**Pirfenidone in heart failure with preserved ejection fraction**

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ABSTRACT

Myocardial fibrosis is a pathophysiological mechanism of heart failure with preserved ejection fraction (HFpEF) that is associated with adverse outcome. Whether pirfenidone, an oral antifibrotic agent without haemodynamic effect, is efficacious and safe for the treatment of ~~heart failure with preserved ejection fraction~~ HFpEF is unknown. In this ~~predictive enrichment,~~ double-blind, phase 2 trial, we enrolled patients with heart failure, an ejection fraction of 45% or higher and elevated natriuretic peptides. Eligible patients underwent cardiovascular magnetic resonance and those with evidence of myocardial fibrosis, defined as a myocardial extracellular volume of 27% or greater, were randomly assigned to receive ~~either~~ pirfenidone (target dose 2403mg daily) or placebo for 52-weeks. The primary outcome was change in myocardial extracellular volume, from baseline to 52-weeks. ~~A total of 94~~ Ninety-four patients underwent randomisation (47 to the pirfenidone group, ~~and~~ 47 to the placebo group). In comparison to placebo, pirfenidone reduced myocardial extracellular volume (between-group difference, -1.21%; 95% confidence interval, -2.12 to -0.31; P=0.009). ~~Pirfenidone also reduced log N-terminal pro-B-type natriuretic peptide compared to placebo (P=0.02).~~ Twelve patients (26%) in the pirfenidone group and 14 patients (30%) in the placebo group experienced one or more serious adverse event. The most common adverse events in the pirfenidone group were nausea, insomnia and rash. In conclusion, among patients with ~~heart failure with preserved ejection fraction~~ HFpEF and myocardial fibrosis, administration of pirfenidone for 52-weeks reduced myocardial fibrosis. ~~(Funded by the United Kingdom National Institute for Health Research; ClinicalTrials.gov number,~~ NCT02932566.~~)~~

**INTRODUCTION**

Heart failure with preserved ejection fraction (HFpEF) is common and is associated with high morbidity and mortality.[1](#_ENREF_1) HFpEF involves a diverse range of pathophysiological mechanisms. Indeed, this heterogeneity may have contributed to the neutral findings of ~~all~~ some phase III trials ~~to date, which~~ that have ~~generally~~ considered ~~it~~ HFpEF as a single entity, and taken a one-size-fits-all approach to its treatment.[2](#_ENREF_2) In contrast, trials that have targeted specific biological mechanisms, such as the Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy (ATTR-ACT) trial, and the Rivaroxaban with or without Aspirin in Patients with Heart Failure and Chronic Coronary or Peripheral Artery Disease (COMPASS) trial, have shown benefit.[3](#_ENREF_3),[4](#_ENREF_4) Predictive enrichment trial design means selecting patients who are more likely to respond to a given therapy on the basis of a biological mechanism or specific disease pathway.[5](#_ENREF_5),[6](#_ENREF_6)

Preclinical studies have identified an important pathophysiological role for myocardial fibrosis in heart failure,[7-9](#_ENREF_7) and, in patients with HFpEF, myocardial fibrosis, measured using cardiovascular magnetic resonance, is associated with death and hospitalisation for heart failure.[10](#_ENREF_10) Pirfenidone is an oral, small molecule, antifibrotic agent, without haemodynamic effect, that is approved for patients with idiopathic pulmonary fibrosis.[11](#_ENREF_11) In preclinical models, pirfenidone is associated with regression of myocardial fibrosis.[12-20](#_ENREF_12) In a novel approach to heart failure that involved specifically targeting the extracellular matrix, we identified patients with HFpEF and myocardial fibrosis, and tested whether pirfenidone would result in regression of myocardial fibrosis.

**RESULTS**

**Patients**

From March 7, 2017, to December 19, 2018, 601 patients were screened at 6 sites in the United Kingdom, of which 136 had a baseline assessment. Twenty-nine patients were excluded for reasons of ineligibility, and 13 further patients were found to have ECV <27% (median ECV 24.7%, IQR 24.5-24.9), i.e., below the threshold for entry. Ninety-four patients were randomly assigned to receive pirfenidone or placebo (Fig. 1). At the end of the trial, 12 patients had withdrawn from the study and 2 had died. No patient was lost to follow-up. A total of 80 patients were included in the final efficacy analysis. Baseline characteristics were similar between treatment groups (Table 1 and Table S3 in the Supplementary Appendix). The mean age of patients was 78 years, and 46% were female. Nearly all patients had New York Heart Association functional class II or III symptoms (95%), mean left ventricular ejection fraction was 64% and median NT-proBNP was 1104 pg/ml. Mean myocardial ECV was 30.1%.

**Outcomes**

The primary outcome, change in myocardial ECV from baseline to 52-weeks, was significant, with a greater reduction in those assigned to pirfenidone rather than placebo ~~reduced significantly in the pirfenidone group compared with the placebo group~~ (between-group difference, -1.21%; 95% confidence interval [CI], -2.12 to -0.31; P=0.009) (Table 2 and Fig. 2). The sensitivity analysis, which used multiple imputation to adjust for missing primary outcome values, yielded similar results (between-group difference, -1.14%; 95% CI, -2.04 to -0.25; P=0.01). The causal analysis demonstrated that for each additional 100 capsules of pirfenidone taken (i.e. 11 days of treatment at target dose), there was a mean reduction in myocardial ECV at 52 weeks of 0.06% (95% CI, -0.10 to -0.01; P=0.01).

Secondary outcomes are presented in Table 3 and Table S4 in the Supplementary Appendix. Pirfenidone was associated with a reduction in log NT-proBNP compared to placebo (P=0.02), with the effect seen by week 13 (reduction in median NT-proBNP from baseline to week 13 with pirfenidone: 415 ng/L vs. placebo: 326 ng/L; ~~Fig 2. and~~ Table S5 in the Supplementary Appendix). Pirfenidone was associated with a small increase in left ventricular ejection fraction (between-group difference, 2.16%; 95% CI unadjusted for multiplicity, 0.51 to 3.81). Pirfenidone was associated with a reduction in left ventricular mass (between-group difference, -7.00g; unadjusted 95% CI, -12.7 to -1.29), and maximal wall thickness (between-group difference, -0.06cm; unadjusted 95% CI, -0.12 to -0.01) but there was no significant change in left ventricular mass indexed for body surface area. There were no differences in left ventricular diastolic function, atrial size and function, or right ventricular size and function. Patients in the pirfenidone group showed a small increase in 6-minute walk distance at 52-weeks, whereas those in the placebo group showed a decrease, but the difference was not significant (between-group difference, 15.54 metres; unadjusted 95% CI, -9.55 to 40.63). Pirfenidone was associated with improvements in 8 out of 10 KCCQ scores, including clinically important improvements[21](#_ENREF_21) in all three summary scores, but the differences were not statistically significant.

**Safety**

Following randomisation, 18 patients (38%) in the pirfenidone group and 6 patients (13%) in the placebo group prematurely discontinued treatment for reasons other than death, predominantly due to adverse events (14 in the pirfenidone group and 3 in the placebo group). Twelve patients (26%) in the pirfenidone group experienced one or more serious adverse event compared to 14 patients (30%), including two deaths, in the placebo group (Table S6 in the Supplementary Appendix). Four of the 12 (33%) participants who withdrew from the study experienced a serious adverse event, compared to 20 of the 80 (25%) participants who completed the study. The most frequent adverse events are detailed in Table 4 (see Table S7 in Supplementary Appendix for a complete list). Treatment-emergent changes in safety outcomes and are summarised in Table S8 in the Supplementary Appendix. The number of cardiac adverse events did not differ between groups.

**Sub study**

Sixty randomised patients (30 per treatment group) and 8 non-randomised patients underwent 31phosphorous magnetic resonance spectroscopy. At baseline, there was a modest inverse correlation between myocardial ECV and PCr:ATP ratio (r=-0.26; p=0.03). There was no difference in change in PCr:ATP ratio between treatment groups (see Tables S10 and 11 in the Supplementary Appendix for further details).

**DISCUSSION**

Among patients with heart failure with preserved ejection fraction and myocardial fibrosis, treatment with pirfenidone for 52 weeks reduced myocardial fibrosis, and log NT-proBNP. Pirfenidone was associated with a side effect profile consistent with that reported in previous studies in idiopathic pulmonary fibrosis. There was no excess of cardiac adverse events.

The historical disconnect between phase II and III drug trials in heart failure means that most phase III trials are neutral, despite often promising phase II results.[22](#_ENREF_22),[23](#_ENREF_23) In the PIROUETTE trial, we aimed to connect a prognostically important disease mechanism (myocardial fibrosis) with drug mechanism of action (antifibrotic), select patients with evidence of this disease mechanism for entry and use a primary outcome measure that is tailored to the mechanism of action (myocardial extracellular volume). In designing the study in this way, we believe that the results inform the decision as to whether or not to progress to phase III more reliably.

Targeting the extracellular matrix is a novel approach to heart failure. Pre-clinical studies have indicated that the extracellular matrix may have a primary role in the development of heart failure.[7-9](#_ENREF_7) Myocardial fibrosis regression has been observed previously in humans following interventions with haemodynamic effect, both drug and mechanical, but our study is the first in humans to demonstrate the efficacy of an antifibrotic intervention without haemodynamic effect.[24-27](#_ENREF_24) The associated reduction in natriuretic peptide levels provides support for the extracellular matrix having a causal role in heart failure and being an efficacious therapeutic target.

The magnitude of the reduction in myocardial ECV that we have observed with pirfenidone in the current trial would be associated with a 9 to 28% reduction in a composite of annual rate of hospitalisation for heart failure or all-cause mortality in recent longitudinal cohort studies of patients with heart failure with preserved ejection fraction.[10](#_ENREF_10),[28](#_ENREF_28) This reduction requires investigation in a prospective trial. Myocardial fibrosis, measured using myocardial ECV, is strongly associated with invasively-measured load-independent intrinsic left ventricular myocardial stiffness.[29](#_ENREF_29) It may be that the reduction in log NT-proBNP that we observed with pirfenidone was due to an improvement in left ventricular myocardial stiffness secondary to myocardial fibrosis regression. This requires further investigation. It is unclear why no change was observed in echocardiographic measures of diastolic function. It may be that the structure of the extracellular matrix, such as the degree of collagen cross linking, as well as total fibrotic burden, is important.[30](#_ENREF_30) Alternatively, it may be because echocardiographic measurements of diastolic function are load dependent and have limited accuracy in the context of preserved left ventricular ejection fraction,[31-33](#_ENREF_31) are not representative of any specific disease process, and may be less reflective of diastolic function than myocardial ECV itself.[29](#_ENREF_29) We also found no effect of pirfenidone on left atrial volume or function. This may reflect the range of factors, other than atrial fibrosis, that influence left atrial size and function, such as atrial fibrillation (49% of patients had atrial fibrillation) and chronicity of atrial remodelling (median age was 79 years). Indeed, in a preclinical study using a canine heart failure model, pirfenidone was associated with attenuation of atrial fibrosis but left atrial size still increased.[34](#_ENREF_34)

This trial has some limitations. The study population was generally older than in other trials in heart failure with preserved ejection fraction, although the condition is associated with older age, and older patients are often underrepresented. The trial was not powered for the secondary outcomes; therefore, the secondary findings are considered exploratory. There was some baseline imbalance in NT-proBNP, although this was adjusted for in the analysis. Finally, we cannot exclude the systemic anti-fibrotic effects of pirfenidone impacting some secondary outcomes,[35](#_ENREF_35) however the specificity of the primary outcome measure to ventricular myocardium, and the parallel reduction in NT-proBNP, indicate a direct cardiac effect.

In conclusion, among patients with ~~heart failure with preserved ejection fraction~~ HFpEF and an increased ECV, a marker of myocardial fibrosis, ECV was reduced by treatment with ~~the antifibrotic~~ pirfenidone over 52-weeks ~~resulted in a reduction of myocardial fibrosis~~. The findings suggest that pirfenidone could have favourable effects in patients with this condition. Further trials are necessary to determine the clinical effectiveness and safety of pirfenidone in heart failure with preserved ejection fraction.

**METHODS**

**Trial design and oversight**

The Pirfenidone in Patients with Heart Failure and Preserved Left Ventricular Ejection Fraction (PIROUETTE) trial was a predictive enrichment, randomised, double-blind, placebo-controlled, phase 2 trial. The design of the trial has been described previously.[36](#_ENREF_36) The trial was sponsored by Manchester University NHS Foundation Trust and funded by the United Kingdom National Institute for Health Research. Trial management, independent data management and independent statistical analyses were performed by Liverpool Clinical Trials Centre, a United Kingdom Clinical Research Collaboration fully-registered Clinical Trials Unit. The study protocol was approved by a research ethics committee and trial conduct was overseen by a trial steering committee and an independent data and safety monitoring committee. The investigational medicinal product was gifted by Roche Products Limited. Roche Products Limited had no role in study design, and were not involved in the preparation, drafting or editing of this manuscript. Roche Products Limited conducted a factual accuracy check of this manuscript, but any decisions to incorporate comments were made solely at the discretion of the authors. All the authors reviewed and approved the manuscript and assume full responsibility for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, which is available with the full text of this article.

**Trial patients**

Eligibility requirements included an age of 40 years or older, symptoms and signs of heart failure, an ejection fraction of 45% or higher at baseline, and elevated natriuretic peptides at baseline (with different thresholds depending on the presence of atrial fibrillation or the occurrence of recent hospitalisation for heart failure). As part of the predictive enrichment strategy, eligible patients underwent cardiovascular magnetic resonance and those with evidence of myocardial fibrosis, defined as an extracellular volume (ECV) of 27% or higher, were randomised. Those without myocardial fibrosis were entered into a registry and invited to take part in a sub-study. Detailed eligibility criteria are provided in Table S1 in the Supplementary Appendix.

**Trial procedures**

All patients provided written informed consent. Baseline procedures included cardiovascular magnetic resonance, echocardiography, electrocardiography, 6-minute walk test, laboratory tests and completion of the Kansas City Cardiomyopathy Questionnaire (KCCQ). The trial procedures have been described previously.[36](#_ENREF_36) Following eligibility confirmation, participants were randomised in a 1:1 ratio to treatment with either pirfenidone or matching placebo for 52 weeks using block randomisation, stratified by sex, with computer generated randomisation allocations and randomly varying block sizes. Randomisation was done using web randomisation software accessed using a secure website provided via the clinical trials unit. Treatment was titrated, as tolerated, over a 2-week period to a target of three capsules three times per day (target pirfenidone dose 2403 mg per day), with adjustments permitted if unacceptable side effects occurred. All background medications were continued. Baseline procedures were repeated at the final visit (week 52). The visit schedule including safety monitoring is detailed in the trial protocol, available online.

**Trial sub-study**

We conducted a sub-study to investigate the relationship between myocardial fibrosis and myocardial energetics, and the impact of pirfenidone. We hypothesised that myocardial fibrosis would be associated with impaired energetics, and regression of fibrosis would be associated with an improvement in energetics. Phosphocreatine (PCr) to adenosine triphosphate (ATP) ratio was measured using 31phosphorous magnetic resonance spectroscopy at baseline in a subgroup of patients due to be randomised and repeated at the final visit (week 52), and at baseline in patients without myocardial fibrosis (ECV less than 27%) but who were otherwise eligible. Patient selection was consecutive until the required number were recruited. The 31phosphorous magnetic resonance spectroscopy procedure has been described previously.[36](#_ENREF_36)

**Trial outcomes**

The primary outcome was absolute change in myocardial ECV from baseline to week 52, measured using cardiovascular magnetic resonance. Secondary outcomes included the following:

a) Absolute change in left ventricular and right ventricular mass, volumes, ejection fraction and tissue characteristics from baseline to week 52, measured using cardiovascular magnetic resonance.

b) Absolute change in absolute myocardial extracellular matrix volume from baseline to week 52, measured using cardiovascular magnetic resonance.

c) Absolute change myocardial cell volume from baseline to week 52, measured using cardiovascular magnetic resonance.

d) Absolute change in left ventricular diastolic function, strain, backscatter and torsion from baseline to week 52, measured using echocardiography.

e) Absolute change in left atrial and right atrial volume, and left atrial function from baseline to week 52, measured using cardiovascular magnetic resonance and echocardiography.

f) Absolute change in pulse wave velocity and aortic distensibility from baseline to week 52, measured using cardiovascular magnetic resonance.

g) Absolute change in myocardial energetic status (phosphocreatine to adenosine triphosphate ratio) from baseline to week 52, measured using 31phosphorous magnetic resonance spectroscopy.

h) Absolute change in NT-proBNP, and high-sensitivity troponin T from baseline to week 13, baseline to week 26 and baseline to week 52.

i) Absolute change in exercise tolerance from baseline to week 52, measured using 6-minute walk distance.

j) Absolute change in health status (quality of life), HF symptoms and physical limitations from baseline to week 52, measured using change in KCCQ score.

k) All-cause mortality, cardiovascular mortality and hospitalisation for heart failure will be recorded.

~~change, from baseline to week 52, in ventricular and atrial structure and function, aortic function, 6-minute walk test distance, KCCQ scores and PCr:ATP ratio. Change in N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high sensitivity troponin T were assessed from baseline to weeks 13, 26 and 52.~~ Safety outcomes included treatment emergent adverse events and changes in vital signs, physical examination, laboratory investigations and ECG measurements (see Table S2 in the Supplementary Appendix for further details ~~full description~~).

**Statistical analysis**

We determined that 37 patients per group would provide the trial with 80% power to detect an absolute minimum difference, between pirfenidone and placebo groups, of 2% in terms of change in myocardial ECV from baseline following 52 weeks of treatment, at a 5% significance level (2-sided), assuming a standard deviation of the within-patient differences from baseline equal to 3%.[37](#_ENREF_37) This effect size was based on an estimate of the magnitude of myocardial fibrosis regression that could be expected to translate into improved clinical outcomes based on the magnitude of fibrotic regression seen with renin–angiotensin inhibition in other conditions.[25](#_ENREF_25) To allow for treatment discontinuation in up to 20% of patients prior to final follow-up,[11](#_ENREF_11),[38](#_ENREF_38) the number randomised to each group was adjusted to 47. ~~The sample size calculation for the sub-study is described in the Supplementary Appendix.~~ An ECV threshold of 27% was chosen as the definition of myocardial fibrosis because it represents one standard deviation above that in healthy volunteers scanned using the same scanner and imaging sequence at the sponsor institution (Manchester University NHS Foundation Trust).

For the trial sub-study, we determined that 33 patients per group were required to detect an absolute minimum difference in Phosphocreatine (PCr) to adenosine triphosphate (ATP) ratio of 0.37 between randomised (myocardial extracellular volume (ECV) ≥27%) and non-randomised (ECV <27%) groups at baseline (80% power, 5% significance level, 2-sided), assuming a standard deviation of the between group differences of 0.52.[39](#_ENREF_39) This effect size was based on that seen in previous studies.[39](#_ENREF_39),[40](#_ENREF_40) Additionally, 26 patients per group were required to detect an absolute minimum difference, between pirfenidone and placebo groups, of 0.4 in terms of absolute change in PCr:ATP ratio from baseline following 52 weeks of treatment (80% power, 5% significance level, 2-sided), assuming a standard deviation of the within-patient differences from baseline equal to 0.5.[41](#_ENREF_41) This effect size was also based on that seen in other studies.[40-43](#_ENREF_40) To allow for treatment discontinuation in up to 20% of patients prior to final follow-up, the number required in each group was inflated to 33.

PCr:ATP ratio and myocardial mechanical parameters at baseline were compared between patients that were due to be randomised (ECV ≥27%) and patients without myocardial fibrosis (ECV less than 27%) but who were otherwise eligible using an independent t test, with transformation as necessary. Correlation analysis was used to assess the relationships between PCr:ATP ratio, myocardial mechanical parameters and ECV at baseline. Similarly, correlation analysis was used to assess the relationships between change from baseline in each of these parameters with change in ECV from baseline. PCr:ATP ratio was compared between treatment groups using analyses of covariance, adjusting for baseline PCr:ATP ratio, stratification factor (sex) and treatment group.

The trial was analysed and reported according to the ‘Consolidated Standard of Reporting Trials’ (CONSORT) and the International Conference on Harmonisation E9 guidelines. All primary analyses were on an intention to treat basis, including all randomised patients retained in their randomised treatment groups. The primary and secondary outcomes were compared between treatment groups using analyses of covariance, adjusting for baseline values of the outcome variable, stratification factor (sex) and treatment group. Repeated measures analyses of covariance were used for NT-proBNP and high sensitivity troponin T. The hypothesis testing on secondary outcomes was considered exploratory. Imputation methods were utilised in a sensitivity analysis to assess the robustness of the primary outcome results to missing data. The degree of missing data was assessed during the blind review phase and imputation methods were only implemented if more than 5% of patients were missing primary outcome data. Multiple imputation, based on baseline NT-proBNP, smoking status, diabetes and hypertension, were used to adjust for missing primary outcome values in a sensitivity analysis of covariance model, adjusting for the same baseline covariates and factors as for the primary analysis. A secondary causal analysis, according to dose and duration of pirfenidone, was undertaken using instrumental variable regression in order to assess the causal impact of pirfenidone received on the primary outcome. Adverse events were coded according to preferred terms in the Medical Dictionary for Regulatory Activities (version 19). The number and percentage of participants experiencing each safety outcomes were reported, and treatment-emergent changes in safety outcomes were described using summary statistics. The statistical analyses for the sub-group are described in the Supplementary Appendix. The conventional 5% significance level was used. All analyses were performed using SAS (Version 9.4, SAS Institute Inc, NC).

**Data availability**

De-identified participant data will be made available on reasonable request one year after date of publication, with no end date to availability, and may be used for any purpose. Requests should be directed to christopher.miller@manchester.ac.uk. Requestors will be required to sign a data access agreement. The study protocol is provided with the manuscript.

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**AUTHOR CONTRIBUTIONS**

Drs Lewis and Miller had full access to all the data and take responsibility for the integrity of the data and accuracy of data analysis. *Study concept and design:* Lewis, Dodd, Bedson, Schelbert, Naish, Duran Jimenez, Williams, Cunnington, Ahmed, Cooper, Viswesvaraiah, Russell, McDonagh, Williamson, Miller. *Acquisition, analysis, or interpretation of data:* All authors. *Drafting of the manuscript:* Lewis, Miler. *Critical revision of the manuscript for important intellectual content:* All authors. *Statistical analysis:* Dodd, Clayton. *Obtained funding:* Miller. *Administrative, technical, or material support:* Eccleson, Naish, Duran Jimenez. *Study supervision:* Bedson, Williamson, Miller.

**COMPETING INTERESTS STATEMENT**

The authors declare no competing interests. The investigational medicinal product was gifted by Roche Products Limited. Immunoassay testing equipment and materials were gifted by Roche Diagnostics International Limited. Roche Products Limited and Roche Diagnostics International Limited had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, or approval of the manuscript; and decision to submit the manuscript for publication. Roche Products Limited and Roche Diagnostics International Limited conducted a factual accuracy check of this manuscript, but any decisions to incorporate comments were made solely at the discretion of the authors.

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**FIGURES**

**Figure 1. Screening, Randomisation, and Follow-up.** #,&All patients that withdrew from the trial are included in the number that prematurely discontinued treatment. CMR – cardiovascular magnetic resonance; ECV – extracellular volume.



**Figure 2. Myocardial extracellular volume (ECV) at baseline and week 52 by treatment group.**

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**TABLES**

**Table 1. Selected characteristics of the patients at baseline.**

|  |  |  |
| --- | --- | --- |
| **Characteristics** | **Pirfenidone****(n=47)** | **Placebo****(n=47)** |
| Age – yr | 78 (72-82) | 81 (76-83) |
| Female sex – no. (%) | 22 (47) | 21 (45) |
| White race – no. (%) \* | 45 (96) | 43 (92) |
| Hypertension – no. (%) | 39 (83) | 40 (85) |
| Diabetes – no. (%) | 16 (34) | 12 (26) |
| Atrial fibrillation / flutter – no. (%) † | 22 (47) | 24 (51) |
| Hospitalisation for heart failure in past 6 months – no. (%) | 8 (17) | 7 (15) |
| Systolic blood pressure - mmHg | 134 (123-148) | 139 (125-145) |
| Body mass index – kg/m2 | 31 (27-34) | 29 (26-33) |
| NYHA functional class – no. (%) |  |  |
| I | 0 (0) | 5 (11) |
| II | 26 (55) | 19 (40) |
| III | 21 (45) | 23 (49) |
| IV | 0 (0) | 0 (0) |
| eGFR – mls/min/1.73m2 | 58 (46-76) | 53 (38-65) |
| Median NT-proBNP – pg/ml (IQR) | 975 (445-2064) | 1372 (626-2817) |
| Left ventricular ejection fraction - % | 67 (60-70) | 65 (55-69) |
| Left ventricular mass index – g/m2 | 62 (54-71) | 66 (53-73) |
| Extracellular volume - % |  28.9 (27.6-31.0) | 30.4 (28.3-32.2) |
| Global longitudinal strain - % ‡ | -15.7 (-19.0--12.1) | -16.2 (-18.3--14.0) |
| E/A ratio ∬ | 1.0 (0.8-1.3) | 1.1 (0.8-1.4) |
| Lateral e’ – cm/s | 10.3 (8.7-12.6) | 10.1 (8.5-10.9) |
| Septal e’ – cm/s | 7.4 (6.3-9.6) | 6.2 (5.4-7.2) |
| Average E/e’ ‡ | 10.4 (9.1-13.6) | 12.8 (10.3-15.5) |
| Left atrial volume index – ml/m2 | 68 (56-83) | 69 (58-85) |
| Left atrial strain S (Reservoir) - % ‡ | 18.3 (10.8-24.6) | 15.6 (9.2-20.4) |
| Right ventricular ejection fraction - % | 53 (48-59) | 51 (43-57) |
| Phosphocreatine to adenosine triphosphate ratio **¶** | 1.2 (1.0-1.4) | 1.1 (0.9-1.4) |
| 6-minute walk test – m | 286 (160-349) | 262 (173-328) |
| KCCQ Overall summary score (0-100) ‖ | 50.7 (38.9-72.6) | 55.9 (39.1-70.8) |

**Table 1 Legend:** Values are mean ± standard deviation unless stated. eGFR – estimated glomerular filtration rate; IQR – interquartile range; NT-proBNP – N-terminal brain natriuretic peptide; NYHA – New York Heart Association.

\* Race was reported by the patient

†Patients in atrial fibrillation or atrial flutter on baseline electrocardiogram.

‡ Due to technical factors the following imaging measurements were unobtainable at baseline: global longitudinal strain (1 patient in the pirfenidone group), average E/e’ (1 patient in the placebo group), left atrial strain S (reservoir) (1 patient in the pirfenidone group and 1 in the placebo group).

∬It is not possible to measure E/A ratio in patients in atrial fibrillation (n=46, 22 in the pirfenidone group and 24 in the placebo group).

**¶** Phosphocreatine to adenosine triphosphate ratio corrected for blood and partial saturation.

‖Values for the Kansas City Cardiomyopathy Questionnaire scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure.

**Table 2. Primary outcome.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Pirfenidone** | **Placebo** |  |
|  | **Baseline****(n=47)** | **52 weeks****(n=39)** | **∆ from baseline to 52 weeks** | **Baseline****(n=47)** | **52 weeks****(n=41)** | **∆ from baseline to 52 weeks** | **Between-group difference (95% CI)\*** | **P-value** |
| **Myocardial ECV (%)** | 29.5 ± 2.5 | 28.6 ± 2.7 | -0.7 ± 1.4 | 30.7 ± 2.9 | 31.1 ± 3.8 | 0.5 ± 2.4 | -1.21 (-2.12 to -0.31) | 0.009 |

**Table 2 Legend:** Data are mean ± standard deviation. \*Analysis of covariance, adjusting for baseline myocardial extracellular volume (ECV), sex and treatment group. CI – confidence interval.

**Table 3. Secondary outcome measures**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Pirfenidone** | **Placebo** |  |
| **SECONDARY OUTCOME** | **Baseline****(n=47)** | **52-weeks****(n=39)** | **∆ from baseline to 52-weeks** | **Baseline****(n=47)** | **52-weeks****(n=41)** | **∆ from baseline to 52-weeks** | **ANCOVA Model between-group difference (95% CI)** |
| **Left Ventricle** |
| LVEDVi - ml/m2 | 59 (50-75) | 59 (50-72) | -2 (-7-8) | 60 (51-76) | 59 (51-66) | -3 (-9-5) | 0.47 (-3.22 to 4.16) |
| LVESVi - ml/m2 † | 19 (14-27) | 19 (15-24) | 0 (-3-2) | 21 (15-32) | 19 (16-28) | -1 (-4-2) | -1.43 (-3.16 to 0.30) |
| LVEF - % † | 67 (60-70) | 68 (64-71) | 1 (-1-2) | 65 (55-69) | 65 (56-69) | 0 (-2-1) | 2.16 (0.51 to 3.81) |
| LV mass index - g/m2 | 62 (54-71) | 60 (52-70) | -1 (-6-2) | 66 (53-73) | 63 (55-75) | 0 (-3-4) | -2.48 (-5.47 to 0.50) |
| Native T1 – ms | 1050 (1032-1071) | 1032 (1018-1043) | -15 (-30-3) | 1056 (1031-1073) | 1058 (1020-1089) | 3 (-15-19) | -24.3 (-39.1 to-9.49) |
| Absolute myocardial ECM volume - ml | 33.5 (27.9-41.9) | 29.0 (24.8-37.2) | -2 (-5.4--0.2) | 32.7 (28.7-46.3) | 36.5 (28.7-44.2) | 0.8 (-1.3-2.3) | -3.06 (-4.96 to -1.16) |
| Absolute myocardial cell volume - ml | 82.3 (66.2-97.7) | 73.4 (64.7-93.1) | -2.9 (-11.1-2.1) | 78.2 (66.6-98.7) | 77.2 (68.1-93.3) | -0.4 (-4.8-3.5) | -3.41 (-7.28 to 0.47) |
| E/A ratio | 1.0 (0.8-1.3) | 0.8 (0.7-1.1) | -0.1 (-0.3-0.1) | 1.1 (0.8-1.4) | 0.8 (0.6-1.0) | -0.1 (-0.3-0.0) | 0.10 (-0.09 to 0.30) |
| Lateral e’ - cm/s | 10.3 (8.7-12.6) | 8.5 (7.0-10.7) | -1.3 (-2.9-0.1) | 10.1 (8.5-10.9) | 9.0 (6.8-10.2) | -0.8 (-2.7-0.2) | -0.16 (-1.18 to 0.86) |
| Septal e’ - cm/s | 7.4 (6.3-9.6) | 6.7 (6.0-8.1) | -0.8 (-2.3-0.2) | 6.2 (5.4-7.2) | 6.5 (5.0-7.7) | 0.0 (-0.8-1.3) | 0.02 (-0.81 to 0.84) |
| Average E/e’ - cm/s ‡ | 10.4 (9.1-13.6) | 12.5 (8.9-14.5) | 0.9 (-0.5-1.9) | 12.8 (10.3-15.5) | 13.1 (11.3-15.7) | -0.1 (-1.6-2.3) | 0.25 (-1.37 to 1.86) |
| GLS - % ∬ | -15.7 (-19.0--12.1) | -17.7 (-19.5--13.0) | -0.4 (-3.5-1.7) | -16.2 (-18.3--14.0) | -16.9 (-18.9--13.3) | 0.1 (-1.1-1.2) | -1.17 (-2.58 to 0.24) |
| PCr:ATP ratio (BCPSC) †† | 1.2 (1.0-1.4) | 1.3 (1.1-1.6) | 0.1 (-0.3-0.4) | 1.1 (0.9-1.4) | 1.2 (1.0-1.6) | 0.0 (-0.2-0.5) | -0.06 (-0.32 to 0.20) |
| **Right Ventricle** |
| RVEDVi - ml/m2 | 68 (60-80) | 70 (59-80) | 2 (-7-10) | 67 (57-78) | 66 (60-78) | 3 (-5-8) | 1.27 (-3.22 to 5.76) |
| RVEF (%) † | 53 (48-59) | 55 (50-59) | 1 (-7-6) | 51 (43-57) | 50 (44-57) | -1 (-4-5) | 1.62 (-1.26 to 4.50) |
| PAP – mmHg **¶** | 34 (22-38) | 33 (26-37) | -3 (-5-0) | 33 (27-40) | 34 (25-43) | 01 (-6-7) | -0.44 (-7.07 to 6.19) |
| **Left Atrium** |
| LA volume - ml | 130 (106-159) | 127 (98-164) | 1 (-10-10) | 131 (108-163) | 136 (115-161) | 6 (-1-13) | -3.24(-11.0 to 4.55) |
| LA volume index - ml/m2 | 68 (56-83) | 63 (54-90) | 1 (-3-6) | 69 (58-85) | 72 (58-87) | 3 (0-8) | 0.64 (-5.15 to 6.44) |
| LA Strain (Reservoir) - % ‖ | 18.3 (10.8-24.6) | 21.1 (12.0-28.5) | 0.8 (-3.8-3.9) | 15.6 (9.2-20.4) | 13.9 (8.5-20.2) | 0.0 (-2.3-3.3) | 0.38 (-2.28 to 3.04) |
| LA Strain (Booster) - % | 13.4 (8.7-15.3) | 14.8 (10.0-18.4) | 1.9 (-1.8-4.1) | 12.4 (9.7-14.6) | 14.9 (10.2-19.4) | 2.5 (-1.2-4.3) | -0.45 (-3.34 to 2.44) |
| LA Strain (Conduit) - % †† | 11.1 (8.6-13.4) | 12.0 (7.5-13.8) | -0.5 (-5.0-2.0) | 8.8 (7.4-10.5) | 8.5 (6.8-10.4) | -0.4 (-1.9-2.2) | 0.56 (-1.08 to 2.20) |
| **6MWT** |
| 6MWT – m ‡‡ | 286 (160-349) | 308 (234-360) | 1 (-27-27) | 262 (173-328) | 245 (183-355) | -9 (37-23) | 15.54 (-9.55 to 40.63) |
| **KCCQ** |
| KCCQ – Overall Summary Score (0-100) | 50.7 (38.9-72.6) | 63.9 (53.8-76.0) | 7.6 (-2.6-20.8) | 55.9 (39.1-70.8) | 60.4 (36.0-79.2) | 1.4 (-5.6-12.9) | 6.45 (-0.19 to 13.09) |
| KCCQ – Clinical Summary Score (0-100) ∬∬ | 52.1 (41.7-69.8) | 64.3 (52.1-74.6) | 6.3 (-1.6-15.6) | 56.8 (41.7-70.3) | 61.5 (40.4-76.3) | 2.1 (-6.8-9.6) | 5.51 (-0.85 to 11.87) |
| KCCQ – Total Symptom Score (0-100) | 57.3 (39.6-78.1) | 70.8 (53.1-82.3) | 10.4 (0.0-18.8) | 66.7 (49.0-79.2) | 64.6 (52.1-81.3) | 0.0 (-8.3-14.6) | 5.90 (-2.42 to 14.22) |

**Table 3 Legend:** Values are mean (SD) unless stated.

Patients in atrial fibrillation at baseline (n=46, 22 in the pirfenidone group and 24 in the placebo group) and at follow up (n=40, 17 in the pirfenidone group and 23 in the placebo group) were unable to have the following parameters measured: A-wave velocity, E/A ratio, left atrial strain A (booster), left atrial strain rate – SR-A.

† Measurement was unobtainable in 1 patient at 52-weeks (1 in the pirfenidone group).

‡ Measurement was unobtainable in 1 patient at baseline (1 in the placebo group) and 1 patient at 52-weeks (1 in the placebo group).

∬Measurement was unobtainable in 1 patient at baseline (1 in the placebo group).

**¶** Measurement was unobtainable at baseline (n=35, 21 in the pirfenidone group and 14 in the placebo group) and at week 52 (n=34, 20 in the pirfenidone group and 14 in the placebo group).

‖Measurements unobtainable in 2 patients at baseline (1 in the pirfenidone group and 1 in the placebo group).

†† Measurement performed in 60 patients at baseline (30 in the pirfenidone group and 30 in the placebo group) and 50 patients at 52-weeks (25 in the pirfenidone group and 25 in the placebo group).

‡ ‡ Measurements not performed in 10 patients at 52-weeks (5 in the pirfenidone group and 5 in the placebo group).

∬∬Kansas City Cardiomyopathy Questionnaire (KCCQ) was completed by all patients at baseline and 52-weeks. If patients answered, ‘Limited for other reasons or did not do’ for a specified number of responses the scores are set to ‘missing value’.

6MWT **–** 6-minute walk test; ANCOVA – analysis of covariance; ATP – adenosine triphosphate; CI – confidence interval; CMR – cardiac magnetic resonance; ECM – extracellular matrix; ECV – extracellular matrix volume; GLS – global longitudinal strain; LA – left atrial; LV – left ventricular; LVEDV – left ventricular end-diastolic volume; LVEF – left ventricular ejection fraction; LVESV – left ventricular end-systolic volume; PAP – pulmonary artery systolic pressure; RVEDV – right ventricular end-diastolic volume; RVEF – right ventricular ejection fraction.

**Table 4. Adverse events occurring in at least 20% of patients in either treatment group.**

|  |  |  |
| --- | --- | --- |
| **Adverse Event** | **Pirfenidone****(N=47)** | **Placebo****(N=47)** |
| Any adverse event  | 46 (98) | 46 (98) |
| Nausea  | 15 (32) | 6 (13) |
| Insomnia  | 14 (30) | 4 (9) |
| Rash  | 13 (28) | 7 (15) |
| Diarrhoea  | 12 (26) | 13 (28) |
| Dyspepsia  | 12 (26) | 4 (9) |
| Blood urea increased  | 11 (23) | 9 (19) |
| Lower respiratory tract infection  | 11 (23) | 13 (28) |
| Lethargy  | 11 (23) | 8 (17) |
| Decreased appetite  | 10 (21) | 8 (17) |
| Dizziness  | 10 (21) | 5 (11) |
| Dyspnoea  | 10 (21) | 15 (32) |
| Hot flush  | 10 (21) | 3 (6) |
| Blood alkaline phosphatase increased  | 7 (15) | 10 (21) |

**Table 4 Legend.** Data are counts (percentages).