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Riociguat in patients with respiratory disease and hypoxia

Submission date	Recruitment status	[_] Prospectively registered
11/03/2015	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
11/03/2015	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
07/05/2021	Respiratory	

Plain English summary of protocol

Background and study aims
This is a proof-of-concept study (i.e. a study to test a concept or theory to see whether it can work) to establish the effects of a drug called Riociguat in patients with lung disease. Pulmonary hypertension is a serious health condition in which the blood pressure in the vessels supplying the lungs (pulmonary arteries) is too high. Over time, this can lead to damage to the right hand side of the heart, which can affect how well it functions. Symptoms of the condition include breathlessness, tiredness, chest pains, palpitations and leg/ankle swelling. Riociguat is a new drug which was recently been approved for the treatment of two forms of pulmonary hypertension: pulmonary arterial hypertension and pulmonary hypertension that arises as a result of persistent blood clots in the lung vessels. Pulmonary hypertension can also arise in patients with lung disease who have low oxygen levels (hypoxia). Treatment options are limited and the outcome for these patients is poor so new treatment approaches are needed. We therefore wish to conduct a pilot study to establish the effects of Riociguat on symptoms, oxygen levels and right heart function in patients with lung disease who have reduced oxygen levels.

Who can participate?
Adults aged 40-80 diagnosed with chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis (IPF).

What does the study involve?
Prior to participants taking the study drug, they undergo an initial right heart catheterisation (a test to measure heart function and the pressures in the heart and lungs) and oxygen flight assessment test (a test to see whether they can fly at altitude without needing a supply of oxygen). Participants are then started on Riociguat. They are initially given a 1mg dose, three times a day. This is slowly increased every two weeks up until a maximum dose of 2.5mg, three times a day. Participants then undergo another right heart catheterisation and oxygen flight assessment test. Once these are done, the study medication is discontinued.

What are the possible benefits and risks of participating?
Due to the nature of the study being proof-of-concept, there will be no direct benefits to the participants but it is hoped that any findings could prompt further large scale studies in this

area. The only risks involved in this study relate to the study interventions, namely right heart catheterisation and taking the study medication, Riociguat. Right heart catheterisation is a routine procedure performed in our centre and the frequency of any risk such as pain, bleeding or abnormal heart rhythms is less than 1%. The amount of radiation used during the procedure in the form of X-ray guidance equates to no more than three times the amount of normal background radiation exposure in one year. Previous trials of Riociguat have shown most of the side effects are non-severe and relate to either dizziness (from reduced blood pressure) or gastro-intestinal symptoms. The only serious problem that has occurred in previous studies is coughing up blood, but less than 1% of participants have experienced this.

Where is the study run from?
Freeman Hospital (UK)

When is the study starting and how long is it expected to run for?
December 2014 to May 2015

Who is funding the study?
Bayer Healthcare (Germany)

Who is the main contact?
Dr Logan Thirugnanasothy

Contact information

Type(s)
Scientific

Contact name
Dr Logan Thirugnanasothy

Contact details
Freeman Hospital
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Additional identifiers

EudraCT/CTIS number
2014-001008-23

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
17131

Study information

Scientific Title
Riociguat in patients with respiratory disease and hypoxia – a proof-of-concept study

Acronym
RIOPRED

Study objectives
Our hypothesis is that Riociguat at a maximum tolerated dose will prevent changes in oxygen saturation, pulmonary vascular resistance and mean pulmonary artery pressure (PAP) that are precipitated by worsening hypoxia in patients with respiratory disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee North East - Newcastle & North Tyneside 2, 16/07/2014, ref: 14/NE1057

Study design
Non-randomised; Interventional; Design type: Treatment

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Other

Study type(s)
Treatment

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
Topic: Respiratory disorders; Subtopic: Respiratory (all Subtopics); Disease: Respiratory

Interventions
Participants will initially undergo right heart catheterisation which measures right heart function and pressure. This is followed by a hypoxic challenge test which is used in routine clinical practice to determine if certain respiratory patients require oxygen for air travel. The right heart function and pressure measurements are then repeated. Participants will then be given the study drug, Riociguat. The study drug will be started initially at 1mg, three times daily and titrated fortnightly according to blood pressure, with a maximum possible dose of 2.5mg, three times daily. When the participant is on the maximum tolerated dose, participants will undergo repeat right heart catheterisation and hypoxic challenge testing. Other assessments that will be

performed for secondary outcome measures will be oxygen saturations, severity of breathlessness and lung function testing.

The following assessments will then be undertaken.

1. Spirometry and diffusing capacity: routine breathing tests to measure lung function
2. Venepuncture: bloods samples will be updated to ensure eligibility for the study and will be repeated as part of the drug safety monitoring process.
3. Right heart catheterisation: the diagnostic procedure performed for suspected pulmonary hypertension where the function and pressure in the right heart is measured.
4. Hypoxic challenge test: a gas mixture of 15% Oxygen is inhaled for up to 20 minutes.
5. Arterial blood gas: a blood test to measure the levels of oxygen and carbon dioxide.
6. Riociguat: the study drug will be started initially at 1mg, three times daily and titrated fortnightly according to blood pressure, with a maximum possible dose of 2.5mg, three times daily.

Intervention Type
Drug

Phase
Phase I

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

Primary outcome measure
The acute effects of Riociguat on:
1. Oxygen saturations (SaO2)
2. The partial pressure of oxygen (PaO2)
3. Mean pulmonary artery pressure (PAP)
4. Pulmonary vascular resistance (PVR)
5. Perceived breathlessness
The information will be recorded at both episodes of right heart catheterisation/hypoxic challenge test.

Measurement tools:
1. Pulse oximeter
2. Arterial blood gas
3. Right Heart Catheterisation
4. Visual analogue scale for breathlessness
5. Pulmonary function test

Secondary outcome measures
The effects of Riociguat on diffusing capacity, SaO2 and on perceived breathlessness, along with safety in respiratory patients, recorded from the screening/consent visit and the final visit of drug titration.

Overall study start date
17/06/2014

Completion date

31/08/2016

Eligibility

Key inclusion criteria
1. Age 40 to 80 years, Male and Female
2. Primary diagnosis of either chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) with recent stability
3.Capacity and willingness to provide fully informed consent for participation in the study

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
Planned Sample Size: 10; UK Sample Size: 10

Total final enrolment
10

Key exclusion criteria
1. On prescribed oxygen therapy, nitrates (tablets or sublingual), dipyridamole, theophylline, warfarin, clopidogrel, rivaroxaban and dabigatran
2. Other concomitant respiratory diagnoses including asthma, interstitial lung disease (not idiopathic), pulmonary hypertension (of any other aetiology), lung cancer, recent respiratory infection, recent acute pulmonary embolism, recent pneumothora
3. Unable to give written, informed consent
•Contraindication to spirometry not included elsewhere: recent eye surgery, glaucoma
4. Uncontrolled arterial hypertension (systolic BP > 180mmHg and/or diastolic BP > 110mmHg
5. Systolic BP < 95mmHg
6. Resting awake heart rate < 50 beats per minute or > 105bpm
7. History of uncontrolled atrial fibrillation within 3 months of screening
8. Left heart failure with an ejection fraction less than 40%
9. Hypertrophic Obstructive Cardiomyopathy (HOCM)
10. Proven or suspected active or recent* coronary artery disease
11. Other active atherosclerotic disease: active peripheral arterial disease, stroke within 3 months of screening
12. Significant valvular heart disease
13. History of active or serious haemoptysis/pulmonary haemorrhage
14. Hepatic dysfunction
15. Bilirubin > 2 times ULN at screening and/or
16. ALT or AST > 3 times ULN at screening and/or
17. Albumin < 32g/L/hepatic encephalopathy > grade 1 at screening
18. Renal insufficiency: GFR < 30ml/min
19. Pregnant or lactating women

Date of first enrolment
17/12/2014

Date of final enrolment
30/06/2016

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Sponsor information

Organisation
Newcastle Hospitals Foundation NHS Trust

Sponsor details
Wolfson Unit of Clinical Pharmacology
Institute of Cellular Medicine
Framlington Place
Newcastle Upon Tyne
England
United Kingdom
NE2 4HH

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Government

Funder Name
Bayer Healthcare

Alternative Name(s)
BHC

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Germany

Results and Publications

Publication and dissemination plan
Plans for publication will be in 2016 in a peer reviewed journal, along with presentation at relevant Pulmonary Hypertension meetings.

Intention to publish date
31/08/2017

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Abstract results		08/11/2016	07/05/2021	No	No