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The PIROUETTE trial

Submission date 09/01/2017	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 11/01/2017	**Overall study status** Completed	
Last Edited 31/08/2021	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims
There are approximately 1 million people in the UK living with heart failure. In around half these patients, the pumping function of the heart is normal. This is known as preserved ejection fraction (HFpEF). At present there are no treatments that improve survival for this type of heart failure. There is evidence to suggest that HFpEF is caused by scarring in the heart tissue. Pirfenidone is a relatively new treatment that reduces scar tissue. In patients with lung scarring it reduces the amount of scar tissue. This leads to an improvement in quality of life and outlook in these patients. The aim of this study is to assess whether pirfenidone reduces the amount of heart scarring in patients with heart failure with normal pumping function.

Who can participate?
Adults aged 40 year and over with HFpEF

What does the study involve?
Participants are randomly allocated to one of two groups. Those in the first group take three capsules containing pirfenidone three times a day for one year. Those in the second group take three capsules containing a placebo (dummy drug) three times a day for one year. Participants are followed up over 11 clinic appointments over the course of one year through clinical assessments, blood testing, heart rhythm monitoring and reviewing diary cards kept by participants.

What are the possible benefits and risks of participating?
Participants benefit from having detailed assessments of their hearts undertaken and receive closer follow-up than usual with more access to heart specialists. There are minimal risks involved with participating, as pirfenidone is not associated with any serious side-effects and any side-effects are often mild and non-serious.

Where is the study run from?
1. Wythenshawe Hospital (UK)
2. Manchester Royal Infirmary (UK)

When is the study starting and how long is it expected to run for?
March 2016 to April 2020

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2016-002647-42

ClinicalTrials.gov (NCT)
NCT02932566

Protocol serial number
31792

Study information

Scientific Title
A randomised, double-blind, placebo-controlled, phase 2 study of the efficacy and safety of pirfenidone in patients with heart failure and preserved left ventricular ejection fraction

Acronym
PIROUETTE

Study objectives

Pirfenidone will target the fundamental underlying pathophysiological mechanism of HFpEF i.e. ECM expansion (myocardial fibrosis), and, as a result, lead to regression of myocardial fibrosis. If true, this should lead onto improvements in cardiac structure and function, fluid status and quality of life, and thus, ultimately, translate into improved outcome.

Ethics approval required
Old ethics approval format

Ethics approval(s)
North West – Liverpool Central NRES, 28/11/2016, ref: 16/NW/0717

Study design
Randomised; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Specialty: Cardiovascular disease, Primary sub-specialty: Heart Failure; UKCRC code/ Disease: Cardiovascular/ Other forms of heart disease

Interventions
Patients will be randomised at visit 1 in a 1:1 ratio to one of two groups. Randomisation will be accomplished over the internet using web randomisation software accessed using a secure website provided via the CTRC. Block randomisation, stratified by gender (because ECM volume is higher in females than males), will be implemented, with computer generated randomisation allocations and randomly varying block sizes.

Intervention group: Participants receive 3 x 267mg capsules of pirfenidone three times daily for 52 weeks.
Control group: Participants receive 3 x capsules of placebo three times daily for 52 weeks.

Follow up takes place at University Hospital of South Manchester, and includes 11 patient visits in total. Follow up involves clinical examination, review of medications, assessment of participant compliance, assessment of adverse events, pregnancy tests (if applicable), review of diary card, electrocardiogram, blood tests for efficacy (NT-proBNP, hsTnT), and blood tests for safety (U&Es, FBC, LFTs).

Intervention Type
Drug

Phase
Phase II

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

Primary outcome(s)
Absolute change in myocardial ECM volume is measured using cardiovascular magnetic resonance (CMR) scanning at baseline and 52 weeks

Key secondary outcome(s))
1. Left ventricular (LV) volumes, mass, ejection fraction and strain is measured using cardiovascular magnetic resonance (CMR) scanning at baseline and 52 weeks
2. Absolute myocardial ECM volume is measured using cardiovascular magnetic resonance (CMR) scanning at baseline and 52 weeks
3. Absolute myocardial cell volume is measured using cardiovascular magnetic resonance (CMR) scanning at baseline and 52 weeks
4. LV diastolic function, strain and torsion, measured using echocardiography at baseline and 52 weeks
5. Left atrial volume and function is measured using cardiovascular magnetic resonance (CMR) scanning at baseline and 52 weeks
6. Myocardial energetic status (phosphocreatine to adenosine triphosphate ratio, PCr/ATP) is measured using 31Phosphorus magnetic resonance spectroscopy (31P MRS) at baseline and 52 weeks
7. Plasma levels of NT-proBNP and hsTn are measured using blood tests at baseline and 52 weeks
8. Exercise tolerance is measured using 6 minute walk distance at baseline and 52 weeks
9. Health status (quality of life), HF symptoms and physical limitations, measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ) score baseline and 52 weeks
10. All-cause mortality, cardiovascular mortality and hospitalisation for heart failure is measured by SAE and SUSAR at baseline and 52 weeks
11. Safety of pirfenidone is measured by recording adverse events (AE), serious adverse events (SAE), serious adverse reactions (SAR) and suspected unexpected serious adverse reactions (SUSAR), vital signs and physical examination findings, haematological and biochemical laboratory blood tests and an electrocardiogram (ECG), measured using patient interviews, clinical examination, blood tests and ECGs, at baseline (Visit 0) and at weeks 2, 4, 8, 13, 26, 39, and 52, and, in addition, a telephone assessment at week 1

Completion date
07/04/2020

Eligibility

Key inclusion criteria
1. Written informed consent
2. Male or female; aged 40 years or older
3. HF, defined as one symptom (dyspnoea on exertion,orthopnoea or paroxysmal nocturnal dyspnoea) present at the time of screening, and one sign (peripheral oedema, crackles on chest auscultation post-cough, raised jugular venous pressure or chest x-ray demonstrating pleural effusion, pulmonary congestion, or cardiomegaly) present at the time of screening or in the previous 12 months
4. LVEF > 45% at Visit 0
5. BNP ≥ 100 pg/ml or NTproBNP ≥ 300 pg/ml at Visit 0. For patients in atrial fibrillation on Visit 0 ECG, BNP > 300pg/ml or NTproBNP > 900 pg/ml at Visit 0

In order to be randomised, patients must also have myocardial fibrosis, defined as ECM volume > 27% by CMR at Visit 0.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
94

Key exclusion criteria
1. Myocardial infarction, coronary artery bypass graft surgery or percutaneous coronary intervention within the previous 6 months.
2. Probable alternative cause of patient's HF symptoms that in the opinion of the investigator primarily accounts for patient's dyspnoea such as significant pulmonary disease, anaemia or obesity. Specifically, patients with the below are excluded:
2.1. Severe chronic obstructive pulmonary disease (COPD) (i.e., requiring home oxygen, chronic nebuliser therapy,or chronic oral steroid therapy), or
2.2. Haemoglobin < 9 g/dl, or
2.3. Body mass index (BMI) > 55 kg/m2
3. Known pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy
4. Clinically significant congenital heart disease
5. Presence of severe valvular heart disease
6. Atrial fibrillation or flutter with a resting ventricular rate > 100bpm
7. Any medical condition, which in the opinion of the Investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study
8. Severe renal dysfunction at Visit 0, defined as eGFR <30 mL/min, or end-stage renal disease requiring dialysis
9. History of severe hepatic impairment or liver dysfunction at Visit 0, defined as total bilirubin above the ULN (excluding patients with Gilbert's syndrome), AST or ALT >3 times the ULN or alkaline phosphatase >2.5 times the ULN.
10. Prolonged corrected QT interval, defined as a corrected QT interval >500 msec on ECG using Bazett formula
11. Known hypersensitivity to any of the components of the IMP
12. Use of other investigational drugs at the time of enrolment, or within 30 days or 5 half-lives of enrolment, whichever is longer.
13. Fluvoxamine use 28 days prior of Visit 0
14. Contraindication to MRI scanning or gadolinium-basedcontrast agent
15. Pregnancy, lactation or planning pregnancy

Date of first enrolment
30/01/2017

Date of final enrolment

30/12/2018

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Wythenshawe Hospital
University Hospital of South Manchester NHS Foundation Trust
Southmoor Road
Manchester
United Kingdom
M23 9LT

Study participating centre
Manchester Royal Infirmary
Central Manchester University Hospital NHS Foundation Trust
Oxford Road
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M13 9WL

Sponsor information

Organisation
University Hospital of South Manchester NHS Foundation Trust

ROR
https://ror.org/00he80998

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		12/08/2021	31/08/2021	Yes	No
HRA research summary			28/06/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes