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Combination therapy for pulmonary hypertension using racecadotril

Submission date	Recruitment status	[X] Prospectively registered
28/06/2013	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
28/06/2013	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
11/09/2019	Circulatory System	

Plain English summary of protocol

Background and study aims
This study aims to measure the safety and effectiveness of racecadotril in patients with pulmonary hypertension taking the drug sildenafil. In this disease, the pressure of blood in the arterial system (network of channels that carry blood from the heart to the organs) of the lungs is increased due to the narrowing of the blood vessels in the lungs. In time it leads to heart failure, symptoms of shortness of breath and ultimately premature death. New treatments that reverse the excessive constriction seen in the blood vessels of the lung are needed. The study will investigate the effect of a drug (racecadotril) that has not been used in pulmonary hypertension before and its effect in addition to patients current medication sildenafil (otherwise known as Revatio) will also be studied. Racecadotril may relax blood vessels in the lungs. It stops a particular enzyme (enzymes are complex proteins that cause a specific chemical change in all parts of the body) from working and by doing this has been shown to reduce blood pressure in the lungs of animals. Racecadotril is already a licensed medicine in over 30 countries, including the UK, for patients with diarrhoea. It is widely available, with a reassuring safety record. Though there are no data describing its use in patients with pulmonary hypertension, it is not contra-indicated in patients with cardiovascular disease. The aim of this study, therefore, is to treat patients suffering with pulmonary hypertension with this combination of medicines to measure accurately if this therapy might improve future treatment of this disease. The study is split into two steps, step one is further split into steps 1a and 1b, which will recruit 12 patients (6 in each step). Step 2 will recruit 12 patients.

Who can participate?
Step 1: Patients currently taking sildenafil, who have not experienced any complications with their treatment, and are scheduled for routine right heart catheterisation
Step 2: Patients who are currently taking sildenafil for pulmonary hypertension and have not experienced any complications with their treatment
Patients can enter either or both steps

What does the study involve?
Patients who take part receive either the active treatment capsule(s) or a placebo (dummy) which looks the same but does not contain active ingredients. Each step involves 12 patients, 8 on racecadotril and 4 on the dummy pill. Each patient is put into a treatment group by chance

using a computer programme. The trial is double blind so neither the patient nor their doctor know which treatment group the patient is in but this can be found out, if necessary. There are a number of screening tests for each step; all screening results must be acceptable for study entry. Step 1: a review of medical history; a physical examination; a walking test for 6 minutes; blood sample for routine testing; routine care right heart catheterisation procedure results. Step 2: Same screening tests as step 1 excluding the right heart catheterisation.
Step 1: The procedures in this step take place in hospital over 1 day. As part of routine care each patient has a procedure called a right heart catheterisation involving the insertion of a tube into a blood vessel in the leg and a wire inserted through the tube and into the heart. The patient then takes 1 or 2 capsules of the study drug. The right heart catheterisation procedure is extended for the study by about 2 hours to enable the measurement of changes in blood flow and blood pressure in the lungs after taking the trial drug.
Each patient has 5 sets of blood samples taken over a period of up to 6 hours 15 minutes; usually these samples are collected via another tube, inserted once (e.g. in the arm) that remains in place until the end of the blood sampling period. Blood flow and pressure in the patients lungs and other areas are monitored, as are emerging side effects.
Step 2: The procedures in this step last for 12 - 14 days. The first and last day of this step takes place in hospital but the patients take the treatment at home. The patient has a walking test for 6 minutes, a blood sample and heart rate and blood pressure taken just before the drug is taken. Each patient takes 1 or 2 capsules, 3 times a day for about 14 days. A nurse calls each patient on the 7th day of treatment to discuss any side effects. After about 14 days, patients return to hospital for a blood sample, a 6-minute walking test, heart rate and blood pressure measurements and a side effects assessment.

What are the possible benefits and risks of participating?
There is no benefit to the patient as a participant in the study but patients may be helping to improve treatment for future patients with pulmonary hypertension. Following consideration of the results it will be known if racecadotril, used in combination with sildenafil, has potential to improve pulmonary hypertension treatment. Racecadotril has not been used in combination with sildenafil before and, although there are no known interactions between the two drugs, there could be some side effects which have not been seen. Racecadotril is licenced for use in the UK, and many other countries for patients with diarrhoea. Racecadotril is not licensed for the treatment of pulmonary hypertension. It has been taken in higher doses than we plan to use in this study without any problems and is not known to interact with other drugs.

Where is the study run from?
This study is being managed by the University College London Clinical Trials Unit. University College London (UCL) is the study sponsor, the organisation legally responsible for the study. Patient care will be carried out by staff at the Royal Free Hospital, London.

When is the study starting and how long is it expected to run for?
August 2013 to August 2015

Who is funding the study?
1. The British Heart Foundation (UK)
2. The Biomedical Research Centre (UCL Hospitals/UCL) (UK)
3. The Clinical Research Development Committee (UCL Hospitals/UCL) (UK)

Who is the main contact?
CCTU Enquiry Desk, Comprehensive Clinical Trials Unit at UCL

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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2012-003921-13

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
14534

Study information

Scientific Title
COMbination therapy for PulmonAry hypertension using RacEcadotril (COMPARE): a randomised trial

Acronym
COMPARE

Study objectives
This trial aims to measure the efficacy and safety of racecadotril in patients with pulmonary hypertension taking sildenafil. In this disease, the pressure of blood in the arterial system of the lungs is increased. In time it leads to heart failure, symptoms of shortness of breath and ultimately premature death. New treatments that reverse the excessive constriction seen in the blood vessels of the lung are needed.

Racecadotril has a novel mechanism of action that we hypothesise will relax blood vessels in the lungs. It inhibits the enzyme neutral endopeptidase and by this mechanism has been shown to reduce pulmonary blood pressure in animal models. Racecadotril is already an existing licensed medicine in 30 European countries (including the UK), Asia and South America for patients with diarrhoea. Inhibition of neutral endopeptidase in the intestine by racecadotril reduces the extent of infectious diarrhoea. Indeed, racecadotril has had an established role in the treatment of patients with infectious diarrhoea since its launch in 1993. It is now widely available as a generic drug, has a reassuring safety record (>1 million adult exposures).

Though there are no data describing its use in patients with pulmonary hypertension, it is not contra-indicated in patients with cardiovascular disease. This trial will explore the pharmacology of racecadotril for the first time in patients with pulmonary hypertension taking sildenafil and in this regard, the drug will be used outside its licensed indication.

The aim of this project, therefore, is to treat patients suffering with pulmonary hypertension with this new combination of medicines to measure accurately if this therapy might improve treatment of this disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
London-Westminster, First MREC approval date 07/06/2013, ref: 13/LO/0387

Study design
Randomised interventional treatment trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheets

Health condition(s) or problem(s) studied
Topic: Cardiovascular, Respiratory; Subtopic: Cardiovascular (all Subtopics), Respiratory (all Subtopics); Disease: Respiratory, Congenital Heart Disease and Pulmonary Hypertension

Interventions
Racecadotril and Placebo capsule(s). Placebo is matched in appearance to active.

Step 1a: 1 racecadotril 100mg capsule OR 1 placebo capsule administered once
Step 1b: 1 or 2 racecadotri 100mg capsules OR 1 or 2 placebo capsules (depending on Independent Data Monitoring review, administered once)
Step 2: 1 or 2 racecadotril 100mg capsules OR 1 or 2 placebo capsules (depending on Independent Data Monitoring review, administered 3 x a day for 12 -14 days)

Study Entry : Randomisation patients may be randomised more than once if they consent to both steps

Intervention Type
Other

Phase
Phase II

Primary outcome measure
The maximum percentage change from baseline in plasma atrial natriuretic peptide (ANP) concentration; Timepoint(s): Step 1: Day 0 baseline & 1, 2, 3 and 6 hours post IMP
Step 2: Day 0 baseline & at 12-14 days of IMP

Secondary outcome measures
Step 1:
1. Additional biomarkers in the blood; timepoints: Day 0 baseline & at 1,2,3 & 6 hours post IMP
2. Pulmonary haemodynamic assessments; timepoints: Day 0 baseline and post IMP at 1.5 hours and 2 hours
3. Systemic haemodynamic assessments; timepoints: Day 0 baseline and over 6 hours, at half hourly intervals post IMP
4. Safety assessment; timepoints: Day 0 baseline and over 6 hours, at half hour post IMP

Step 2:
1. 6 minute walk test; timepoints: Day 0 baseline and at 12-14 days post treatment with IMP.
2. Additional biomarkers in the blood; timepoints: Day 0 baseline and at 12-14 days post treatment with IMP
3. Systemic haemodynamic assessments; timepoints: Day 0 baseline and at 12-14 days post treatment with IMP.
4. Safety assessment timepoints: At 7 days of IMP treatment and at 12-14 days post treatment with IMP

Overall study start date
01/08/2013

Completion date
05/04/2017

Eligibility

Key inclusion criteria
1. WHO Group I pulmonary hypertension (i.e. idiopathic, familial or associated with connective tissue diseases
2. 18-80 years old
3. Technically satisfactory routine right heart catheterisation (Step 1 only)*

4. On sildenafil (20-100 mg; t.i.d.)
5. Six minute walk distance of >150 m
6. No changes to PH specific therapies for 1 month
7. Not pregnant (women only). Women of child-bearing potential must have a negative pregnancy test within seven days prior to randomisation they must be willing to use an effective method of contraception (including hormonal or barrier method of birth control) from the time consent is signed until six weeks after treatment discontinuation.
8. Able to provide consent for the trial
* Technically satisfactory means that the PI or delegated physician is content that the patient is able to have the catheter in for longer and that the necessary trial information is able to be extracted.
9. Target Gender: Male & Female

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
80 Years

Sex
Both

Target number of participants
Planned Sample Size: 24; UK Sample Size: 24; Description: Patients will be randomised 2:1, active: placebo

Total final enrolment
21

Key exclusion criteria
1. Known sensitivity to racecadotril or its excipients
2. Clinical diagnosis of liver cirrhosis or ALT/AST >2 X ULN
3. Kidney disease with an eGFR of <50 ml/min
4. History of angioedema
5. Systolic blood pressure <85 mmHg
6. Known history of drug or alcohol abuse within six months of enrolment
7. Participation in a clinical study involving another investigational drug
8. Women who are breastfeeding
9. Patients taking ACE inhibitors
10.Any clinical condition for which the investigator would consider the patient unsuitable for the trial

Date of first enrolment
12/02/2014

Date of final enrolment
11/10/2016

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University College London
London
United Kingdom
WC1E 6BT

Sponsor information

Organisation
University College London (UK)

Sponsor details
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Sponsor type
University/education

Website
http://www.ucl.ac.uk/

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation (BHF) (UK) Grant Codes: PG/11/88/28992

Alternative Name(s)
the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Funder Name
NIHR Biomedical Research Centre (BRC) (UK)

Funder Name
University College London Hospitals NHS Foundation Trust

Alternative Name(s)
University College London Hospitals, UCLH

Funding Body Type
Private sector organisation

Funding Body Subtype
Universities (academic only)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Participants were able to find out their treatment allocation and the results of the study (including access to the journal publication) by contacting the site research team. A summary of the final study results was produced for participants should they have requested/ request this.

(updated 11/09/2019, previously: Not provided at time of registration)

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results			03/09/2019	No	No
Results article	results	01/05/2019	03/09/2019	Yes	No
HRA research summary			28/06/2023	No	No