants must agree to practice an acceptable and reliable method of contraception listed below: Highly effective contraceptive methods with typical-use failure rate <1% i.e.

• Male or female sterilisation and long-acting reversible contraceptive methods (intrauterine devices and implants) prior to the female subject's entry into the study
• Progestogen-only injections if repeat rejections are documented as having been administered on schedule by a healthcare professional.

- Female participants of childbearing potential will be closely followed to ensure that they are not pregnant throughout the study. A negative serum pregnancy test result will be required before taking the study drug for the first time at a screening visit. If there is any suspicion that a female subject of childbearing potential might be pregnant (for example: a delay in menses or any other reason to suspect a pregnancy), subjects will be advised to immediately stop taking the study treatment, contact the site as soon as possible, and come to the site for further evaluation. If the blood test shows that a female subject is pregnant, they will not be allowed to continue to take the study drug and their participation in the study will be stopped. In such a case, they will be requested to consult the study doctor regarding potential risks to the unborn

baby and discuss all possibilities, including pregnancy termination. If it is decided to continue the pregnancy, subjects will be requested to inform the study doctor of the outcome of the pregnancy and the health of the baby up to 8 weeks of age.
Breastfeeding
Imatinib should not be taken during breastfeeding. It is possible that imatinib can pass into breast milk and potential side effects in the baby cannot be excluded. If a female subject is breastfeeding, they will have to notify the study doctor/clinical study team immediately.

Where is the study run from?
Imperial College London, UK

When is the study starting and how long is it expected to run for?
October 2024 to December 2027

Who is funding the study?
NIHR Efficacy and Mechanism Evaluation Programme, UK

Who is the main contact?
Dr Andreas A. Roussakis (Clinical Project Manager), a.roussakis@imperial.ac.uk

Contact information

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1010855

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
174836

Study information

Scientific Title
Repositioning oral imatinib for pulmonary arterial hypertension (REPIPAH)

Acronym
REPIPAH

Study objectives
The principle research question is "Does imatinib 200mg once daily reduce the resistance to blood flow through the lungs of patients with pulmonary arterial hypertension (PAH)?", thereby relieving the workload on the right side of the heart.

1. What is the frequency of dosing with Imatinib 200mg that is required to maintain a reduction response in TPR values in patients who achieve the primary endpoint?
2. Can we identify patients who will respond to imatinib based on circulating plasma proteins or patients' genotypes?

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 20/12/2024, South Central - Berkshire B Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +442071048276; berkshireb.rec@hra.nhs.uk), ref: 24/SC/0345

Study design

Phase II open-label clinical trial

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Pulmonary arterial hypertension

Interventions
This study involves one treatment arm so no randomisation; it is open-label. All subjects start on an oral dose of 200 mg imatinib mesylate (100 mg (x2) per dose) daily for 8 weeks. The dosing frequency is then adjusted and titrated to the change in total pulmonary resistance (TPR). The study design is dynamic depending on individual responses. The duration of treatment is up to 24 weeks and the frequency is variable i.e. once daily; once every other day; once every four days; or once weekly.

In more detail, patients will be asked at Baseline to take Imatinib 100 mg (x2) once daily. All patients will be assessed at the end of Week 8.
- Patients who demonstrate a reduction in TPR ≥20% from Baseline will be asked to take Imatinib 100 mg (x2) once every week until Week 24. They will be followed weekly and the frequency of dosing of Imatinib titrated to keep their TPR ≥20% below the Baseline, but never exceed the 200 mg daily dose.
-Patients who show less than a 20% reduction in TPR from baseline, at Week 8, might be considered for early termination of the drug (judged by the study physician).

All patient data, particularly TPR values and safety data, will be monitored on a weekly basis. TPR values and safety data will inform the dose decision-making process.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Imatinib mesylate [Imatinib mesylate]

Primary outcome(s)
Total pulmonary resistance (TPR) measured using CardioMEMS medical device measurements at baseline and 8 weeks

Key secondary outcome(s))
1. The distance walked on a flat surface in 6 minutes measured using the six-minute walk test (6MWD) at baseline, and at weeks 8 and 24 (or earlier if there is an early termination).
2. Right ventricular ejection fraction (RVEF) values measured using MR imaging of the heart (cardiac MRI scan) at baseline assessment, and at weeks 8 and 24 (or earlier if there is an early termination).
3. Plasma brain natriuretic peptide (NT-proBNP) levels measured using a validated assay on

peripheral blood samples at baseline, and at weeks 8 and 24 (or earlier if there is an early termination).
4. Quality of Life (QoL) scores measured using the EmPHasis-10 Quality of Life questionnaire at baseline, and at weeks 8 and 24 (or earlier if there is an early termination).

Exploratory:
1. The proportion of patients who respond and require dosing with Imatinib 200mg less frequently than once daily measured using CardioMEMs-derived TPR values weekly, from baseline to Week 24 (or earlier, if there is an early termination).
2. Total pulmonary resistance (TPR) measured using the CardioMEMS devices in relation to genes that regulate PDGF activity at baseline, and at weeks 8 and 24 (or earlier, if there is an early termination).
3. Total pulmonary resistance (TPR) measured using the CardioMEMS devices according to circulating plasma proteins measured using peripheral plasma samples at baseline, and at weeks 8 and 24 (or earlier, if there is an early termination)

Completion date
31/12/2027

Eligibility

Key inclusion criteria
1. Subjects aged between 18-80 years old
2. Idiopathic PAH; PAH heritable; PAH associated with connective tissue disease; PAH after ≥ 1-year repair of congenital systemic to pulmonary shunt, or PAH associated with anorexigens or other drugs
3. PAH management assisted by remote monitoring using implanted devices i.e. a CardioMEMS™ device to measure pulmonary artery pressure, and a LINQ™ device to measure heart rate and physical activity
4. Resting mean pulmonary artery pressure ≥25 mmHg, TPR >5 wood units, and normal or reduced cardiac output at entry
5. Six-minute walking distance >50m at entry
6. Stable on an unchanged PAH therapeutic regime comprising at least 2 therapies licensed for PAH (any combination of endothelin receptor antagonist, phosphodiesterase inhibitor or prostacyclin analogue) for at least 1 month prior to screening
7. Able to provide written informed consent prior to any study-mandated procedures
8. Contraception: Fertile females (women of childbearing potential) are eligible to participate after a negative highly sensitive pregnancy test, if they are taking a highly effective method of contraception during treatment and until the end of relevant systemic exposure. Fertile males who make use of condoms and contraception methods during treatment and until the end of relevant systemic exposure in women of childbearing potential.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
80 years

Sex
All

Key exclusion criteria
1. Unable to provide informed consent and/or are non-fluent speakers of the English language
2. Hypersensitivity to Imatinib or to any of the excipients
3. Clinically significant renal disease (confirmed by creatinine clearance <30 ml/min per 1.73m2)
4. Clinically significant liver disease (confirmed by serum transaminases >3 times the upper normal limit)
5. Patients receiving oral and/or parenteral anticoagulants*
6. Anaemia confirmed by haemoglobin concentration <10 g/dl
7. History of thrombocytopenia
8. Individuals known to have haemoglobinopathy sickle cell disease, thalassaemia
9. Hospital admission related to PAH or change in PAH therapy within 3 months prior to screening
10. History of left-sided heart disease and/or clinically significant cardiac disease, including but not limited to any of the following:
10.. Aortic or mitral valve disease (stenosis or regurgitation) defined as greater than mild aortic insufficiency, mild aortic stenosis, mild mitral stenosis, moderate mitral regurgitation
10.1. Mechanical or bioprosthetic cardiac valve.
10.2. Pericardial constriction, effusion with tamponade physiology, or abnormal left atrial size.
10.3. Restrictive or congestive cardiomyopathy
10.4. Left ventricular ejection fraction ≤50% (measured in echocardiogram at screening)
10.5. Symptomatic coronary disease
10.6. Significant (2+ for regurgitation) valvular disease other than tricuspid or pulmonary regurgitation
10.7. Acutely decompensated left heart failure within 1 month of screening
10.8. History of untreated obstructive sleep apnoea
11. Evidence of significant lung disease on high-resolution CT (if available) or recent (performed within 12 months) lung function, where FEV1 < 50% predicted FVC < 70% predicted, and DLCO (or TLCO) < 50% predicted if any CT abnormalities; judged by the Site Physician.
12. Patients with a history of uncontrolled systemic hypertension.
13. Acute infection (including eye, dental, and skin infections).
14. Chronic inflammatory diseases including HIV, and Hepatitis B
15. Women of childbearing potential who are pregnant or breastfeeding (if applicable).
16. Previous intracerebral haemorrhage.
17. Patients who have received an Investigational Medicinal Product (IMP) within 5 half-lives of the last dose of the IMP or 1 month (whichever is greater) before the baseline visit.
*This does not apply to single antiplatelet therapy

Date of first enrolment
15/11/2025

Date of final enrolment
31/03/2027

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Hammersmith Hospital
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Study participating centre
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Sponsor information

Organisation
Imperial College London

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Government

Funder Name
Efficacy and Mechanism Evaluation Programme

Alternative Name(s)
NIHR Efficacy and Mechanism Evaluation Programme, Efficacy and Mechanism Evaluation (EME), EME

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 disseminated [i. e. peer-reviewed scientific journal(s), conference presentation(s), publication to the HRA website and ISCRTN registry] at the end of the clinical trial with scientists and clinical experts in Pulmonary Hypertension. Results are expected to be shared with the research participants by the end of the clinical trial. Clinical and non-clinical research data can be shared with researchers at Imperial College London and the members of the UK National PAH network, upon request, for further research in the disease under study, following the Chief Investigator and Sponsor's explicit approvals.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes