



## Double-blind randomised controlled trial of Pirfenidone in patients with heart failure and preserved ejection fraction

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### Participant Information Sheet and Consent form

Version 3.0: 7 December 2016

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#### How to contact us

If you have any questions about this study or research in general, please contact:

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#### You are invited to take part in a research study

- ✿ This clinical trial is being carried out by a team of trained doctors, nurses and researchers under the supervision of Dr Chris Miller, the study is sponsored by the University Hospital of South Manchester NHS Foundation Trust
- ✿ Before you decide if you would like to take part, it is important for you to understand why this research is being done and what taking part would involve for you.
- ✿ Please take your time to read the information carefully. Discuss it with your friends, relatives, or GP if you wish to. Take time to consider whether or not you wish to take part.
- ✿ Your participation is entirely voluntary so you do not have to take part if you do not want to.
- ✿ Please ask a member of the research team if there is anything that is not clear, or if you would like more information.
- ✿ Thank you for reading this information. We hope this research will be of interest to you.

#### Important things that you need to know

- ✿ This clinical trial has been designed to test whether a drug called pirfenidone leads to a reduction in heart muscle scarring and improves heart function in patients with heart failure.
- ✿ Taking part involves 11 visits to the hospital and 1 telephone call. Study tests include: blood tests, heart trace (ECG), echo (ultrasound scan of your heart), heart magnetic resonance imaging (MRI scan of your heart), short questionnaire, walk test. If you are female and of child bearing age you will need to have regular pregnancy tests and there will be additional phone calls to check the results of the pregnancy tests

### Why have I been asked to take part?

You have been invited to take part because you have heart failure with preserved ejection fraction.

### Why are we doing this research?

Heart failure with normal heart pumping function (so called “preserved ejection fraction”) is very common. However, there is no treatment that leads to an improvement in quality of life or life expectancy.

Heart muscle scarring (fibrosis) is an important process in the development of heart failure with preserved ejection fraction. We want to find out if a medicine called pirfenidone leads to a reduction in heart muscle scarring and improves heart function. Ultimately we want to find out if pirfenidone leads to improved quality of life and life expectancy of patients with heart failure.

### What is pirfenidone?

Pirfenidone is currently used in patients with lung scarring. In patients with lung scarring, pirfenidone leads to a reduction in the amount of lung scarring. This leads to improved lung function, improved exercise capacity (i.e. patients can walk further before they have to stop) and improved life expectancy (i.e. patients live longer). We want to find out if pirfenidone has the same effects in patients with scarring and heart failure as it does in patients with lung scarring.

### What will happen if I agree to take part?

If you agree to participate you will be seen by a doctor or nurse who will go through your medical history. You will have a blood sample taken (approximately 20ml or 4 teaspoons), a heart trace (ECG), an echo, a heart MRI scan (some patients will undergo 2 heart MRI scans), answer a short questionnaire and undergo a measurement of how far you can walk in 6 minutes. The visit will take up to about half a day in total.

If the results of these tests show that you are eligible to take part in the trial you will then be assigned to treatment with either pirfenidone or placebo. A placebo is a medication with no active ingredients and is used to work out how effective the pirfenidone is. Whether you receive pirfenidone or placebo will be decided at random by computer. You and the research team will not be able to choose which treatment you receive. The pirfenidone and the placebo capsules are identical and therefore you and the research team will not know which treatment you will take during the study.

The study will last for 1 year. We will keep a close eye on you during the study. We will phone you 1 week after starting the medication and see you in clinic, take a blood sample and do an ECG at approximately 2, 4, 8, 13, 17, 21, 26 and 39 weeks after you begin the study. After 1 year we will repeat the echo scan, the heart MRI scan (if you had 2 MRI scans at the start of the study, you will have 2 at the end), the questionnaire and the walk test. In total you will have 1 telephone call and 11 clinic visits during the study. Women of childbearing age will have 6 additional telephone calls to follow up the results of home pregnancy testing.

The clinic visits will usually be at Wythenshawe Hospital. If you are usually seen at Manchester Royal Infirmary some of your visits may take place there. Travel costs will be reimbursed.

If the results of the initial tests show that you are not eligible to take part in the trial we will record your results and use them to improve the medical community’s understanding of heart failure.

### What tests/procedures will take place?

Blood test: A blood sample (approximately 20ml or 4 teaspoons) will be taken in the usual manner. Optionally, and with your consent some of the sample will be kept for use in future research (other research

studies), which may include analysis for genetic markers of heart diseases.

**ECG (heart trace):** An ECG measures the electrical activity of the heart. An ECG will be done in the usual way – stickers will be put on your chest and limbs to which the leads will be attached.

**Echo (heart ultrasound scan):** An echo measures the structure and function of the heart. You will most likely have had an echo scan as part of your clinical care. This will be no different. An ultrasound probe and some gel will be put on the outside of your chest. It will take about 20 minutes. It is the same technique as is used for pregnancy scanning and is completely safe.

**Heart MRI scan:** Heart MRI scanning gives detailed information about the structure and function of the heart and measures the amount of scar in the heart muscle. The scanner is a ‘doughnut-shaped’ scanner. You will be asked to lie still on a comfortable bed and the bed will move into the scanner. During the scan you will receive some imaging contrast agent (‘dye’) called “gadolinium” through a cannula, or a small plastic tube, placed into a vein in your arm before the scan. The scan will last about 40 minutes. Some patients in the study will have a second MRI scan that will measure how much energy the heart is making and using. This will take about 20 minutes and will not involve dye.

MRI scanning is considered to be very safe. It uses magnetic fields to make the pictures. It does not use harmful radiation. The NHS website describes MRI scanning as “painless and harmless”, and “one of the safest medical procedures currently available”. Gadolinium contrast is used routinely in clinical heart MRI scanning. It is very well tolerated. Allergic reaction occurs very rarely (1 in 10,000 patients). Some people who are claustrophobic do not like being in the scanner, although the bore of the scanner (the hole in the doughnut) is wide and you will be able to talk with the radiographers at all times and the majority of

people tolerate the scan well. **Walk test:** The walk test is a measure of exercise capacity. It simply involves you walking up and down a corridor at your own pace for up to 6 minutes and us measuring how far you walk. You can stop at any time.

You will also be asked to record any symptoms you may experience or if you miss any tablets in a diary.

### Study time line

The timeline for the study visits is given in the figure below. The timing of the visits does not have to be exact – there is leeway in each visit. The review in clinic will include a check of how you are, a physical examination (e.g. height, weight, blood pressure), blood test and ECG. Women of child bearing potential will also have a pregnancy test at each visit and be asked to do a home pregnancy test at weeks 24, 28, 32, 36, 44 and 48, which will be followed by a phone call by the research team to check the result.

0 Week -1	• Consent, blood sample, ECG, echo, heart MRI scan/s, walk test
1 Week 0	• Prescribed pirfenidone or placebo
2 Week 1	• Telephone call
3 Week 2	• Review in clinic
4 Week 4	• Review in clinic
5 Week 8	• Review in clinic
6 Week 13	• Review in clinic, prescribed pirfenidone or placebo
7 Week 17	• Blood sample
8 Week 21	• Blood sample
9 Week 26	• Review in clinic, prescribed pirfenidone or placebo
10 Week 39	• Review in clinic, prescribed pirfenidone or placebo
11 Week 52	• Review in clinic, blood sample, ECG, echo, heart MRI scan/s, walk test

### Will my details be kept confidential?

Yes, only people working on the study, or working to ensure the study is run correctly, will have access to the data. All information collected about you during this study and any future follow up will be confidential, and will be handled, stored and destroyed in accordance with the Data Protection Act 1998. With your permission we will inform your GP.

### What are the benefits and risks of taking part?

You will have a more detailed assessment of your heart than you usually would. You will receive closer follow-up than you would usually have, and have more access to heart specialists than normal. You will also help to determine whether pirfenidone will be of benefit to patients with heart failure, and contribute to a better understanding of heart failure, all of which may lead to benefits for you and other people with heart failure.

The safety of pirfenidone has been evaluated in many thousands of patients with lung scarring. Pirfenidone is not associated with any serious side effects. Side effects that are most common include decreased appetite, weight loss, nausea, heart burn, abdominal discomfort, fatigue, headache, rash and sensitivity to the sun. However, these side effects are generally mild to moderate in severity, resolve on reducing the dose or stopping it, and are not associated with any significant clinical effects. A full list of possible side effects is provided in the Product Information Leaflet in Appendix 1. Rarely, an increase in liver function blood tests can occur with pirfenidone, however the tests return to normal on reducing the dose or stopping it and no clinically significant consequences have been reported.

You will be monitored very closely while you are in the study, with regular checks in clinic as described above. In addition, there will always be a doctor or nurse who is part of the research team that you can phone 24 hours a day if you are concerned about anything or for

advice. You will be given the phone number to call at the start of the study. If you do develop side effects the research team will speak with you about reducing the dose or stopping it.

Grapefruit juice and Seville oranges can potentially reduce the effect of pirfenidone therefore you are asked to avoid these during the study. Pirfenidone capsules contain gelatine.

Patients who are pregnant cannot take part in the study. Women who could become pregnant will be asked to have pregnancy tests before and during the study and must use an effective contraceptive during the study. Men who have partners who could become pregnant must also use an effective contraception method. If you find that you have become pregnant while taking part in the study or within 12 weeks of taking the last dose, you should immediately tell the research team. Similarly, if partners of male participants become pregnant during the study or within 17 weeks of taking the last dose you must immediately inform the research team. The partner will be asked to complete a consent form so medical information about their pregnancy and its outcomes can be collected.

### What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to one of the researchers who will do their best to answer your questions. Our contact number is 0161 291 4075. If you remain unhappy and wish to complain formally, you can do this by contacting the Patient Liaison Service. The contact number for the **Patient Liaison service** is **0161 291 5600** and the email address is **pls@uhsm.nhs.uk**. In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against University Hospital of South Manchester NHS Trust but you may have to pay your legal costs. The normal National

Health Service complaints mechanisms will still be available to you.

### Who has reviewed the study?

Research involving using licenced drugs being used in new ways is reviewed by an authority called the Medicines and Healthcare products Regulatory Agency (MHRA). If the MHRA believe it is safe then they will approve the study. This study has been approved by the MHRA.

Research in the NHS is also looked at by an independent group of people called a Research Ethics Committee. The Research Ethics Committee is made up of experts, non-experts and members of the general public. Together they review research applications to ensure your safety, rights, wellbeing and dignity are protected at all times. This study has been reviewed and given favourable opinion by the North West - Liverpool Central Research Ethics Committee.

### What will happen to the study results?

It is intended that the results of the study will be presented at conferences and published in medical journals so that we can explain to the medical community what our research results have shown. Members of the research team (including patients) will present the results to heart failure patient groups and write a summary of the results for patients, which will be made available on request. Your name will never appear in any report or publication arising from this study.

### Do I have to take part?

You do not have to take part if you do not wish to and your decision will not affect any standard of care you receive.

### What happens if I change my mind?

It is okay if you agree to take part in the study but later change your mind. You do not need to give a reason.

The study doctor may also choose to withdraw you if it is necessary for your health.

If you decide that you would like to withdraw from the study before the final visit

all information collected up until the time of withdrawal will be included in the study analysis, unless you request that it is removed. If you do withdraw we advise that you attend the follow-up visit so that we can make sure that you are still well.

### Additional information

The research is being co-ordinated by the Heart team at University Hospital of South Manchester, but a number of Heart teams across Greater Manchester are involved. The study is being funded by the National Institute for Health Research. The day to day running of the study is being completed by the Clinical Trials Research Centre, part of the University of Liverpool. There is no financial incentive for the hospital or doctor for each individual recruited into the study.

At the end of the trial (Week 52), the study medication will be stopped.

**Thank you for reading this information sheet. We hope it has been of interest to you.**